# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Grafalon 20 mg/ml concentrate for solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

20 mg anti-human T-lymphocyte immunoglobulin from rabbits per 1 ml Grafalon (100mg/5ml vial or 200mg/10ml vial).

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, pH = 3.4 – 4.0

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Grafalon is indicated in combination with other immunosuppressive medicinal products for the suppression of immune competent cells, which are the cause for acute rejection. It is usually administered for the following indications:

Prevention of acute transplant rejection in patients receiving allogeneic solid organ transplants
Grafalon is indicated in combination with other immunosuppressive medicinal products (e.g., glucocorticosteroids, purine antagonists, calcineurin inhibitors or mTOR inhibitors) to enhance immunosuppression following allogeneic solid organ transplantation.

Therapy of acute corticosteroid-resistant rejection after allogeneic solid organ transplantation
Grafalon is indicated for the treatment of acute corticosteroid-resistant rejection episodes after allogeneic solid organ transplantation if the therapeutic effect of methyl-prednisolone treatment has proven unsatisfactory.

### 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).

Unless otherwise prescribed, the recommended daily dose of Grafalon is:

Prophylaxis following organ transplantation:

0.1-0.25 ml (=2-5 mg) Grafalon/kg BW. The most common daily dosages are in the range of 3-4 mg/kg BW.

Depending on the patient's condition, dosage, and concomitant medication, the required duration of therapy will be in the range of 5-14 days, starting with the day of transplantation.

Therapy of acute steroid-resistant rejection:
0.15-0.25 ml (=3-5 mg) Grafalon/kg BW. The most common daily dosages are in the range of 3-4 mg/kg BW.

Duration of therapy will vary according to the condition of the graft organ and therapy plan. The treatment will usually last 5-14 days, starting with the day of rejection crisis.

*Paediatric population*
Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made. Available information indicates that paediatric patients do not require a different dosage than adult patients.

*Elderly patients*
The experience in elderly patients (≥65 years) is limited, but there is no evidence that these patients require a different dosage than other age groups.

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 should 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 (i.e., dilute 1 ml of Grafalon with 6 ml of sodium chloride solution) to maintain the required level of osmolality. Higher dilution ratios, with attendant higher pH levels, may result in particle formation. Solutions containing visible particles must not be used. Grafalon should be infused intravenously over a period of at least 4 hours.

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 large high flow vein can be chosen. The administration of methylprednisolone and/or antihistamines prior to infusion is recommended in order to improve systemic and local tolerance. 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 route 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 or mycotic and parasitic 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/microlitre because Grafalon may enhance thrombocytopenia and thus increase the risk of hemorrhage.

Grafalon is contraindicated in patients with malignant tumors 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/microlitre) 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, mycotic, and/or parasitic 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 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.

Sodium
Grafalon contains sodium, but less than 1 mmol (23 mg) sodium per dosing unit, i.e., it is nearly "sodium-free". The sodium content of the ready-to-use infusion solution is higher and depends on the amount of sodium chloride solution used for the dilution.

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 interactions**

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**

Pregnancy
For Grafalon no clinical or animal data on exposed pregnancies and breastfeeding mothers are available. The potential risk for the fetus is unknown. Caution should be exercised when prescribing to pregnant women.

Breastfeeding
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 stem cell transplantation (106 patients). Approximately 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 |

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| **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 if 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, otherwise documented as thrombocytopenia and leukopenia are commonly observed after Grafalon administration. Anemia is 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 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 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 was fatal in isolated cases.

Paediatric population
Currently available data are limited. Available information indicates that the safety profile of Grafalon in paediatric patients is not fundamentally different to that seen in adults.

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

**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: immunosuppressive drug, immunoglobulin against human T lymphocytes (rabbit), ATC code: L04AA04

Grafalon is a high-titre anti-T-lymphocyte immunoglobulin preparation with immunosuppressive activity.

Grafalon is isolated from the serum of rabbits previously immunised with human T-lymphoblasts from the human Jurkat cell line. Grafalon as polyclonal anti-T-lymphocyte antibody solution is described to have a direct effect on T-lymphocyte, thus resulting in a T-lymphocyte depletion after administration.

Among other effects published results of in vivo and in vitro tests indicate that the effect of Grafalon is due to the binding to CD2+, CD3+, CD4+/CD28+, CD5+, CD7+, LFA-1+, and ICAM-1+ lymphocytes. Mainly T-lymphocytes express these surface markers.

Paediatric population
Multiple reports regarding the use of Grafalon in children have been published. These reports reflect the broad clinical experience with this product in paediatric patients and suggest that the safety and efficacy profiles in paediatric patients are not fundamentally different to those seen in adults.

However, there is no clear consensus with regards to the dosing in paediatrics. As in adults, the posology in paediatrics depends on the indication, the administration regimen, and the combination with other immunosuppressive agents. This should be considered by physicians before deciding on the appropriate dosage in paediatrics.

**5.2 Pharmacokinetic properties**

Grafalon is administered by the intravenous route and therefore is 100 % bioavailable.
Pharmacokinetic studies showed that during intravenous administration of 4 mg/kg BW/d (for 7 days) Grafalon serum levels increased from 48 ± 5 microgram/ml on day 1 to 204 ± 13 microgram/ml on day 7 with a half-life of approximately 14 days after the last dose. However, the serum level of Grafalon does not correlate with its immunosuppressive activity.
Grafalon is subject to protein metabolism as are other body proteins.

**5.3 Preclinical safety data**

After intravenous administration of 900 mg/kg BW in rabbits, the animals demonstrated no pathological changes in either the clinical picture or in the haematological test results.

With a dosage of 100 mg/kg BW in the rhesus monkey, only in the first 3 days a slight motory inhibition, a shift in the neutrophilic granulocytes in the haemogram and a temporary decrease of the reticulocytes and thrombocytes were observed.

The determination of the sub-acute (chronic) toxicity was performed on the rhesus monkey. The intravenous application of 300 and 500 mg/kg BW/day lead on the 7th day (300 mg) and on the 5th day (500 mg) to the death of the experimental animals. The toxic symptoms indicate an anaphylactic shock with circulatory collapse as the cause of death.

In comparison to the control group, there was a decreasing lymphocyte count in all dosage groups. The histological findings and the other haematological findings lay within the normal range. An activation of the lymphatic organs could not be determined in any of the experimental animals.

An influence on the CNS through the administration of Grafalon can be excluded by the results of the trials on the conscious cat.

The trials on the anaesthetised cat gave no indications of cardiovascular side-effects.

Furthermore, Grafalon showed no mutagenic effect in 3 different in vitro-test, both with and without metabolic activation.

**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 must not be mixed with glucose, blood, blood-derivatives and solutions containing lipids and sodium heparin.

**6.3 Shelf life**

3 years.
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.

**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 medicinal product, 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 precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

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

**7 MARKETING AUTHORISATION HOLDER**

Neovii Biotech GmbH
Am Haag 6+7
82166 Graefelfing
Germany

**8 MARKETING AUTHORISATION NUMBER**

PA1015/001/001

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

Date of first authorisation: 05 June 2001
Date of last renewal: 05 June 2006

**10 DATE OF REVISION OF THE TEXT**

March 2022