ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zenapax 5 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Daclizumab*……5 mg per 1 ml infusion

One vial of 5 ml contains 25 mg of daclizumab* (5 mg/ml).

* Recombinant humanized IgG1 anti-Tac antibody produced in a murine NSO myeloma cell line using a glutamine synthetase (GS) expression system (NS_GSO) by recombinant DNA technology

Excipients:
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to slightly yellowish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zenapax is indicated for the prophylaxis of acute organ rejection in *de novo* allogenic renal transplantation and is to be used concomitantly with an immunosuppressive regimen, including cyclosporine and corticosteroids in patients who are not highly immunised.

4.2 Posology and method of administration

Zenapax should be prescribed only by physicians who are experienced in the use of immunosuppressive therapy following organ transplantation.

The recommended dose for Zenapax in adult and paediatric patients is 1 mg/kg. The volume of Zenapax containing the appropriate dose is added to 50 ml of sterile 0.9% saline solution and is administered intravenously over a 15 minute period. It may be given via a peripheral or central vein.

Zenapax should initially be given within 24 hours before transplantation. The next and each subsequent dose should be given at intervals of fourteen days, for a total of five doses.

Elderly

Experience with Zenapax in elderly patients (older than 65 years) is limited because of the small number of older patients who undergo renal transplantation, but there is no evidence that elderly patients require a different dosage from younger patients.

Patients with severe renal impairment

No dosage adjustment is necessary for patients with severe renal impairment.

Patients with severe hepatic impairment

No data are available for patients with severe hepatic impairment.

Instructions for the preparation of Zenapax infusions are described in section 6.6.

4.3 Contraindications

Zenapax is contraindicated in patients with known hypersensitivity to daclizumab or to any excipients of this product (see section 6.1).

Zenapax is contraindicated during lactation (see section 4.6).

4.4 Special warnings and precautions for use

There is no experience of the use of Zenapax in patients who are highly immunised.

Anaphylactic reactions following the administration of proteins can occur. Severe, acute (onset within 24 hours) hypersensitivity reactions on both initial and subsequent exposure to Zenapax have been reported rarely. The clinical manifestations of these reactions include hypotension, tachycardia, hypoxia, dyspnoea, wheezing, laryngeal oedema, pulmonary oedema, flushing, diaphoresis, temperature increase, rash and pruritus. Medications for the treatment of severe hypersensitivity reactions should therefore be available for immediate use.

Patients on immunosuppressive therapy following transplantation are at increased risk for developing lymphoproliferative disorders (LPDs) and opportunistic infections. While Zenapax is an immunosuppressive drug, to date no increase in LPDs or opportunistic infections have been observed in patients treated with Zenapax.

In transplant recipients there is no experience of exposure to second or subsequent treatment courses using Zenapax.

In a single randomized controlled clinical trial in cardiac transplant recipients which compared Zenapax to placebo, each used in combination with mycophenolate mofetil (CellCept 1.5 g bid), cyclosporine, and corticosteroids, there were more infection related deaths among patients who received Zenapax. At 1 year post-transplant 14 of 216 patients (6.5%) who received Zenapax and 4 of 207 (1.9%) patients who received placebo died of an infection, a difference of 4.6% (95% CI: 0.3%, 8.8%). Of these 14 Zenapax patients, 4 died more than 90 days after receiving their last dose of Zenapax, making it unlikely that Zenapax had a role in the infection related death. Overall, use of polyclonal antilymphocyte antibody therapy (OKT3, ATG, ATGAM) was similar in patients who received Zenapax and in patients who received placebo, 18.5% and 17.9%, respectively. However, of the 40 patients who received both Zenapax and antilymphocyte therapy, 8 (20.0%) died whereas of the 37 patients who received both placebo and antilymphocyte therapy, 2 (5.4%) died. Concomitant use of Zenapax with another antilymphocyte antibody therapy in the context of intensive immunosuppression with cyclosporine, mycophenolate mofetil and corticosteroids may be a factor leading to fatal infection.

4.5 Interaction with other medicinal products and other forms of interaction

Because Zenapax is an immunoglobulin, no metabolic drug-drug interactions are to be expected.

The following transplant medications have been administered in clinical trials with Zenapax without any interactions: cyclosporine, mycophenolate mofetil, gancyclovir, acyclovir, tacrolimus, azathioprine, antithymocyte immune globulin, muromonab-CD3 (OKT3), and corticosteroids.

4.6 Pregnancy and lactation

Pregnancy

There are limited data from the use of daclizumab in pregnant women. A study in cynomolgus monkeys has not shown teratogenic effects but did show an increase of early prenatal loss which remains in the historical spontaneous abortion rate (see section 5.3). The clinical relevance is unknown.

Zenapax should not be used in pregnant women unless it is clearly necessary.

Women of childbearing potential must use an effective contraceptive method during Zenapax therapy and continue its use for an additional 4 months following the last dose of Zenapax.

Lactation
Daclizumab is excreted in cynomolgus monkey milk (see section 5.3). It is not known if Zenapax is excreted in human milk. However due to potential harmful effects for the newborn, breast-feeding is contraindicated during the treatment and up to 4 months following the last dose of Zenapax.

4.7 Effects on ability to drive and use machines

Zenapax has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The safety profile of Zenapax was studied in comparison to placebo in patients who concomitantly received immunosuppressive regimens containing cyclosporine and corticosteroids alone, with the addition of azathioprine or with the addition of mycophenolate mofetil. The data from the four studies (O14392, O14393, O14874 and O15301) showed that the incidence and types of adverse events were similar in both placebo-treated and Zenapax-treated patients. Adverse events were reported by 95% of placebo and 96% of daclizumab treated patients. Serious adverse events were reported by 44.4% of the patients in the placebo-treated group and 39.9% of the patients in the Zenapax-treated group.

Adverse events occurring with a frequency of ≥2% in patients in either group during the first 3 months post-transplant are listed below.

Within the system organ classes, undesirable effects are listed under headings of frequency, using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Frequency category	Adverse event	Zenapax (%) n=336	Placebo (%) n=293
Infections and infestations	Common	Pharyngitis	2.4	3.8
		Rhinitis	3.0	3.1
Metabolism and nutrition disorders	Common	Diabetes mellitus	3.3	4.8
		Fluid overload	3.3	5.8
		Dehydration	3.0	3.1
Psychiatric disorders	Very common	Insomnia	12.5	13.7
	Common	Depression	3.3	2.0
		Anxiety	2.1	5.5
Nervous system disorders	Very common	Tremor	19.3	15.7
		Headache	15.5	14.7
	Common	Dizziness	5.1	4.4
		Paraesthesia	3.6	0.9
Eye disorders	Common	Vision blurred	2.7	4.4
Cardiac disorders	Common	Tachycardia	6.5	6.8
Vascular disorders	Very common	Hypertension(incl. aggravated)	32.1	27.7
	Common	Hypotension	8.6	10.2
		Haemorrhage	7.4	10.6

System organ class	Frequency category	Adverse event	Zenapax (%) n=336	Placebo (%) n=293
		Lymphocele	7.4	6.5
		Thrombosis	5.4	4.4
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea	11.9	15.4
	Common	Pulmonary oedema	6.3	4.4
		Pleural effusion	2.1	1.4
		Atelectasis	3.3	3.8
		Hypoxia	2.7	3.1
		Respiratory tract congestion	3.3	3.8
		Rales	3.3	1.4
		Cough	5.1	4.8
		Breath sounds abnormal	2.7	1.7
Gastrointestinal disorders	Very common	Constipation	34.8	37.9
		Diarrhoea	15.2	16.4
		Vomiting	14.9	14.3
		Nausea	27.4	25.9
		Dyspepsia (incl. pyrosis)	15.1	14.7
	Common	Abdominal distension	5.7	4.4
		Gastritis	2.4	0.7
		Abdominal pain	9.8	13.0
		Abdominal pain upper (epigastric pain)	5.4	3.8
		Haemorrhoids	2.1	0.7
		Flatulence	3.9	4.1
Skin and subcutaneous tissue disorders	Common	Rash	3.3	4.4
		Acne	8.9	7.2
		Pruritus	3.9	5.8
		Night sweats	2.1	2.0
		Hyperhidrosis	2.1	1.7
		Hirsutism	4.8	2.0
Musculoskeletal, connective tissue and bone disorders	Very common	Musculoskeletal pain	12.3	12.5
	Common	Back pain	6.5	8.2
		Muscle spasms	2.4	1.4
		Arthralgia	2.7	2.7
		Myalgia	2.1	1.0
General disorders and administration site conditions	Very common	Oedema	15.8	18.4
		Oedema peripheral	28.0	30.0
		Impaired healing (without infection)	12.2	10.2
	Common	Chest pain	8.6	8.9
		Pain	7.1	8.2
		Fatigue	7.4	9.6
		Application site reaction	4.8	5.1
		Pyrexia	5.4	10.2
		Asthenia	3.3	2.7
		Chills	3.0	5.1
Renal and urinary disorders	Common	Renal failure	3.6	3.3
		Renal tubular necrosis	7.4	6.8
		Hydronephrosis	2.1	4.4
		Renal disorder (damage)	4.5	7.8
		Haemorrhage urinary tract	2.1	3.4
		Urinary retention	2.1	3.1
		Urinary tract disorder	2.7	2.4
		Oliguria	9.5	10.6
		Dysuria	6.0	12.3
Injury and poisoning	Common	Post-traumatic pain	20.8	20.1

Incidence of malignancies: Three years after treatment, the incidence of malignancies was 7.8% in the placebo group compared with 6.4% in the Zenapax group. Addition of Zenapax did not increase the

number of post-transplant lymphomas, which occurred with a frequency of 1.5% in the placebo-treated group and 0.7% in the Zenapax-treated group.

Hyperglycaemia: No differences in abnormal haematologic or chemical laboratory test results were seen between placebo-treated and Zenapax-treated groups with the exception of fasting blood glucose. Fasting blood glucose was measured in a small number of placebo- and Zenapax-treated patients. A total of 16% (10 of 64 patients) of placebo-treated and 32% (28 of 88 patients) of Zenapax-treated patients had high fasting blood glucose values. Most of these high values occurred either on the first day post-transplant when patients received high doses of corticosteroids or in patients with diabetes.

Deaths occurring during the first 6 months post-transplant were reported in 3.4% of the placebo- and in 0.6% of the Zenapax-treated groups. The twelve months mortality was 4.4% in the placebo- and 1.5% in the Zenapax-treated groups.

Infectious episodes, including viral infections, fungal infections, bacteraemia and septicaemia, and pneumonia, were reported in 72% of the placebo-treated patients and in 68% of Zenapax-treated patients. The type of infections reported was similar in both the Zenapax- and the placebo-treated groups. Cytomegalovirus infection was reported in 16% of the patients in the placebo group and in 13% of the patients in the Zenapax group.

In rare cases severe hypersensitivity reactions following administration of Zenapax have been reported (see section 4.4).

Paediatric patients: The safety profile for the use of Zenapax in paediatric patients was shown to be comparable to that in adult patients. However, the following adverse events occurred more frequently in paediatric patients: diarrhoea (41%), postoperative pain (38%), fever (33%), vomiting (33%), hypertension (28%), pruritus (21%) and infections of the upper respiratory tract (20%) and urinary tract (18%).

4.9 Overdose

A maximum tolerated dose has not been determined in patients and could not be achieved in animals that received Zenapax. A dose of 1.5 mg/kg has been administered to bone marrow transplant recipients without any associated adverse events. In a single dose toxicity study a dose of 125 mg/kg was administered intravenously to mice and showed no evidence of toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressive agents
ATC code: L04A A08

Clinical Pharmacology
Zenapax contains daclizumab, a recombinant, humanized IgG1 anti-Tac antibody, and functions as an interleukin 2 (IL-2) receptor antagonist. Daclizumab binds with high specificity to the alpha or Tac subunit of the high affinity IL-2 receptor complex (expressed on activated T cells), and inhibits IL-2 binding and biological activity. Administration of Zenapax inhibits IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection. Daclizumab saturates the Tac receptor for approximately 90 days at the recommended dosage regimen for the majority of patients. Antibodies to daclizumab developed in approximately 9% of Zenapax-treated patients in clinical studies but did not appear to affect efficacy, safety, serum daclizumab levels, or any other clinically relevant parameter examined.

No gross changes to circulating lymphocyte numbers or cell phenotypes were observed by fluorescence-activated cell sorter (FACS) analysis other than the expected transient decrease in Tac+ cells.

Combination Therapy in Renal Allograft Recipients

In Phase III trials Zenapax was added to a standard immunosuppressive regimen of cyclosporine (5 mg/kg) and steroids (prednisone or methylprednisolone), with or without addition of azathioprine (4 mg/kg).

Both trials showed a statistically significant superiority to placebo in reducing the rate of acute renal allograft rejection at six months post-transplant as confirmed by biopsy. From pooled data the difference in biopsy-proven acute rejection remained statistically different at one-year posttransplant (43% as compared with 28%). Three year graft survival rates were significantly higher among those patients who did not experience acute rejection within the first year posttransplant (n=345) compared with those who experienced acute rejection during the first year (n=190) regardless of treatment. The three year graft survival was not significantly different between placebo and daclizumab in the triple immunosuppressant trial (83% Vs. 84%) or the double immunosuppressant trial (78% Vs. 82%). The three year patient survival rate was significantly different between placebo and daclizumab in the double immunosuppressant trial (88% Vs. 96%; p = 0.017), but not in the triple immunosuppressant trial (94% Vs. 92%).

Renal function evaluated by serum creatinine and GFR was similar in both groups at three years posttransplant.

The beneficial effect of Zenapax prophylaxis upon the incidence of acute rejection after renal transplantation was not associated with adverse clinical sequelae, including the development of Post-Transplant Lymphoproliferative Disease (PTLD), at 3 years posttransplant.

5.2 Pharmacokinetic properties

In clinical trials involving renal allograft patients-treated with 1 mg/kg of Zenapax every 14 days for a total of 5 doses, average peak serum concentrations (mean ± standard deviation) rose between the first dose (21 ± 14 µg/ml) and fifth doses (32 ± 22 µg/ml). The mean ± standard deviation trough serum concentration prior to fifth dose was 7.6 ± 4.0 µg/ml. Serum levels of 0.5 to 0.9 µg/ml are needed to saturate the IL-2 receptor and levels of 5-10 µg/ml are needed to inhibit IL-2 mediated biologic activity. The recommended regimen of daclizumab will maintain serum concentrations sufficient to saturate IL-2R alpha receptors on activated T lymphocytes for more than 90 days post transplantation in the majority of patients. This first three months, is the most critical period post-transplantation.

The estimate terminal elimination half-life of daclizumab ranged from 270 to 919 hours (average 480 hours) in renal allograft patients and is equivalent to that reported for human IgG which ranged from 432 to 552 hours (average 480 hours). This is attributable to the humanisation of the protein.

Population pharmacokinetic analysis showed that the systemic clearance of daclizumab was influenced by total body weight, age, gender, proteinuria, and race.

The identified body weight influence on systemic clearance supports the dosing of Zenapax on a mg/kg basis and maintains drug exposure within 30% of the reference exposure for patient groups with wide range of demographic characteristics. No dosage adjustments based on other identified covariates (gender, proteinuria, race and age) are required for renal allograft patients.

Paediatric Patients: Pharmacokinetic and pharmacodynamic properties were evaluated in 61 paediatric patients treated with 1 mg/kg IV dose of Zenapax every 14 days for a total of 5 doses. Peak serum concentrations (peak ± SD) rose between the first dose (16 ± 12 µg/ml) and the fifth dose (21 ± 14 µg/ml). The mean trough serum concentration before the fifth dose was 5.0 ± 2.7 µg/ml. The Tac

subunit of the IL-2 receptor was saturated immediately after the first dose of 1.0 mg/kg of daclizumab and remained saturated for at least the first three months post-transplant. Saturation of the Tac subunit of the IL-2 receptor was similar to that observed in adult patients receiving the same dose regimen.

There is no pharmacokinetic interaction between Zenapax and mycophenolic acid, the active metabolite of mycophenolate mofetil (CellCept).

5.3 Preclinical safety data

Daclizumab was well tolerated after single bolus intravenous or subcutaneous doses ranging from 50 to 125 mg/kg in mice, rats, and rabbits and after 28 days administration of 15 mg/kg to monkeys. One of 18 monkeys had an anaphylactic reaction to daclizumab. Appreciable daclizumab serum levels were maintained except in 2 out of 18 monkeys that developed anti-daclizumab antibodies. There was no cross reactivity in-vitro between daclizumab and human cryosections (28 organs) at concentrations up to 56 mg/ml, demonstrating the absence of non-specific binding. Daclizumab was not genotoxic in standard tests.

A non-clinical reproduction toxicity study with daclizumab has shown an increased risk of early prenatal loss in cynomolgus monkeys compared to placebo. However, the data show considerable inter-animal variation and were within the historical control range for this species. The overall prenatal losses for the entire gestational period ranged from 20% to 45%. The incidence of stillbirth, caesarean section and breech delivery were comparable between the control and treatment groups.

In the same non-clinical reproduction toxicity study with daclizumab, four out of seven lactating cynomolgus monkeys given a 5 – 10 fold multiple (10 mg/kg) of the normal human dose were found to secrete very low levels of daclizumab (0.17 – 0.28% of maternal serum levels) in breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80
Sodium chloride
Sodium dihydrogen phosphate anhydrous
Disodium phosphate anhydrous
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

No incompatibility between Zenapax and polyvinyl chloride bags or infusion sets has been observed.

6.3 Shelf life

3 years

After dilution an immediate use is recommended. Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C - 8 °C or for 4 hours at 25 °C. From a microbiological point of view, however, the diluted product should be used immediately. The product is not intended to be stored after dilution unless the dilution has taken place under controlled and validated aseptic conditions. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

- Store in a refrigerator (2 °C – 8 °C).
- Do not freeze.
- Store in the original package in order to protect from light.

6.5 Nature and contents of container

5 ml in a vial (Type I glass). Pack sizes of 1 or 3.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Instructions for use and handling

Zenapax is NOT for direct injection. It should be diluted in 50 ml of sterile 0.9% sodium chloride solution before intravenous administration to the patients. For mixing the solution, do not shake, gently invert the bag in order to avoid foaming. Care must be taken to assure sterility of prepared solution, since the drug product does not contain any antimicrobial preservative or bacteriostatic agents. Zenapax is a colourless solution provided as a single use vial. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration. Once the infusion is prepared it should be administered intravenously immediately. If diluted aseptically it may be stored for 24 hours when refrigerated between 2 °C - 8 °C or for 4 hours at 25 °C.

Other drug/substances should not be added or infused simultaneously through the same intravenous line.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/098/001 (single vial pack)
EU/1/99/098/002 (3 vial pack)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 February 1999
Date of renewal: 14 April 2004

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley
New Jersey
USA

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Str. 1
D-79639 Grenzach-Wyhlen
GERMANY

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zenapax 5 mg/ml concentrate for solution for infusion
Daclizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Daclizumab*……5 mg per 1 ml infusion

One vial of 5 ml contains 25 mg of daclizumab* (5 mg/ml).

* Recombinant humanized IgG1 anti-Tac antibody produced in a murine NSO myeloma cell line using a glutamine synthetase (GS) expression system (NS_GSO) by recombinant DNA technology.

3. LIST OF EXCIPIENTS

Polysorbate 80, sodium chloride, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous, hydrochloric acid concentrated, sodium hydroxide, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of 5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use, for infusion after dilution
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 °C – 8 °C)
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/098/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zenapax 5 mg/ml concentrate for solution for infusion
Daclizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Daclizumab*……5 mg per 1 ml infusion

One vial of 5 ml contains 25 mg of daclizumab* (5 mg/ml).

* Recombinant humanized IgG1 anti-Tac antibody produced in a murine NSO myeloma cell line using a glutamine synthetase (GS) expression system (NS_GSO) by recombinant DNA technology.

3. LIST OF EXCIPIENTS

Polysorbate 80, sodium chloride, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous, hydrochloric acid concentrated, sodium hydroxide, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

3 vials of 5 ml each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use, for infusion after dilution
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 °C – 8 °C)
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/098/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zenapax 5 mg/ml concentrate for solution for infusion
Daclizumab

2. METHOD OF ADMINISTRATION

For intravenous use after dilution
Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Zenapax 5 mg/ml concentrate for solution for infusion
Daclizumab

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Zenapax is and what it is used for
2. Before you use Zenapax
3. How to use Zenapax
4. Possible side effects
5. How to store Zenapax
6. Further information

1. WHAT ZENAPAX IS AND WHAT IT IS USED FOR

Daclizumab belongs to a group of medicines called immunosuppressants. These medicines help to suppress your body's natural response to reject your transplanted organ.

Daclizumab is a humanised monoclonal antibody produced in a murine NSO myeloma cell line using a glutamine synthetase (GS) expression system (NS_GSO) by recombinant DNA technology. Monoclonal antibodies are proteins which recognise and bind to other unique proteins in the body called antigens. Daclizumab binds to an antigen found on the surface of specific white blood cells called T lymphocytes. This activity suppresses the body's natural immune response which otherwise might cause transplant rejection.

Zenapax is used to prevent your body from rejecting transplanted kidneys. Zenapax is used together with other immunosuppressive drugs, including cyclosporine and corticosteroids.

2. BEFORE YOU USE ZENAPAX

Do not use Zenapax
- if you are allergic (hypersensitive) to daclizumab or to any of the other ingredients of Zenapax.
- if you are breast-feeding.

Please read the section below on breast-feeding.

Take special care with Zenapax
- if you have ever had an allergic reaction to other immunosuppressive medicines, which help to suppress the body's natural defence mechanisms.

Therapy with medicines which help to suppress the body's natural defence mechanisms can increase the risk for developing malignancies or infections. Zenapax does not increase this risk when it is used together with other immunosuppressive drugs, including cyclosporine and corticosteroids.

Serious allergic reactions may occur following the administration of proteins. Allergic reactions following the infusion of Zenapax have been reported rarely. In the event that you do develop an allergic reaction, your doctor will treat you with appropriate medication.

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is extremely important because using more than one medicine at the same time may strengthen or weaken the effect of the medicines you are taking. Therefore, Zenapax should not be used with other drugs without your doctor's consent.

Pregnancy and breast-feeding
You must not use this medicine if you are breast-feeding.

You should not use this medicine if you are pregnant unless your doctor decides that it is necessary for you.

Zenapax may cause damage to your unborn or breast-feeding baby. Tell your doctor straightaway if you are pregnant, breast-feeding, become pregnant or plan to start a family in the near future.

Your doctor should advise you about using contraception before treatment with Zenapax is started, during treatment with Zenapax, and for an additional 4 months following the last dose of Zenapax.

Driving and using machines
There is no evidence to indicate that Zenapax has an effect on your ability to drive a car or operate machinery.

3. HOW TO USE ZENAPAX

Zenapax is NOT for direct injection. It should be diluted in 50 ml of sterile 0.9% sodium chloride solution before administration to patients.

A health care professional will give you a suitable dose (normally 1 mg/kg of body weight) in the form of an intravenous infusion over a 15- minute period. The first dose is given within 24 hours before your transplant. You will receive 4 subsequent doses which are spaced 14 days apart from each other. In total you should receive 5 doses of Zenapax for a complete treatment course. A course of treatment usually lasts for 8 weeks.

You may receive subsequent infusions within a day before or after the scheduled administration.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zenapax can cause side effects, although not everybody gets them.

Tell your doctor immediately if you notice any of the following side effects occur: cough and shortness of breath, including when laying flat, vomiting, confusion or passing less urine then normal. These side effects may occur when using Zenapax. These side effects can be serious and you may need urgent medical attention.

Very common side effects (occurring in 1 or more patients out of 10) are:
- difficulty sleeping
- shaking (tremor)
- headache
- high blood pressure (hypertension)

- difficulty breathing
- constipation; diarrhoea; vomiting; nausea; or heartburn
- pain in joints and muscles
- excess fluid in the body (oedema); swelling of the arms and legs (peripheral oedema)
- problems with wound healing

Common side effects (occurring in between 1 and 10 patients out of 100) are inflammation of the throat (pharyngitis); runny nose (rhinitis); diabetes mellitus; high blood sugar (hyperglycaemia); fluid overload; dehydration; anxiety; depression; dizziness; sensation of pins and needles; blurred vision; fast heart rate (tachycardia); bleeding (haemorrhage); blood clot (thrombosis); low blood pressure (hypotension); accumulation of lymph fluid in one part of the body (lymphocele); severe shortness of breath, including when laying flat at night (pulmonary oedema); fluid on the lungs (pleural effusion); collapsed lung (atelectasis); lack of oxygen in the body (hypoxia); congestion; cough; noisy or abnormal breath sounds, including crackling breath sounds (rales); bloated stomach; stomach pain or discomfort; flatulence; haemorrhoids; rash; itchy skin; acne; night sweats; increased sweating; excessive hair growth (hirsutism); back pain; muscle cramps, particularly in the legs; pain in the joints (arthralgia); pain in the muscles (myalgia); chest pain; pain in general; tiredness; skin irritation at the site of injection; fever; chills; general weakness; pain in the loins and changes or difficulty in passing urine (hydronephrosis); blood in the urine; pain on passing urine (dysuria); reduced urine output (oliguria); pain following surgery.

Rarely, allergic reactions (hypersensitivity) to Zenapax may occur.

Some side effects are more likely to occur in children than in adults, these include diarrhoea, pain following surgery, fever, vomiting, high blood pressure, itchy skin, infections of the nose and throat and infections in the urine.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ZENAPAX

Keep out of the reach and sight of children.

Store in a refrigerator (2 °C – 8 °C).

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

Do not freeze.

Do not use Zenapax after the expiry date which is stated on the outer carton and on the vial label after the abbreviation EXP. The expiry date refers to the last day of that month..

6. FURTHER INFORMATION

What Zenapax contains

- The active substance is daclizumab.
- The other ingredients are polysorbate 80, sodium chloride, sodium dihydrogen phosphate, anhydrous, disodium phosphate anhydrous, hydrochloric acid concentrated, sodium hydroxide, water for injections.

What Zenapax looks like and contents of the pack

Zenapax 5 mg/ml concentrate for solution for infusion is a clear, colourless to slightly yellowish liquid is supplied in vials containing 5 ml of solution. One vial with 5 ml concentrate for solution for infusion contains 25 mg daclizumab.

Zenapax is available in pack sizes of 1 or 3 vials.
Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.eu.int/