



The European Agency for the Evaluation of Medicinal Products

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

CellCept 500 mg powder for concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains the equivalent of 500 mg mycophenolate mofetil (as hydrochloride salt).

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

CellCept 500 mg powder for concentrate for solution for infusion must be reconstituted and further diluted with glucose intravenous infusion 5% prior to administration to the patient. (See section 6.6 Instructions for use and handling).

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

CellCept 500 mg powder for concentrate for solution for infusion is indicated in combination with cyclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal transplants.

### 4.2 Posology and method of administration

Treatment with CellCept should be initiated and maintained by appropriately qualified transplant specialists.

**CAUTION: CELLCEPT I.V. SOLUTION SHOULD NEVER BE ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION.**

CellCept 500 mg powder for concentrate for solution for infusion is an alternative dosage form to CellCept oral forms (capsules and tablets) that may be administered for up to 14 days. The initial dose of CellCept 500 mg powder for concentrate for solution for infusion should be given within 24 hours following transplantation.

Following reconstitution to a concentration of 6 mg/ml, CellCept 500 mg powder for concentrate for solution for infusion must be administered by slow intravenous infusion over a period of 2 hours by either a peripheral or a central vein. (See section 6.6 Instructions for use and handling). Oral administration should be initiated as soon as patients tolerate oral medication.

The recommended dose in renal transplant patients is 1.0 g administered twice daily (2 g daily dose). Although daily doses of both 2 g and 3 g were studied in clinical trials using CellCept oral, an efficacy advantage for the 3 g dose could not be established for renal transplant patients. In renal transplant, patients receiving 2 g per day of CellCept oral had an overall better safety profile than patients receiving 3 g per day.

Use in children: safety and effectiveness in paediatric patients have not been established. Very limited pharmacokinetic data are available for paediatric renal transplant patients.

Use in elderly: the recommended dose of 1.0 g administered twice a day is appropriate for elderly patients. This recommendation is based on limited numbers of elderly patients treated with CellCept in the pivotal renal (7% n=73) transplant trials. Patients in this age group may generally be at increased risk of adverse events compared to younger individuals; this is similarly true for patients receiving CellCept as part of a combination immunosuppressive regimen. (See 4.8 Undesirable Effects).

Use in renal impairment: in patients with severe chronic renal impairment (glomerular filtration rate  $<25\text{ml}/\text{min}/1.73\text{m}^2$ ), outside of the immediate post-transplant period, doses greater than 1g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed graft function post-operatively (see Section 5.2 Pharmacokinetic properties).

Use in severe hepatic impairment: no dose adjustments are needed for patients with severe hepatic parenchymal disease.

Other Considerations for Use: if neutropenia develops (absolute neutrophil count  $<1.3 \times 10^3/\mu\text{l}$ ), physicians should perform appropriate diagnostic tests, manage the patients appropriately, and consider interrupting dosing with CellCept.

MPA (mycophenolic acid) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics requiring dosage reduction or interruption of CellCept.

### **4.3 Contra-indications**

Allergic reactions to CellCept have been observed. Therefore, CellCept is contra-indicated in patients with a hypersensitivity to mycophenolate mofetil or mycophenolic acid. CellCept 500 mg powder for concentrate for solution for infusion is contra-indicated in patients who are allergic to polysorbate 80. For information on use in pregnancy and contraceptive requirements, see section 4.6 Use during pregnancy and lactation.

### **4.4 Special warnings and special precautions for use**

As in patients receiving immunosuppressive regimes involving combinations of drugs, patients receiving CellCept as part of an immunosuppressive regime are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8 Undesirable effects). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections and sepsis. In three controlled trials for prevention of renal transplant rejection, patients receiving 2 g per day of CellCept demonstrated an overall better safety profile than did patients receiving 3 g of CellCept.

Patients receiving CellCept should be monitored for neutropenia. The development of neutropenia may be related to CellCept itself, concomitant medications, viral infections, or some combination of these causes. Patients on CellCept should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year (see section 4.2 Posology and method of administration).

**Patients receiving CellCept should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.**

Because CellCept has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation. CellCept should be administered with caution in patients with active serious digestive system disease.

Administration of doses greater than 1 g BID to patients with severe chronic renal impairment should be avoided and they should be carefully observed. No dose adjustment is recommended for patients with delayed renal graft function post-transplant, however, they should be carefully observed (see section 4.2 Posology and method of administration, and section 5.2 Pharmacokinetic properties).

It is recommended that CellCept not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of CellCept with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of CellCept. Some degree of enterohepatic recirculation is anticipated following intravenous administration of CellCept.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

**acyclovir:** higher MPAG and acyclovir plasma concentrations were observed when mycophenolate mofetil was administered with acyclovir in comparison to the administration of each drug alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for the two drugs to compete for tubular secretion and thus further increases in concentrations of both drugs may occur.

**cholestyramine:** following single dose, oral administration of 1.5g of mycophenolate mofetil to normal healthy subjects pretreated with 4g TID of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA.

**cyclosporin A:** cyclosporin A pharmacokinetics were unaffected by mycophenolate mofetil.

**ganciclovir:** Based on the results of a single dose administration study of recommended doses of oral mycophenolate and iv ganciclovir and the known effects of renal impairment on the pharmacokinetics of MMF (see Section 4.4 Special warnings and precaution for use) and ganciclovir, it is anticipated that coadministration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics are anticipated and MMF dose adjustment is not required. In patients with renal impairment in which MMF and ganciclovir are coadministered the dose recommendations for ganciclovir should be observed and patients monitored carefully.

**oral contraceptives:** no pharmacokinetic interaction was observed between mycophenolate mofetil and 1mg norethisterone/35 µg ethinyloestradiol. This single dose study demonstrates the lack of a gross pharmacokinetic interaction, but cannot exclude the possibility of changes in the pharmacokinetics of the oral contraceptive under long term dosing conditions with CellCept which might adversely affect the efficacy of the oral contraceptive.

**trimethoprim/sulphamethoxazole:** no effect on the bioavailability of MPA was observed.

***other interactions:*** co-administration of probenecid with mycophenolate mofetil in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion. Single dose studies of CellCept with ganciclovir and trimethoprim/sulphamethoxazole did not reveal a pharmacokinetic interaction between either of these agents and CellCept. All these types of compounds operate through inhibition of nucleoside synthesis and therefore one cannot exclude a clinical interaction between them.

#### **4.6 Use during pregnancy and lactation**

Adverse effects on foetal development (including malformations) occurred when pregnant rats and rabbits were dosed during organogenesis (see section 5.3 Preclinical safety data). Because there are no adequate and well controlled studies in pregnant women, CellCept should be used in pregnant women only if the potential benefit outweighs the potential risk to the foetus.

It is recommended that CellCept therapy should not be initiated until a negative pregnancy test has been obtained. Patients should be instructed to consult their physician immediately should pregnancy occur.

Effective contraception must be used before beginning CellCept therapy, during therapy, and for six weeks following discontinuation of therapy. Although the results of a single dose drug interaction study with an oral contraceptive suggest the lack of a gross pharmacokinetic interaction, the results cannot exclude the possibility of changes in the pharmacokinetics of the oral contraceptive under long term dosing conditions with CellCept which might adversely affect the efficacy of the oral contraceptive (see section 4.5 Interaction with other medicaments).

Studies in rats have shown mycophenolate mofetil to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from mycophenolate mofetil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

#### **4.7 Effects on ability to drive and use machines**

No specific studies have been performed. The pharmacodynamic profile and the reported adverse reactions indicate that an effect is unlikely.

#### **4.8 Undesirable effects**

The principal adverse reactions associated with the administration of CellCept in combination with cyclosporine and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting and there is evidence of a higher frequency of certain types of infections (see section 4.4 Special warnings and special precautions for use). The adverse event profile associated with the administration of CellCept 500 mg powder for concentrate for solution for infusion has been shown to be similar to that observed after oral administration.

As in patients receiving immunosuppressive regimes involving combinations of drugs, patients receiving CellCept as part of an immunosuppressive regime are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.4 Special warnings and special precautions for use). Within 3 years post-transplant, lymphoproliferative disease or lymphoma developed in patients receiving CellCept in immunosuppressive regimens in 1.6% of the patients receiving 3 g daily and 0.6% in patients receiving 2 g daily in the controlled studies of prevention of renal rejection compared to the placebo (0%) and azathioprine groups (0.6%). All patients are at increased risk of opportunistic infections, the risk increased with dose (see section 4.4 Special warnings and special precautions for use).

Elderly patients, particularly those who are receiving CellCept as part of a combination immunosuppressive regimen, may be at greater increased risk of certain infections (including CMV tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals (see section 4.2 Posology and method of administration).

The following data refer to the safety experience of oral CellCept. Adverse reactions reported in =10% of patients treated with CellCept in the three Phase III controlled trials for prevention of rejection are listed in the following table (Table 1).

**Table 1: Adverse Events Reported in = 10% of Renal Transplant Patients Treated with CellCept in Combination with Cyclosporine and Corticosteroids**

<b>Body System</b>	<b>Adverse Events</b>
<b>Body as a Whole</b>	asthenia, fever, headache, infection, pain, (includes abdominal, back, and chest ), oedema
<b>Blood and Lymphatic</b>	anaemia (including hypochromic anaemia) , leukocytosis, leukopenia, thrombocytopenia
<b>Urogenital</b>	urinary tract infection, haematuria, renal tubular necrosis
<b>Cardiovascular</b>	Hypertension
<b>Metabolic/ Nutritional</b>	hypercholesterolaemia, hyperglycaemia, hyperkalaemia, hypokalaemia, hypophosphataemia
<b>Gastrointestinal</b>	constipation, diarrhoea, dyspepsia, oral moniliasis, nausea, vomiting
<b>Respiratory</b>	cough increased, dyspnoea, pharyngitis, pneumonia, bronchitis
<b>Skin and Appendages</b>	acne, herpes simplex
<b>Nervous</b>	dizziness, insomnia, tremor

Adverse events, not mentioned above, reported in =3% and <10% in renal transplant patients are listed in the following table (Table 2).

**Table 2: Adverse Events Reported in = 3% and < 10% of Renal Transplant Patients Treated With CellCept in Combination With Cyclosporine and Corticosteroids**

<b>Body System</b>	<b>Adverse Events</b>
<b>Body as a Whole</b>	enlarged abdomen, cysts (including lymphocele and hydrocele), fever, flu syndrome, facial oedema, haemorrhage, malaise, pelvic pain, hernia
<b>Blood and Lymphatic</b>	ecchymosis, polycythaemia
<b>Urogenital</b>	dysuria, impotence, urinary frequency, albuminuria, hydronephrosis, pyelonephritis
<b>Cardiovascular</b>	angina pectoris, atrial fibrillation, postural hypotension, hypotension, tachycardia, thrombosis, vasodilatation
<b>Metabolic/Nutritional</b>	alkaline phosphatase increased, dehydration, hypervolaemia, hypocalcaemia, hypoglycaemia, hypoproteinaemia, acidosis, elevated enzyme levels (gamma glutamyl transpeptidase, lactic dehydrogenase, SGOT and SGPT), elevated creatinine, hypercalcaemia, hyperlipaemia, hyperuricaemia, weight gain
<b>Gastrointestinal</b>	anorexia, gastritis, gastroenteritis, gingivitis, gum hyperplasia, liver function tests abnormal, oesophagitis, flatulence, gastrointestinal haemorrhage, gastrointestinal moniliasis, hepatitis, ileus, stomatitis
<b>Respiratory</b>	lung oedema, asthma, pleural effusion, rhinitis, sinusitis
<b>Skin and Appendages</b>	benign neoplasm of skin, skin carcinoma, fungal dermatitis, skin hypertrophy, pruritus, sweating, skin ulcer, alopecia, herpes zoster, hirsutism, rash
<b>Nervous</b>	anxiety, depression, hypertonia, paresthesia, somnolence
<b>Musculoskeletal</b>	Arthralgia, leg cramps, myalgia, myasthenia
<b>Special Senses</b>	Conjunctivitis, amblyopia, cataract
<b>Endocrine</b>	diabetes mellitus, paathyroid disorder

Adverse events attributable to peripheral venous infusion were phlebitis and thrombosis, both observed at 4% in patients treated with CellCept 500 mg powder for concentrate for solution for infusion.

Adverse reactions during Post Marketing Experience with CellCept are similar to those seen in the controlled renal transplant studies.



## **Post-marketing experience:**

**Gastro-intestinal:** colitis (sometimes caused by cytomegalovirus), pancreatitis.

**Disorders of immunosuppression:** Serious Life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of infections such as tuberculosis and atypical mycobacterial infection.

## **4.9 Overdose**

There has been no reported experience of overdosage of mycophenolate mofetil in humans.

At clinically encountered concentrations, MPA and MPAG are not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/ml), small amounts of MPAG are removed. By interfering with enterohepatic circulation of the drug, bile acid sequestrants, such as cholestyramine, reduce the MPA AUC.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: immunosuppressant, ATC code L04AA06

Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines whereas other cell types can utilize salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

### **5.2 Pharmacokinetic properties**

MPA at clinically relevant concentrations, is 97% bound to plasma albumin.

Following intravenous administration, mycophenolate mofetil undergoes rapid and complete metabolism to the active metabolite, MPA. The parent drug mycophenolate mofetil can be measured systemically during intravenous infusion; however, after oral administration it is below the limit of quantitation (0.4 µg/ml).

MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active.

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6-12 hours post-dose. A reduction in the AUC of MPA of approximately 40% is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.

Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabeled mycophenolate mofetil resulted in complete recovery of the administered dose; with 93% of the administered dose recovered in the urine and 6%

recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG.

Immediately post-transplant (<40 days), mean MPA AUC and C<sub>max</sub> are approximately 50% lower in renal transplant patients than that observed in healthy volunteers or in stable renal transplant patients. MPA AUC values obtained following administration of 1 g BID of CellCept 500 mg powder for concentrate for solution for infusion at the recommended infusion rate to patients in the immediate post-transplant phase are comparable to those observed following oral dosing.

In a single dose study (6 subjects per group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate <25ml/min/1.73m<sup>2</sup>) were 28-75% higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single dose MPAG AUC was 3-6 fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects, consistent with the known renal elimination of MPAG. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied.

In patients with delayed graft function post-transplant, mean MPA AUC<sub>0-12</sub> was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC<sub>0-12</sub> was 2-3 fold higher than in post-transplant patients without delayed graft function.

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on this process probably depend on the particular disease. However, hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Pharmacokinetic behaviour of CellCept in the elderly has not been formally evaluated.

### **5.3 Preclinical safety data**

In experimental models, mycophenolate mofetil was not tumorigenic and did not demonstrate mutagenic activity. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 to 3 times the systemic exposure (AUC or C<sub>max</sub>) observed in renal transplant patients at the recommended clinical dose of 2 g per day.

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 to 3 times the clinical exposure at the recommended clinical dose of 2 g per day. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g per day. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at

6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels are approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g per day.

Refer to section 4.6 Use during pregnancy and lactation.

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g per day. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended dose. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The nonclinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials which now provide safety data of more relevance to the patient population (see 4.8 Undesirable Effects).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Polysorbate 80, citric acid, hydrochloric acid and sodium chloride.

### **6.2 Incompatibilities**

CellCept 500 mg powder for concentrate for solution for infusion infusion solution should not be mixed or administered concurrently via the same catheter with other intravenous drugs or infusion admixtures.

### **6.3 Shelf-life**

Powder for concentrate for solution for infusion: CellCept 500 mg powder for concentrate for solution for infusion has a shelf-life of three years when stored below 30° C.

Reconstituted solution and infusion solution: If the infusion solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 3 hours from reconstitution and dilution of the drug product.

### **6.4 Special precautions for storage**

Powder for concentrate for solution for infusion: Store below 30° C.

Reconstituted solution and infusion solution: Store at 15-30° C.

### **6.5 Nature and content of container**

20 ml type I clear glass vials with grey butyl rubber stopper and aluminium seals with plastic flip-off caps. CellCept 500 mg powder for concentrate for solution for infusion is available in packs containing 4 vials.

### **6.6 Instructions for use and handling, and disposal (if appropriate)**

### **Preparation of Infusion Solution (6 mg/ml)**

CellCept 500 mg powder for concentrate for solution for infusion does not contain an antibacterial preservative; therefore, reconstitution and dilution of the product must be performed under aseptic conditions.

CellCept 500 mg powder for concentrate for solution for infusion must be prepared in two steps: the first step is a reconstitution step with glucose intravenous infusion 5% and the second step is a dilution step with glucose intravenous infusion 5%. A detailed description of the preparation is given below:

#### Step 1

- a. Two vials of CellCept 500 mg powder for concentrate for solution for infusion are used for preparing each 1 g dose, Reconstitute the content of each vial by injecting 14 ml of glucose intravenous infusion 5%.
- b. Gently shake the vial to dissolve the drug yielding a slightly yellow solution.
- c. Inspect the resulting solution for particulate matter and discoloration prior to further dilution. Discard the vial if particulate matter or discoloration is observed.

#### Step 2

- a. Further dilute the content of the two reconstituted vials (approx. 2 x 15 ml) into 140 ml of glucose intravenous infusion 5%. The final concentration of the solution is 6 mg mycophenolate mofetil per ml.
- b. Inspect the infusion solution for particulate matter or discoloration. Discard the infusion solution if particulate matter or discoloration is observed.

If the infusion solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 3 hours from reconstitution and dilution of the drug product. Keep solutions at 15-30° C.

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, avoid direct contact of prepared solutions of CellCept 500 mg powder for concentrate for solution for infusion with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

## **7. MARKETING AUTHORISATION HOLDER**

Roche Registration Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire, AL7 3AY, United Kingdom.

## **8. NUMBERS IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**

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

## **10. DATE OF REVISION OF THE TEXT**

**ANNEX II**  
**THE MANUFACTURING AUTHORISATION HOLDER**  
**RESPONSIBLE FOR IMPORT AND BATCH RELEASE AND CONDITIONS OR**  
**RESTRICTIONS REGARDING SUPPLY AND USE**

## **A. MANUFACTURING AUTHORISATION HOLDER**

### Manufacturer responsible for import and batch release in the European Economic Area

#### **Capsules and Tablets**

- Hoffman-La Roche AG, Emil-Barell-Str. 1, D-79639 Grenzach-Wyhlen, Germany  
Manufacturing Authorisation issued on 26 April 1990 by Regierungspräsidium Freiburg, Germany.
- Roche Products Ltd., 40 Broadwater Road, Welwyn Garden City, UK.  
Manufacturing Authorisation issued on 10 April 1995 by Department of Health, Medicines Control Agency, UK.

#### **Powder for Concentrate for Solution for Infusion**

- Hoffman-La Roche AG, Emil-Barell-Str. 1, D-79639 Grenzach-Whyhlen, Germany  
Manufacturing Authorisation issued on 16 August 1996 by Regierungspräsidium Freiburg, Germany.

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (See Annex 1: Summary of Product Characteristics; 4.2).

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**



Outer carton text

CellCept 500 mg

Powder for concentrate for solution for infusion  
Mycophenolate mofetil

4 vials

Each vial contains the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt. Also contains polysorbate 80, citric acid, hydrochloric acid and sodium chloride.

**Reconstitute and dilute before use**

**For intravenous infusion only**

Keep out of sight and reach of children  
Avoid skin contact with infusion solution

Medicinal product subject to medical prescription  
Refer to package leaflet, also for method of preparation and directions for use

Store below 30 °C

Marketing Authorisation Holder: Roche Registration Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire AL7 3AY, United Kingdom

Marketing Authorisation Number:

Batch number

Expiry date

Vial label

CellCept 500 mg

Powder for concentrate for solution for infusion  
Mycophenolate mofetil

Each vial contains the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt.

**For intravenous infusion only**

Roche Registration Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire AL7  
3AY, United Kingdom

(-Batch number-)

(-Expiry date-)

**B. PACKAGE LEAFLET**

## Package Leaflet

### CellCept 500 mg powder for concentrate for solution for infusion mycophenolate mofetil

#### Name of the medicinal product

CellCept 500 mg powder for concentrate for solution for infusion  
(mycophenolate mofetil)

#### Composition

Each vial contains 500 mg of the active ingredient mycophenolate mofetil (as hydrochloride salt). It also contains polysorbate 80, citric acid, hydrochloric acid and sodium chloride.

#### Pharmaceutical form

Powder for concentrate for solution for infusion

CellCept 500 mg powder for concentrate for solution for infusion is available in cartons of 4 vials.

CellCept 500 mg powder for concentrate for solution for infusion must be reconstituted and further diluted with glucose intravenous infusion 5% prior to administration to the patient.

#### Uses

Mycophenolate mofetil belongs to a group of medicines which help to stop your body's natural defence mechanism attacking transplants.

**Pharmacotherapeutic classification:** Immunosuppressant

#### Marketing Authorisation holder and manufacturer

The Marketing Authorisation holder is Roche Registration Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire AL7 3AY, United Kingdom. The manufacturer responsible for batch release is Hoffmann-La Roche AG, Emil-Barell-Str.1, D-79639 Grenzach-Wyhlen, Germany

#### Indications

CellCept 500 mg powder for concentrate for solution for infusion is used to prevent your body rejecting transplanted kidneys. CellCept 500 mg powder for concentrate for solution for infusion is used together with other drugs known as cyclosporin and corticosteroids.

#### Contraindications

CellCept 500 mg powder for concentrate for solution for infusion must not be used if you are allergic to mycophenolate mofetil, mycophenolic acid or polysorbate 80.

#### Special warnings and precautions for use

If the answer to any of the following questions is 'yes', talk to your doctor before you start to take CellCept:

*Precautions:*

- Do you now, or have you ever had any problems with your digestive system, e.g., stomach ulcers?

CellCept reduces your body's defence mechanism. Because of this, there is an increased risk of skin cancer. Therefore you should limit your exposure to sunlight and UV light by wearing appropriate protective clothing and using a sunscreen with high protection factor.

**In case of any evidence of infection (e.g. fever, sore throat), unexpected bruising and/or bleeding you should inform your doctor immediately.**

*Interactions:*

- Are you taking any medicines containing: azathioprine or other immunosuppressive agents (which are sometimes given to patients after a transplant operation), cholestyramine, or any other drugs (including those you can buy without a prescription) that your doctor does not know about?

*Pregnancy and breast-feeding:*

- Are you pregnant, breast-feeding or planning to start a family in the near future? Your doctor should advise you about using contraception before starting treatment with CellCept, during treatment with CellCept, and for six weeks after you have stopped treatment with CellCept. This is because CellCept may cause damage to your unborn baby. Tell your doctor straight away if you become pregnant.

## **How to take your medicine**

### **Dosage**

The first dose should be given within 24 hours after the transplant operation. The recommended dose in renal transplant patients is 1.0 g administered twice daily (2g daily dose).

### **Method and route of administration**

CellCept 500 mg powder for concentrate for solution for infusion does not contain an antibacterial preservative; therefore, reconstitution and dilution of the product must be performed under aseptic conditions.

The content of CellCept 500 mg powder for concentrate for solution for infusion vials must be reconstituted with 14 ml of glucose intravenous infusion 5% each. A further dilution with glucose intravenous infusion 5% is required to a final concentration of 6 mg/ml. This means that to prepare a 1 g dose of mycophenolate mofetil the content of 2 reconstituted vials (approx. 2 x 15 ml) must be further diluted into 140 ml glucose intravenous infusion 5% solution. If the infusion solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 3 hours from reconstitution and dilution of the drug product.

Avoid skin contact with prepared solutions. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

CellCept 500 mg powder for concentrate for solution for infusion must be given as intravenous infusion. The infusion flow rate should be controlled to equate a 2 hour period of administration.

**CellCept IV solution should never be administered by rapid or bolus intravenous injection.**

As soon as you are able to tolerate oral medication your doctor will switch you to CellCept Capsules or Tablets. The duration of treatment will be decided by your doctor.

During your treatment with CellCept 500 mg powder for concentrate for solution for infusion your doctor will want to test your blood regularly.

### **Undesirable effects**

In addition to the beneficial effects of CellCept, it is possible that unwanted effects will occur in some patients, even when used as directed. Some of the more usual problems are diarrhoea, fewer white cells in your blood, infection and vomiting.

CellCept reduces your body's own defence mechanisms to stop you rejecting your transplanted kidney. Your body will therefore also not be as good as normal at fighting infections. People receiving CellCept 500 mg powder for concentrate for solution for infusion may therefore catch more infections than usual, such as infections of the skin, mouth, gut, lungs, urinary tract. As can happen in patients taking this type of medicine, a very small number of CellCept patients have developed cancer of the lymphoid tissues and skin.

Your doctor will do regular blood tests to monitor any changes in the number of your blood cells or changes in the levels of any of the substances carried in your blood, e.g. sugar, fat, cholesterol.

General unwanted effects affecting the body as a whole could include fever, lethargy, difficulty in sleeping, pains (such as abdominal, back, chest, joint/muscle, pain on passing water), headache, hernia, cyst, flu symptoms, swelling and impotence.

### **Other unwanted effects may include:**

**Disorders of the skin** such as acne, cold sores, skin ulcer, shingles, skin growth, sweating, hair loss or growth, rash, itching.

**Urinary disorders** such as kidney problems and blood in the urine or the urgent need to pass water.

**Disorders of the digestive system and mouth** such as constipation, nausea, indigestion, pancreas inflammation, intestinal disorders including bleeding, inflammation of the stomach, swollen wind pipe, liver problems, problems with the rectum, inflammation of the colon, loss of appetite, flatulence, problems with your gums and mouth ulcers.

**Disorders of the nerves and senses** such as tremor, dizziness, depression, drowsiness, numbness, muscle spasms, anxiety, cataract, inflammation of the eyelids, impairment of vision, changes in thinking or mood.

**Metabolic, blood and vascular disorders** such as dehydration, weight gain, diabetes, problems with the heart or thyroid, bleeding, clots and bruises, change in blood pressure, abnormal heart beat and dilation of blood vessels may be seen. Other unwanted effects caused by the intravenous infusion include local inflammation of the veins.

**Disorders of the lungs** such as pneumonia, bronchitis, inflammation of the throat, shortness of breath, cough, fluid on the lungs/chest cavity, sinus problems, asthma, hiccoughs.

If you do have any side effects, or other problems during your treatment with CellCept, please talk to your doctor about these

### **Expiry date**

The expiry date is printed on the carton and on the vials. Do not use past the expiry date.

**Storage Conditions**

The powder for concentrate for solution for infusion should be stored below 30° C. The reconstituted solution and the diluted solution should be stored at 15-30° C.

Keep out of sight and reach of children.

Disposal should be handled safely according to local institutional guidelines.

**Date of revision of the text**

## Other information

For further information about this product, please contact the local representative of the Marketing Authorisation holder:

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