PROFESSIONAL INFORMATION LEAFLET

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

CellCept® Capsules

CellCept® OS 200 mg/mℓ Powder for Oral Suspension

CellCept® I.V. Infusion (Parenteral)

CellCept® 500 mg Tablets

WARNING 1: CONTRAINDICATIONS

CellCept is contraindicated in pregnancy and lactation, and in women intending to become pregnant (see CONTRAINDICATIONS and HUMAN REPRODUCTION).

WARNING 2: IMMUNOSUPPRESSION: RISK OF INFECTIONS AND MALIGNANCY

Immunosuppression caused by CellCept may result in an increased susceptibility to infection and the development of lymphoma and other malignancies, especially of the skin.

Only medical practitioners experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe CellCept.

Patients receiving CellCept should be managed in facilities equipped with adequate laboratory and supportive medical resources.

The medical practitioner responsible for maintenance therapy should have complete information as required for the follow-up of the patient.

WARNING 3: TERATOGENICITY

CellCept is a potent teratogenic and mutagenic medicine.

Congenital malformations and spontaneous abortions have been reported with the use of CellCept in pregnancy.

Women of childbearing potential must have two negative medical practitioner or laboratory-supervised serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mℓ (IU/L); and the second test should be performed 8-10 days after the first one and 24 hours before CellCept therapy is initiated. Repeat pregnancy tests should be performed during routine follow-up visits.

Women of childbearing potential should use two reliable forms of contraception simultaneously, including at least one highly effective method, before CellCept therapy is initiated, during therapy, and for 90 days following discontinuation of therapy; unless abstinence is the chosen method of contraception.

Sexually active men are recommended to use condoms during treatment and for 90 days after cessation of treatment. Condom use applies both for reproductively competent and vasectomised men, because the risk associated with the transfer of seminal fluid also apply to men who have had a vasectomy.

Female partners of male patients are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of CellCept.

COMPOSITION

- Each capsule contains 250 mg mycophenolate mofetil. Excipients of CellCept capsules include pregelatinised maize starch, croscarmellose sodium, polyvidone (K-90) and magnesium stearate.

The capsule shell contains gelatine, sodium lauryl sulphate, sodium carboxymethyl cellulose, silicon dioxide, titanium dioxide (E171), indigo carmine (E132), red, yellow and black iron oxide (E172).

- Each 5 ml of the reconstituted suspension contains 1 g mycophenolate mofetil. 1 mℓ of the reconstituted suspension contains 200 mg mycophenolate mofetil. Contains 0,3 % *m/v* methyl parahydroxybenzoate as preservative.

Excipients: colloidal anhydrous silica, xanthum gum, soybean lecithin, sorbitol, aspartame, citric acid, sodium citrate, methyl parahydroxybenzoate, mixed fruit flavour (274869).

Contains sugar (sorbitol).

Contains aspartame.

- Each vial contains the equivalent of 500 mg mycophenolate mofetil (as hydrochloride salt). It also contains polysorbate, citric acid and sodium chloride.
- Each film-coated tablet contains 500 mg mycophenolate mofetil. Excipients of CellCept tablets are microcrystalline cellulose, polyvidone (K-90), croscarmellose sodium and magnesium stearate. The tablet coating consists of hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide (E171), polyethylene glycol, indigo carmine (E132) and red iron oxide (E172).

CATEGORY AND CLASS

A 34 Other (Immuno-suppressants)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA is a selective, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis. The mechanism by which MPA inhibits the enzymatic activity of IMPDH appears to be related to the ability of MPA to structurally mimic both nicotinamide adenine dinucleotide cofactor and a catalytic water molecule. This prevents the oxidation of IMP to xanthose-5'-monophosphate which is the committed step in *de novo* guanosine nucleotide biosynthesis. MPA has more potent cytostatic effects on lymphocytes than on other cells, because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines, whereas other cell types can utilise salvage pathways.

Pharmacokinetic properties

The pharmacokinetics of MMF have been studied in renal, cardiac and hepatic transplant patients.

In general, the pharmacokinetic profile of MPA is similar in renal and in cardiac transplant patients. In the early transplant period, hepatic transplant patients receiving a 1,5 g oral MMF dose or 1 g I.V. MMF dose have similar MPA levels compared to renal transplant patients receiving 1 g oral or I.V. MMF.

Absorption: Following oral and intravenous administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete pre-systemic metabolism to the active metabolite, MPA. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94 % relative to I.V. mycophenolate mofetil. Mycophenolate mofetil can be measured systemically during intravenous infusion; however, after oral administration it is below the limit of quantification (0,4 µg/mℓ).

Immediately post-transplant (< 40 days) renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30 % lower and C_{max} approximately 40 % lower compared to the late transplant period (3-6 months post-transplant). MPA AUC levels obtained following administration of 1 g twice a day intravenous CellCept at the recommended infusion rate to renal patients in the immediate post-transplant phase are comparable to those observed following oral dosing. In hepatic transplant patients, administration of 1 g twice a day intravenous CellCept followed by 1,5 g twice a day oral CellCept resulted in MPA AUC values similar to those found in renal transplant patients administered 1 g CellCept twice a day.

Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil administered at doses of 1,5 g twice a day to renal transplant patients. However, MPA C_{max} was decreased by 40 % in the presence of food.

Distribution: MPA, at clinically relevant concentrations, is 97 % bound to plasma albumin. As a result of enterohepatic recirculation, after oral administration 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 three times a day), indicating that there is a significant amount of enterohepatic recirculation.

Metabolism: Mycophenolate mofetil undergoes complete pre-systemic metabolism to MPA, the active metabolite. MPA is metabolised principally by glucuronyl transferase, to form the phenolic glucuronide of MPA (MPAG) that is not pharmacologically active. *In vivo,* MPAG is converted to free MPA via enterohepatic recirculation.

Elimination: Oral administration of radio-labelled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93 % of the administered dose recovered in the urine and 6 % recovered in faeces. Most (about 87 %) of the administered dose is excreted in the urine as mycophenolic acid glucuronide (MPAG). A negligible amount of medicine (< 1 % of dose) is excreted as MPA in the urine. MPA and MPAG are usually not removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 μg/ml), small amounts of MPAG are removed. By interfering with enterohepatic circulation of the medicine, bile acid sequestrants, such as cholestyramine, reduce MPA AUC (see SYMPTOMS OF OVERDOSAGE).

Bioequivalence

Bioequivalence of CellCept oral dosage forms have been evaluated. Two 500 mg tablets have been shown to be bioequivalent to four 250 mg capsules. Likewise 1 g/5 mℓ of CellCept constituted powder for oral suspension have been shown to be bioequivalent to four 250 mg capsules (see DOSAGE AND DIRECTIONS FOR USE).

Pharmacokinetics in special populations:

Patients with severe renal impairment: Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied.

In a single-dose study (6 subjects per group), mean plasma MPA AUC after a single oral dose in subjects with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1,73 m^2), was 28 - 75 % higher than that observed in normal healthy subjects or subjects with lesser degrees of renal impairment. In addition, the mean single-dose plasma 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.

Patients with delayed renal graft function post-transplant: In patients with delayed renal graft function post-transplant, mean MPA AUC_{0-12} was comparable to that seen in post-transplant patients without delayed renal graft function. Mean plasma MPAG AUC_{0-12} was 2 – 3 fold higher than in post-transplant patients without delayed renal graft function.

In patients with primary renal non-functioning graft following renal transplantation, plasma concentrations of MPAG accumulated; accumulation of MPA, if any, was much smaller.

Patients with hepatic impairment: In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. The effect on MPA glucuronidation processes in patients with hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, has not been established.

Children aged < 18 years: Pharmacokinetic parameters in paediatric renal transplant patients (ranging from 1 year to 18 years of age) given 600 mg/m^2 CellCept orally twice daily achieved MPA AUC values similar to those seen in adult renal transplant patients receiving CellCept at a dose of 1 g twice daily in the early and late post-transplant period. MPA AUC values across age groups were similar in the early and late post-transplant period.

Elderly: Pharmacokinetics in the elderly has not been formally evaluated.

INDICATIONS

CellCept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, hepatic or cardiac transplants.

CellCept I.V. is indicated when oral formulations cannot be used. It should preferably not be used for longer than 5 days.

CellCept should be used concomitantly with ciclosporin and corticosteroids.

CONTRAINDICATIONS

- Allergic reactions to CellCept have been observed. Therefore, CellCept is contraindicated in patients with a hypersensitivity to mycophenolate mofetil or mycophenolic acid or any of the excipients of CellCept.
- CellCept I.V. is contraindicated in patients who are allergic to polysorbates (Tween).
- Pregnancy and breastfeeding (see HUMAN REPRODUCTION).
- Women of childbearing potential not using highly effective methods of contraception.
- CellCept is an IMPDH (inosine monophosphate dehydrogenase) inhibitor; and it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmillar syndrome.
- CellCept oral suspension contains aspartame, a source of phenylalanine and should not be given to patients with phenylketonuria.

WARNINGS AND SPECIAL PRECAUTIONS

CAUTION:

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

Patients receiving CellCept as part of an immuno-suppressive regimen are at an increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immuno-suppression rather than to the use of any specific agent (see **BOXED WARNING**).

Exposure to sunlight and UV light should be limited by wearing protective clothing and using sunscreen with a high protection factor.

Disorders of immuno-suppression:

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

Oversuppression of the immune system can increase susceptibility to infection, including opportunistic infections, fatal infections and sepsis.

Such infections include latent viral reactivation, such as by polyomaviruses: Progressive Multifocal Leukoencephalopathy (PML) associated with the *Polyomavirus JC*, sometimes fatal, have been reported in CellCept-treated patients. Medical practitioners should consider PML in the differential diagnosis in patients reporting neurological symptoms while using CellCept and consultation with a neurologist should be considered as clinically indicated.

BK virus-associated nephropathy has been observed during the use of CellCept in patients post renal transplant. This infection can be associated with serious outcomes, sometimes leading to

renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil induced-PRCA is unknown. In some cases PRCA was found to be reversible with dose reduction or cessation of CellCept therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

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.

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

Patients should be advised that during treatment with CellCept, vaccinations may be less effective and the use of live attenuated vaccines should be avoided. Influenza vaccination with killed virus may be of value.

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 twice a day to renal transplant patients with severe chronic renal impairment should be avoided and these patients should be carefully observed.

No data is available for cardiac transplant patients with severe chronic renal impairment.

In patients with delayed renal graft function post-transplant, mean MPA AUC_{0-12} was comparable, but MPAG AUC_{0-12} was 2 - 3 fold higher, compared to that seen in post-transplant patients without delayed renal graft function. No dose adjustment is recommended for these patients, however, they should be carefully observed (see PHARMACOLOGICAL ACTION – Pharmacokinetic properties).

It is recommended that CellCept not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied. The risk:benefit relationship of mycophenolate mofetil in combination with tacrolimus has not been established (see INTERACTIONS).

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be exercised in the concomitant administration of oral CellCept with medicines that interfere with

enterohepatic re-circulation, because of the potential to reduce the efficacy of CellCept. Elderly patients may be at an increased risk of adverse events compared to younger individuals.

CellCept therapy should not be initiated until a negative pregnancy test has been obtained. Patients should be instructed to consult their medical practitioner immediately should pregnancy occur. Effective contraception must be used before beginning CellCept therapy, during therapy, and for 6 weeks following discontinuation of therapy. Two reliable forms of contraception must be used simultaneously, unless abstinence is the chosen method. See HUMAN REPRODUCTION.

CellCept has been administered in combination with the following medicines in clinical trials: antithymocyte globulin, antilymphocyte globulins, OKT3, ciclosporin and corticosteroids. Patients should be advised that during treatment with CellCept, vaccinations may be less effective and the use of live attenuated vaccines should be avoided.

Laboratory monitoring: 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. The development of neutropenia may be related to CellCept, concomitant medications, viral infections or some combination of these causes. If neutropenia develops (absolute neutrophil count < 1,3 x 10^9/ℓ) dosing with CellCept should be interrupted, or the dose reduced, and these patients should be carefully observed.

Gastrointestinal tract haemorrhage has been observed in approximately 3 % of patients treated with CellCept. Gastrointestinal perforations (colonic, gall bladder) have been observed.

Effects on ability to drive and use machines*:* CellCept may affect the patient's ability to drive and use machines. Patients should be advised to first take note of how they are affected by CellCept before attempting to drive or operate machines (see SIDE EFFECTS).

CellCept contains aspartame (see CONTRAINDICATIONS).

CellCept contains sugar (sorbitol) which may have a laxative effect in some patients. Patients with a rare hereditary condition of sorbitol intolerance should not take CellCept.

INTERACTIONS

Acyclovir: Higher MPAG and acyclovir plasma AUC's were observed when mycophenolate mofetil was administered with acyclovir, compared to the administration of each medicine alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for the two medicines to compete for tubular secretion, and thus further increases in concentrations of both medicines may occur.

Antacids and proton pump inhibitors (PPIs): Decreased mycophenolic acid (MPA) exposure has been observed when antacids, such as magnesium and aluminium hydroxides in combination with PPIs, including lansoprazole and pantoprazole, the exposure to CellCept was 25-30 % decreased. These data support extrapolation of this finding to all antacids.

Cholestyramine: Following single dose administration of 1,5 g of mycophenolate mofetil to normal healthy subjects, pre-treated with 4 g of cholestyramine three times daily for 4 days, there was a 40 % reduction in the AUC of MPA.

Ciclosporin A: Ciclosporin A (CsA) pharmacokinetics were unaffected by mycophenolate mofetil. However, in renal transplant patients concomitant administration of CellCept and CsA resulted in reduced MPA exposures by 30-50 % compared with patients receiving the combination of sirolimus and similar doses of CellCept.

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 and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanism of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and MMF dose adjustment is not required. In patients with renal impairment in which MMF and ganciclovir are co-administered, patients should be carefully monitored.

Oral contraceptives: The pharmacokinetics of oral contraceptives were unaffected by co-administration of CellCept. A study of co-administration of CellCept (1 g twice a day) and combined oral contraceptives containing ethinylestradiol (0,02 – 0,04 mg) and levonorgestrel (0,05 – 0,2 mg), desogestrel (0,15 mg) or gestodene (0,05 – 0,10 mg) conducted in 18 women with psoriasis over 3 menstrual cycles showed no clinically relevant influence of CellCept on serum levels of progesterone, LH and FSH, thus indicating no influence of CellCept on the ovulation-suppressing action of the oral contraceptives.

Rifampicin: After correction for dose a 70 % decrease in MPA exposure (AUC_{0-12h}) has been observed with concomitant rifampicin administration in a single heart-lung transplant patient. It is therefore recommended to monitor MPA exposure levels and to adjust CellCept doses accordingly to maintain clinical efficacy when the medicines are administered concomitantly.

Trimethoprim/sulphamethoxazole, norfloxacin and metronidazole: No effect on the systemic exposure of MPA was observed when CellCept was concomitantly administered with any antibiotic separately. In contrast, the combination of norfloxacin and metronidazole reduced the MPA AUC_{0-48} by 30 % following a single dose of CellCept.

Ciprofloxacin and amoxicillin plus clavulanic acid: Reductions in pre-dose (trough) MPA concentrations of 54 % have been reported in renal transplant recipients in the first 7 days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid.

Effects tended to diminish with continued antibiotic use and cease after discontinuation. The change in predose level may not accurately represent changes in overall MPA exposure therefore clinical relevance of these observations is unclear.

Tacrolimus: Exposure to tacrolimus concomitantly administered with CellCept had no effect on the AUC or C_{max} of MPA in liver transplant recipients. A similar finding was observed in a recent study in kidney transplant recipients.

In renal transplant patients it was shown that the tacrolimus concentration did not appear to be altered by CellCept (see WARNINGS AND SPECIAL PRECAUTIONS).

However, in hepatic transplant patients there was an increase of approximately 20 % in tacrolimus AUC when multiple doses of CellCept (1,5 g b.i.d.) were administered to patients taking tacrolimus.

Other interactions: Medicines known to undergo renal tubular secretion e.g. probenecid, may compete with MPAG and thereby raise plasma concentrations of MPAG, or the other compound undergoing tubular secretion. Concomitant administration of sevelamer and CellCept in adults and paediatric patients decreased the MPA C_{max} and AUC_{0-12} by 30 % and 25 % respectively. The data suggests that sevelamer and other calcium free phosphate binders preferentially should be given 2 hours after CellCept intake to minimise the impact on the absorption of MPA.

Live vaccines: Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished (see WARNINGS AND SPECIAL PRECAUTIONS).

HUMAN REPRODUCTION

CellCept is contraindicated in pregnancy and lactation (see CONTRAINDICATIONS).

CellCept is teratogenic and mutagenic. Congenital abnormalities and spontaneous abortions have been reported with the use of CellCept during pregnancy.

The following malformations were frequently reported**:**

- facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits
- abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos)
- malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly)
- cardiac abnormalities such as atrial and ventricular septal defects
- oesophageal malformations (e.g. oesophageal atresia)
- nervous system malformations (such as spina bifida)

DOSAGE AND DIRECTIONS FOR USE

Dosage for prophylaxis of renal rejection

Adults: The recommended dose is 1,0 g, administered orally or intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 2 g) is recommended for renal transplant patients. Although a dose of 1,5 g, administered twice daily (daily dose of 3 g), was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established for renal transplant patients. Patients receiving 2 g per day of CellCept, demonstrated an overall better safety profile than patients receiving 3 g/day.

Children aged 3 months to 18 years: The recommended dose of CellCept OS powder for oral suspension is 600 mg/m^2 administered twice daily (up to a maximum of 2 g daily). Patients with a body surface area of 1,25 to 1,5 m^2 may be prescribed CellCept capsules at a dose of 750 mg twice daily (1,5 g daily dose). Patients with a body surface area > 1,5 m^2 may be prescribed CellCept tablets at a dose of 1 g twice daily (2 g daily dose).

Standard dosage for prophylaxis of cardiac rejection

Adults: A dose of 1,5 g administered orally or intravenously (over NO LESS THAN 2 HOURS), twice a day (daily dose of 3 g), is recommended for use in cardiac transplant patients.

Children: No data are available for paediatric cardiac transplant patients.

Standard dosage for prophylaxis of hepatic rejection

Adults: A dose of 1 g administered intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 2 g), or 1,5 g administered orally, twice a day (daily dose of 3 g), is recommended for use in hepatic transplant patients.

Children: No data are available for paediatric hepatic transplant patients.

Standard dosage for treatment of first or refractory renal rejection

Adults: a dose of 1,5 g administered orally or intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 3 g) is recommended for management of first or refractory rejection.

Children: no data are available for treatment of first or refractory renal rejection in paediatric renal transplant patients.

Oral administration: See Bioequivalence under PHARMACOLOGICAL ACTION.

The initial dose of CellCept should be given as soon as possible following renal, cardiac or hepatic transplantation.

Intravenous administration

Adults: CellCept I.V. is an alternative dosage form to CellCept capsules, tablets and oral suspension recommended for patients unable to take oral CellCept.

CellCept I.V. should be administered within 24 hours following transplantation. CellCept I.V. can be administered for up to 14 days. Patients should be switched to oral CellCept as soon as they can tolerate oral medication.

Children: No data are available for CellCept I.V. in paediatric patients.

Following reconstitution and dilution with 5 % Dextrose intravenous infusion to a concentration of 6 mg/mℓ, CellCept I.V. must be administered by slow intravenous infusion over a period of NO LESS THAN 2 HOURS by either a peripheral or a central vein.

Special Dosage Instructions

Renal impairment:

Use in severe renal impairment: In patients with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1,73 m^2), outside of the immediate post-transplant period, doses greater than 1 g, administered twice a day, should be avoided. These patients should also be carefully observed.

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Patients with delayed renal graft function post-transplant: No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively.

Hepatic impairment:

No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Elderly:

The recommended dose of 1 g, administered twice a day for renal transplant patients and 1,5 g, twice a day for cardiac and hepatic transplant patients, is appropriate for elderly patients (see WARNINGS AND SPECIAL PRECAUTIONS).

Patients with neutropenia*:*

If neutropenia develops (absolute neutrophil count < 1,3 x 10^9/ℓ), dosing with CellCept should be interrupted or the dose reduced.

Note: CellCept OS powder for oral suspension can be administered via a nasogastric tube with a minimum size of 1,7 mm interior diameter. For the reconstituted suspension: Shake the bottle before use***.***

Preparation of CellCept OS powder for oral suspension:

It is recommended that CellCept OS powder for oral suspension be reconstituted by the pharmacist prior to dispensing to the patient. CellCept OS powder for oral suspension should not be mixed with any other medication.

1. Tap the closed bottle several times to loosen the powder.
2. Measure 94 mℓ purified water in a graduated cylinder.
3. Add approximately half of the total amount of purified water to the bottle and shake the closed bottle well for about 1 minute.
4. Add the remainder of the water and shake the closed bottle well for about 1 minute.
5. Remove the child-resistant cap and push the bottle adapter into the neck of the bottle.
6. Close the bottle with the child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap.
7. Write the date of expiration of the constituted suspension on the bottle label. The shelf–life of the reconstituted suspension is 60 days when stored below 30 °C.

Method of administration for CellCept I.V.

CAUTION:

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

CellCept I.V. is an alternative dosage form to CellCept capsules, CellCept tablets and CellCept oral suspension and recommended for patients unable to take oral medication.

CellCept I.V. should be administered within 24 hours following transplantation. Administration of CellCept oral formulations should be initiated as soon as the patient is able to tolerate oral medication.

Renal transplant recipients:

Clinical studies in renal transplant recipients with the I.V. formulation have been conducted up to 5 days.

Intravenous administration of CellCept I.V. should not exceed 5 days.

The recommended dose in renal transplant patients is 1 g administered twice a day (2 g daily dose).

Cardiac transplant patients:

The recommended dose in cardiac transplant patients is 1,5 g administered twice a day (3 g daily dose).

General:

Following reconstitution to a concentration of 6 mg/mℓ, CellCept I.V. must be administered by slow intravenous infusion over a period of NOT LESS THAN 2 hours. The appropriate infusion rate is approximately 84 mℓ /h.

Preparation of Infusion Solution (6 mg/mℓ): CellCept I.V. must be diluted with 5 % dextrose intravenous infusion, prior to use. Two vials of CellCept I.V. are used for preparing each 1 g dose. Three vials of CellCept I.V. are used for preparing each 1,5 g dose. A 2-step dilution is required to prepare the infusion solution at the recommended concentration of 6 mg/mℓ.

CellCept I.V. infusion solution should not be mixed or administered concurrently via the same catheter with other intravenous medicines or infusion admixtures.

CellCept I.V. is physically incompatible with the following infusion solutions: 0,9 % sodium chloride, Ringer's and lactated Ringer's solutions.

CellCept I.V. does not contain an antibacterial preservative; therefore, reconstitution and dilution of the product must be performed under aseptic conditions.

Step 1.

Reconstitute the content of each vial by injecting 14 mℓ of 5 % dextrose intravenous infusion. Care must be taken to ensure sterility of the prepared solution.

(a) Gently shake the vial to dissolve the medicine.

(b) Inspect the resulting solution for particulate matter and discolouration prior to further dilution. Discard the vial if particulate matter or discolouration is observed.

Step 2.

(a) To prepare a 1 g dose of mycophenolate, further dilute the content of the two reconstituted vials into 140 mℓ of 5 % dextrose intravenous infusion for a total volume of 168 mℓ and a final concentration of 6 mg mycophenolate mofetil per mℓ.

To prepare a 1,5 g dose of mycophenolate, further dilute the content of the three reconstituted vials into 210 mℓ of 5 % dextrose intravenous infusion for a total volume of 252 mℓ and a final concentration of 6 mg mycophenolate mofetil per mℓ.

(b) Inspect the infusion solution for particulate matter or discolouration. Discard the infusion solution of particulate matter or discolouration is observed.

If the solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 4 hours of reconstitution and dilution. Keep solutions at 15 – 30 °C.

Because mycophenolate mofetil has demonstrated teratogenic effects, avoid direct contact with the prepared solutions of CellCept I.V. with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, rinse eyes with plain water.

SIDE EFFECTS

Experience from clinical trials: The principle adverse reactions associated with the administration of CellCept include diarrhoea, leucopenia, sepsis and vomiting and there is

evidence of a higher frequency of certain types of infections. See WARNINGS AND SPECIAL PRECAUTIONS.

Adverse Events Reported in ≥ 10 % and in 3 – < 10 % of Patients Treated with CellCept in Clinical Trials in Adults when Used in Combination with Ciclosporin and Corticosteroids

Body System		**Adverse Events Reported in Renal Transplant Patients (n = 991) ***	**Adverse Events Reported in Cardiac Transplant Patients (n = 289) ****	**Adverse Events Reported in Hepatic Transplant Patients (n = 277) *****
Body as a whole	≥ 10 %	asthenia, fever, headache, infection, pain (includes abdominal, back, and chest), oedema, sepsis	asthenia, fever, chills, headache, infection, pain (includes abdominal, back, and chest), oedema, sepsis	ascites, asthenia, chills, enlarged abdomen, fever, headache, hernia, infection, pain (includes abdominal, back and chest), oedema, peritonitis, sepsis
Body as a whole	3 – < 10 %	cysts (including lymphocele and hydrocele), enlarged abdomen, facial oedema, flu syndrome, haemorrhage, hernia, malaise, pelvic pain	cellulitis, cysts (including lymphocele and hydrocele), enlarged abdomen, facial oedema, flu syndrome, haemorrhage, hernia, malaise, neck pain, pallor, pelvic pain	abscess, cellulitis, cyst (including lymphocele and hydrocele), flu syndrome, haemorrhage, malaise, neck pain
Blood and lymphatic	≥ 10 %	anaemia (including hypochromic anaemia), leucocytosis, leucopenia, thrombocytopenia	anaemia (including hypochromic anaemia), ecchymosis, leucocytosis, leucopenia, thrombocytopenia	anaemia (including hypochromic anaemia), leucocytosis, leucopenia, thrombocytopenia
Blood and	3 –	ecchymosis,	petechia, prothrombin	ecchymosis,

Body System		**Adverse Events Reported in Renal Transplant Patients (n = 991) ***	**Adverse Events Reported in Cardiac Transplant Patients (n = 289) ****	**Adverse Events Reported in Hepatic Transplant Patients (n = 277) *****
lymphatic	< 10 %	polycythaemia	time increased, thromboplastin time increased	pancytopenia, prothrombin time increased
Urogenital	≥ 10 %	haematuria, renal tubular necrosis, urinary tract infection	abnormal kidney function (decrease in renal function, elevated serum creatinine), oliguria, urinary tract infection	abnormal kidney function (decrease in renal function, elevated serum creatinine), oliguria, urinary tract infection
Urogenital	3 – < 10 %	albuminuria, dysuria, hydronephrosis, impotence, pyelonephritis, urinary frequency	dysuria, haematuria, impotence, nocturia, renal failure, urinary frequency, urinary incontinence, urinary retention	acute renal failure, dysuria, haematuria, renal failure, scrotal oedema, urinary frequency, urinary incontinence
Cardio-vascular	≥ 10 %	hypertension	dysrhythmia, bradycardia, cardiac failure, hypertension, hypotension, pericardial effusion	hypertension, hypotension, tachycardia
Cardio-vascular	3 – < 10 %	angina pectoris, atrial fibrillation, hypotension, postural hypotension, tachycardia, thrombosis, vasodilatation	angina pectoris, dysrhythmias (including supraventricular and ventricular extrasystoles, atrial flutter, supraventricular and ventricular	arterial thrombosis, atrial fibrillation, dysrhythmia, bradycardia, vasodilatation, syncope

Body System		**Adverse Events Reported in Renal Transplant Patients (n = 991) ***	**Adverse Events Reported in Cardiac Transplant Patients (n = 289) ****	**Adverse Events Reported in Hepatic Transplant Patients (n = 277) *****
			tachycardias), atrial fibrillation, cardiac arrest, congestive heart failure, postural hypotension, pulmonary hypertension, syncope, vasospasm, venous pressure increased	
Metabolic/ Nutritional	≥ 10 %	hypercholesterolaemia, hyperglycaemia, hyperkalaemia, hypokalaemia, hypophosphataemia	acidosis (metabolic or respiratory), bilirubinaemia, elevated blood urea elevated creatinine, elevated enzyme levels (lactic dehydrogenase, AST and ALT, hypercholesterolaemia, hyperglycaemia, hyperkalaemia, hyperlipaemia, hyperuricaemia, hypervolaemia, hypokalaemia, hypomagnesaemia, hyponatraemia, weight gain	bilirubinaemia, elevated blood urea, elevated creatinine, abnormal healing, hyperglycaemia, hyperkalaemia, hypocalcaemia, hypokalaemia, hypoglycaemia, hypomagnesaemia, hypophosphataemia, hypoproteinaemia
Metabolic/	3 –	acidosis (metabolic or	abnormal healing,	acidosis (metabolic or

Body System		**Adverse Events Reported in Renal Transplant Patients (n = 991) ***	**Adverse Events Reported in Cardiac Transplant Patients (n = 289) ****	**Adverse Events Reported in Hepatic Transplant Patients (n = 277) *****
Nutritional	< 10 %	respiratory), alkaline phosphatase increased, dehydration, elevated enzyme levels (gamma glutamyl transpeptidase, lactic dehydrogenase, AST and ALT, elevated creatinine, hypercalcaemia, hyperlipaemia, hypervolaemia, hypocalcaemia, hypoglycaemia, hypoproteinaemia, hyperuricaemia, weight gain	alkaline phosphatase increased, alkalosis, dehydration, gout, hypocalcaemia, hypochloraemia, hypoglycaemia, hypoproteinaemia, hypophosphataemia, hypovolaemia, hypoxia, respiratory acidosis, thirst, weight loss	respiratory), alkaline phosphatase increased, dehydration, elevated enzyme levels AST, and ALT, hypercholesteraemia, hyperlipaemia, hyperphosphataemia, hypervolemia, hyponatraemia, hypoxia, hypovolaemia, weight gain
Gastro-intestinal	≥ 10 %	constipation, diarrhoea, dyspepsia, nausea and vomiting, oral moniliasis	constipation, diarrhoea, dyspepsia, flatulence, nausea and vomiting, oral moniliasis	elevated liver function tests (incl. AST, ALT), anorexia, cholangitis, cholestatic jaundice, constipation, diarrhoea, dyspepsia, flatulence, hepatitis, nausea and vomiting, oral moniliasis
Gastro-intestinal	3 – < 10 %	elevated liver function tests (incl. AST, ALT), anorexia, flatulence,	elevated liver function tests (incl. AST, ALT), anorexia, dysphagia,	dysphagia, gastritis, gastrointestinal haemorrhage,

Body System		**Adverse Events Reported in Renal Transplant Patients (n = 991) ***	**Adverse Events Reported in Cardiac Transplant Patients (n = 289) ****	**Adverse Events Reported in Hepatic Transplant Patients (n = 277) *****
		gastroenteritis, gastrointestinal haemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, oesophagitis, stomatitis	gastroenteritis, gingivitis, gum hyperplasia, jaundice, melaena, oesophagitis, stomatitis	ileus, jaundice, melaena, mouth ulceration, oesophagitis, rectal disorder, stomach ulcer
Respiratory	≥ 10 %	cough increased, dyspnoea, pharyngitis, pneumonia, bronchitis	asthma, cough increased, dyspnoea, pharyngitis, pleural effusion, pneumonia, rhinitis, sinusitis	atelectasis, cough increased, dyspnoea, pharyngitis, pleural effusion, pneumonia, sinusitis
Respiratory	3 – < 10 %	asthma, pleural effusion, pulmonary oedema, rhinitis, sinusitis	apnoea, atelectasis, bronchitis, epistaxis, haemoptysis, hiccough, neoplasm, pneumothorax, pulmonary oedema, sputum increased, voice alteration	asthma, bronchitis, epistaxis, hyperventilation, pneumothorax, pulmonary oedema, respiratory moniliasis, rhinitis
Skin and Append-ages	≥ 10 %	acne, herpes simplex	acne, herpes simplex, herpes zoster, rash	pruritus, rash, sweating
Skin and Append-ages	3 – < 10 %	alopecia, benign neoplasm of skin, fungal dermatitis, herpes zoster,	benign neoplasm of skin, fungal dermatitis, haemorrhage,	acne, fungal dermatitis, haemorrhage, herpes simplex, herpes

Body System		**Adverse Events Reported in Renal Transplant Patients (n = 991) ***	**Adverse Events Reported in Cardiac Transplant Patients (n = 289) ****	**Adverse Events Reported in Hepatic Transplant Patients (n = 277) *****
		hirsutism, pruritus, skin carcinoma, skin hypertrophy (incl. actinic keratosis), sweating, skin ulcer, rash	pruritus, skin carcinoma, skin hypertrophy, skin ulcer, sweating	zoster, hirsutism, skin benign neoplasm, skin ulcer, vesiculobullous rash
Nervous	≥ 10 %	dizziness, tremor	agitation, confusion, dizziness, hypertonia, paraesthesia, tremor	confusion, dizziness, paraesthesia, tremor
Psychiatric	≥ 10 %	insomnia	anxiety, depression, insomnia, somnolence	anxiety, depression, insomnia
Nervous	3 – < 10 %	hypertonia, paraesthesia	convulsion, neuropathy, vertigo	agitation, convulsion, dry mouth, hypertonia, hyperaesthesia, neuropathy
Psychiatric	3 – < 10 %	anxiety, depression, somnolence	emotional lability, hallucinations, abnormal thinking	delirium, psychosis, somnolence, abnormal thinking
Musculo-skeletal	≥ 10 %	–	leg cramps, myalgia, myasthenia	–
Musculo-skeletal	3 – < 10 %	arthralgia, leg cramps, myalgia, myasthenia	arthralgia	arthralgia, leg cramps, myalgia, myasthenia, osteoporosis

Body System		**Adverse Events Reported in Renal Transplant Patients (n = 991) ***	**Adverse Events Reported in Cardiac Transplant Patients (n = 289) ****	**Adverse Events Reported in Hepatic Transplant Patients (n = 277) *****
Special Senses	≥ 10 %	–	amblyopia	–
Special Senses	3 – < 10 %	amblyopia, cataract, conjunctivitis	abnormal vision, conjunctivitis, deafness, ear pain, eye haemorrhage, tinnitus	abnormal vision, amblyopia, conjunctivitis, deafness
Endocrine	≥ 10 %	–	–	–
Endocrine	3 – < 10 %	diabetes mellitus, parathyroid disorder (elevated PTH level)	diabetes mellitus, Cushing's syndrome, hypothyroidism	diabetes mellitus
*(total n = 1,483) ** (total n = 578) *** (total n = 564)				

Children (aged 3 months to 18 years):

The type and frequency of adverse drug reactions in a clinical study of 100 paediatric patients aged 3 months to 18 years given 600 mg/m^2 mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g CellCept twice daily. However, the following treatment-related adverse events occurred with a frequency of ≥ 10 % in children and were more frequent in the paediatric population, particularly in children under 6 years of age, when the frequency of treatment-related adverse events was compared to adults: diarrhoea, leucopenia, sepsis, infection, anaemia.

Elderly patients (> 65 years):

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 cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals. See WARNINGS AND SPECIAL PRECAUTIONS.

Adverse events profile for intravenous administration:

The adverse event profile of CellCept administered intravenously was determined from a single, double blind, controlled comparative study of the safety of CellCept 2 g/day administered intravenously or orally in the immediate post-transplant period (administered for the first 5 days). The potential venous irritation of CellCept administered intravenously was evaluated by comparing the adverse events attributable to a peripheral venous infusion of CellCept with those observed in the IV placebo group; patients in the latter group received active medication by the oral route.

The adverse event profile associated with the administration of CellCept I.V. has been shown to be similar to that observed after oral administration. Adverse events attributable to peripheral venous infusion were phlebitis and thrombosis, both observed at 4 % in patients treated with CellCept intravenously.

Post-marketing experience:

Gastrointestinal: Colitis (sometimes caused by cytomegalovirus), pancreatitis, isolated cases of intestinal villous atrophy.

Disorders of immuno-suppression: Serious life-threatening infections such as meningitis and infectious endocarditis have been reported and there is evidence of a higher frequency of certain types of infections such as tuberculosis and atypical mycobacterial infection (see WARNINGS AND SPECIAL PRECAUTIONS).

Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, has been reported in CellCept-treated patients. *BK virus-associated nephropathy* has been observed in patients treated with CellCept. This infection can be associated with serious outcomes, sometimes leading to renal graft loss.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept in combination with other immunosuppressive agents.

Congenital disorders: Various congenital malformations including ear malformations have been reported in offspring of patients exposed to MMF in combination with other immunosuppressants during pregnancy (see BOXED WARNING 2, CONTRAINDICATIONS, WARNINGS AND SPECIAL PRECAUTIONS, AND HUMAN REPRODUCTION).

Other adverse reactions seen during post-marketing experience with CellCept were similar to those seen in the controlled renal, cardiac and hepatic transplant studies.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In cases of overdose, side effects would be exacerbated and exaggerated (see SIDE EFFECTS).

Reports of overdose with mycophenolate mofetil have been received from clinical trials and during post-marketing experience. Overdose of mycophenolate mofetil may result in over-suppression of the immune system and could increase susceptibility to infections and bone marrow suppression (see WARNINGS AND SPECIAL PRECAUTIONS).

If neutropenia develops, dosing with CellCept should be interrupted or the dose reduced.

MPA cannot be removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 mg/mℓ) small amounts of MPAG are removed. By increasing excretion of the medicine, MPA can be removed by bile acid sequestrants, such as cholestyramine.

IDENTIFICATION

CellCept 250 mg capsules: An opaque hard gelatine capsule containing a white to off white powder, branded with black ink “CellCept 250” on the blue capsule cap, and “Roche” on the brown capsule body.

CellCept OS powder for oral suspension: White to off-white powder contained in a white plastic bottle.

Reconstituted suspension: A white to off-white, odourless suspension.

CellCept I.V.: 20 ml glass vials with grey butyl rubber stopper and aluminium seals and with plastic flip-off caps. Vials contain a sterile white to off-white lyophilised powder.

Reconstituted solution and diluted infusion solution: A slightly yellow solution.

CellCept 500 mg tablets: Lavender coloured caplet-shaped tablet, engraved with “CellCept 500” on one side and “Roche” on the other side.

PRESENTATION

CellCept 250 mg capsules: Packs containing multiple opaque PVC blister strips, each strip containing 10 capsules.

CellCept OS powder for oral suspension: White plastic bottle with a child-resistant closure and a closure liner. A plastic press-in bottle adapter and a 5 mℓ graduated plastic oral dispenser.

CellCept I.V: Packs of 4 vials.

CellCept 500 mg tablets: Packs containing multiple opaque PVC blister strips, each strip containing 10 tablets.

STORAGE INSTRUCTIONS

CellCept 250 mg capsules and CellCept 500 mg tablets: Store at or below 25 ^{o}C.

CellCept I.V. and CellCept OS powder for oral suspension: Store at or below 30 ^{o}C.

The shelf life of the constituted suspension is 60 days when stored below 30 °C. Any unused suspension must be discarded after 60 days.

Keep well-closed and out of reach of children.

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, CellCept capsules should not be opened or crushed. Avoid inhalation, or direct contact with skin or mucous membranes, of the powder contained in CellCept capsules. If such contact occurs, wash thoroughly with soap and water, rinse eyes with plain water.

Do not use the medicine after the expiry date that has been printed on the container.

Reconstituted solution and diluted infusion solution

Store at 15 – 30 °C.

REGISTRATION NUMBERS

CellCept 250 mg capsules:	31/34/0134
CellCept OS powder for oral suspension:	35/34/0057
CellCept I.V. Infusion (Parenteral):	33/34/0201
CellCept 500 mg tablets:	A39/34/0230

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE

Roche Products (Pty) Ltd
24 Fricker Road
Illovo
Gauteng
South Africa
Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

DATE OF PUBLICATION

Registration:	20 May 1997 (31/34/0134)
	7 March 2003 (35/34/0057)
	2 April 2004 (33/34/0201)
	7 July 2006 (A39/34/0230)
Last revision:	23 November 2017

CellCept® capsules	Namibia: NS2 12/34/0119	CellCept® 500 mg tablets	Namibia: NS2 12/34/0120

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM

CellCept® I.V. 500 mg Infusion (Parenteral)

WARNING 1: DO NOT USE CELLCEPT I.V.

If you are pregnant or planning to become pregnant, or breastfeeding your baby, you must not receive CellCept (see BEFORE USING CellCept I.V. and Pregnancy and breastfeeding).

WARNING 2: IMMUNE SYSTEM SUPPRESSED: RISK OF INFECTIONS AND CANCER

Increased likelihood of infection and the possible development of a cancer of the lymph nodes or tissues and other cancers, especially of the skin, may result from the body's immune system being suppressed. Only doctors experienced in medicines which suppress the body's immune response and management of kidney, heart or liver transplant patients should prescribe CellCept. Patients receiving CellCept should be managed by healthcare professionals experienced in relevant laboratory and medical resources and knowledge. The doctor responsible for your maintenance therapy will have complete information available for your follow-up.

WARNING 3: RISK OF BIRTH DEFECTS

CellCept can cause malformations and mutations in unborn foetuses. Before birth malformations and spontaneous abortions have been reported with use of CellCept in pregnancy. Women of childbearing potential must have two negative medical practitioner or laboratory-supervised blood or urine pregnancy tests; the second test should be performed 8-10 days after the first one and 24 hours before starting treatment with CellCept. Repeat pregnancy tests should be performed during routine follow-up visits.

Women of childbearing potential should use two reliable forms of birth control simultaneously, including at least one highly effective method, before beginning CellCept therapy, during therapy, and for 90 days following discontinuation of therapy; unless not having intercourse is the chosen method of birth control.

Sexually active men are recommended to use condoms during treatment and for 90 days after stopping treatment. Condom use applies both for reproductively able men and men who have had a vasectomy, because the risk associated with the transfer of semen also applies to men who have had a vasectomy.

Female partners of male patients are recommended to use highly effective birth control methods during treatment and for a total of 90 days after the last dose of CellCept.

Read all of this leaflet carefully before you start to take/use CellCept I.V.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- CellCept has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

WHAT CellCept I.V. CONTAINS

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

WHAT CellCept I.V. IS USED FOR

CellCept is used to prevent your body rejecting a transplanted kidney, heart or liver. CellCept is used together with other medicines.

BEFORE USING CellCept I.V.

Do not use CellCept:

- If you are allergic (hypersensitive) to mycophenolate mofetil, mycophenolic acid or any of the other ingredients of CellCept.
- If you are pregnant or breastfeeding.
- If you have Lesch-Nyhan or Kelley-Seegmiller syndrome or another rare inherited deficiency hypoxanthine-guanine phosphoribosyl-transferase (HGPRT). You should not take CellCept if you have one of these disorders.

Take special care with CellCept I.V.:

You should inform your doctor immediately:

- If you experience any evidence of infection (e.g. fever, sore throat), unexpected bruising and/or bleeding.
- If you have or have ever had any problems with your digestive system, e.g., stomach ulcers.
- If you are planning to become pregnant or if you become pregnant while taking CellCept.

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

Taking CellCept I.V. with food and drink:

Taking food and drink has no influence on your treatment with CellCept.

Pregnancy and breastfeeding:

Do not take CellCept if you are pregnant or breastfeeding.

Use of CellCept during pregnancy may cause miscarriage or damage to your unborn baby (abnormal development of ears for example).

If you plan to become pregnant, discuss with your doctor alternative medicines to best prevent rejection of your transplanted organ. In certain situations, you and your doctor may decide that the benefits of taking CellCept for your health are more important than the possible risks to your unborn baby.

Tell your doctor straight away if:

- You think you may be pregnant
- You are breastfeeding
- You plan to start a family in the near future

You must use 2 different types of effective birth control at the same time –

- four weeks before you start taking CellCept

- during your entire treatment with CellCept
- for 6 weeks after you stop taking CellCept

unless you choose to avoid sexual intercourse (abstinence)

You should talk to your doctor about the most suitable methods for birth control for you, based on your individual situation.

If you could possibly become pregnant, you must have a pregnancy test with a negative result BEFORE starting treatment with CellCept.
If you are pregnant or breastfeeding your baby please consult your doctor, pharmacist or healthcare professional for advice before you are given CellCept.

Driving and using machinery:

- Do not drive because CellCept could interfere with your ability to drive safely.
- Do not operate any tools or machines.

Taking other medicines with CellCept I.V.

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.) This is because CellCept can affect the way some medicines work. Some other medicines may also affect the way CellCept works.
Are you taking any medicines containing:

- azathioprine or other immunosuppressive agents (which are sometimes given to patients after a transplant operation);
- cholestyramine (used to treat patients with high blood cholesterol);
- rifampicin (used to treat TB);
- oral ciprofloxacin or amoxicillin plus clavulanic acid (antibiotics); antacids, proton pump inhibitors (PPIs) including lansoprazole and pantoprazole;
- phosphate binders (used in patients with chronic renal failure to reduce the absorption of phosphate)

or any other medicines (including those you can buy without a prescription) that your doctor does not know about?
Do you need to receive vaccines (live vaccines)? Your doctor will have to advise you what is indicated for you.
If any of the above applies to you, or if you are not sure, talk to your doctor, nurse, midwife or pharmacist before you are given CellCept.

HOW CellCept I.V. WILL BE ADMINISTERED

You will not be expected to give yourself CellCept. It will be given to you by a person qualified to do so.

Do not share medicines prescribed for you with another person.

You should check with your doctor or pharmacist if you are not sure. Your doctor will manage how you will be given CellCept.

The usual dose is:

Method and route of administration

Cellcept is usually given by a doctor or nurse in hospital. It is given as a slow drip (infusion) into a vein.

How much will be given

The amount you need depends on the type of transplant you have had. The usual doses are shown below. Treatment will continue for as long as your doctor considers you will need to prevent your body from rejecting your transplant organ.

When you are able to swallow, you will be given your medicine by mouth.

Your doctor will tell you how long your treatment with CellCept will last. Do not stop treatment early. If you have the impression that the effect of CellCept is too strong or too weak for you, tell your doctor or pharmacist.

If you are given more CellCept I.V. than you should:

Since a healthcare professional will administer CellCept, he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

If you forget to have CellCept:

Your doctor will manage the time that you are given your drip infusion.

If you stop taking CellCept I.V.:

Effects when treatment with CellCept is stopped

Stopping your treatment with CellCept may increase the chance of rejection of your transplanted organ.

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

POSSIBLE SIDE EFFECTS

CellCept can have side effects.

Not all side effects reported for CellCept are included in this leaflet. Should your general health worsen or if you experience any untoward effects while using CellCept, please consult your doctor, pharmacist or other healthcare professional for advice.

Frequent:

Some of the more usual problems are diarrhoea, fewer white cells and/or red cells in your blood, infection and vomiting. 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.

Children may be more likely than adults to have side effects such as diarrhoea, infections, fewer white cells and fewer red cells in the blood.

CellCept reduces your body's own defence mechanisms to stop rejection of your transplanted kidney, heart or liver. Consequently your body will not be as good as normal at fighting infections. So if you are taking CellCept you may therefore catch more infections than usual, such as infections of the brain, skin, mouth, stomach and intestines, lungs and urinary tract**.**

Less frequent:

A small number of CellCept patients have developed cancer of the lymph tissues and skin.

General side effects affecting your body as a whole could include **hypersensitivity** (such as anaphylaxis, angioedema, fever, lethargy, difficulty in sleeping, pains (such as abdominal, chest, joint/muscle, pain on passing urine), headache, flu symptoms and swelling.

Other unwanted effects may include:

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

Urinary disorders such as kidney problems or the urgent need to pass urine.

Disorders of the digestive system and mouth such as constipation, nausea, indigestion, pancreas inflammation, intestinal disorders including bleeding, inflammation of the stomach, liver problems, inflammation of the colon, loss of appetite, flatulence and mouth ulcers.

Disorders of the nerves and senses such as convulsions, tremor, dizziness, depression, drowsiness, numbness, muscle spasms, anxiety, changes in thinking or mood.

Metabolic, blood and vascular disorders such as weight loss, gout, high blood sugar, bleeding, clots and bruises, change in blood pressure, abnormal heart beat and dilation of blood vessels may be seen.

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

If you are concerned about these or any other unexpected effect(s), talk to your doctor. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORING AND DISPOSING OF CellCept I.V.

Store all medicines out of reach of children.

CellCept I.V.: Store at or below 30 °C.

Keep the container tightly closed.

Do not use CellCept after the expiry date that has been printed on the container.

Diluted infusion solution

Store at 15 – 30 °C.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

PRESENTATION OF CellCept I.V.

CellCept I.V: Packs of 4 vials.

IDENTIFICATION OF CellCept I.V.

CellCept I.V.: 20 mℓ glass vials with grey butyl rubber stopper and aluminium seals and with plastic flip-off caps. Vials contain a sterile white to off-white lyophilised powder.

REGISTRATION NUMBER

CellCept I.V. Infusion (Parenteral): 33/34/0201

NAME AND ADDRESS OF REGISTRATION HOLDER

Roche Products (Pty) Ltd
24 Fricker Road
Illovo
Gauteng
South Africa
Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

DATE OF PUBLICATION

Registration: 2 April 2004 (33/34/0201)
Last revision: 23 November 2017

PASIËNT INLIGTINGSTUK

SKEDULERINGSTATUS

S4

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM

CellCept® I.V. 500 mg Infusie (Parenteraal)

WAARSKUWING 1: MOENIE CELLCEPT I.V. GEBRUIK NIE

Indien u swanger is of beplan om swanger te raak, of borsvoed, moet u nie CellCept ontvang nie (kyk VOORDAT U CellCept I.V. GEBRUIK en Swangerskap en borsvoeding).

WAARSKUWING 2: IMMUUNONDERDRUKKING: RISIKO VAN INFEKSIES EN KANKER

Immuunonderdrukking kan dalk ’n verhoogde vatbaarheid vir infeksie en die ontwikkeling van kanker van die limfkliere of -weefsel en ander kankers, veral van die vel, tot gevolg hê. Slegs dokters wat in immuunonderdrukkingmedisyne en -bestuur van nier-, hart- of leweroorplantingspasiënte opgelei is, kan CellCept voorskryf. Pasiënte wat CellCept ontvang, moet deur gesondheidsorgdeskundiges bestuur word wat voldoende laboratorium- en mediese hulpbronne en kennis het. Die dokter wat vir u instandhoudingsterapie verantwoordelik is, moet volledige inligting vir u opvolg beskikbaar hê.

WAARSKUWING 3: RISIKO VAN GEBOORTE-AFWYKINGS

CellCept kan wanvormings en mutasies in ongebore fetusse veroorsaak. Kongenitale wanvorming en spontane aborsies is met die gebruik van CellCept in swangerskap aangemeld. Vroue wat kan swanger raak, moet twee negatiewe serum- en urienswangerskapstoetse onder toesig van ’n mediese dokter of ’n laboratorium hê; die tweede toets moet 8-10 dae ná die eerste een en 24 uur voor CellCept-terapie begin, uitgevoer word. Swangerskapstoetse moet gedurende roetine-opvolgbesoeke herhaal word.

Vroue wat kan swanger raak, moet twee betroubare geboortebeperkingsmetodes gelyktydig neem, insluitend ten minste een hoogs doeltreffende metode voor CellCept-terapie begin en vir 90 dae ná afloop van beëindiging van terapie; tensy geheelonthouding die geboortebeperkingsmetode van keuse is.

Daar word aanbeveel dat seksueelaktiewe mans kondome gedurende behandeling en vir 90 dae ná afloop van behandeling gebruik. Kondoomgebruik is van toepassing op mans wat kan voortplant én mans wat ’n vasektomie gehad het, want die risiko wat met die oordrag van saadvloeistof verband hou, is ook van toepassing op mans wat ’n vasektomie gehad het.

Daar word aanbeveel dat vroulike seksmaats van manlike pasiënte hoogs doeltreffende geboortebeperking gedurende behandeling en vir ’n totaal van 90 dae ná die laaste dosis CellCept moet gebruik.

Lees hierdie inligtingstuk noukeurig voordat u CellCept I.V. begin gebruik

- Hou hierdie inligtingstuk. U sal dit dalk weer moet lees.
- Indien u verdere vrae het, vra asseblief u dokter of u apteker.
- CellCept is vir u persoonlik voorgeskryf en u behoort nie u medisyne met enige iemand te deel nie. Dit kan hulle kwaad aandoen, selfs al het hulle dieselfde simptome as u.

WAT CellCept I.V. BEVAT

Elke flessie bevat die ekwivalent van 500 mg mikofenolaatmofetiel (as hidrochloriedsout). Dit bevat ook polisorbaat, sitroensuur en natriumchloried.

WAARVOOR CellCept I.V. GEBRUIK WORD

CellCept word gebruik om te voorkom dat u liggaam ’n oorgeplante nier, hart of lewer verwerp. CellCept word in kombinasie met ander middels gebruik.

VOORDAT u CellCept I.V. GEBRUIK

Moenie CellCept neem:

- indien u allergies (hipersensitief) is vir mikofenolaatmofetiel, mikofenoliesesuur of enige van die ander bestanddele van CellCept nie.
- Indien u swanger is of borsvoed nie.
- Indien u Lesch-Nyhan- of Kelley-Seegmiller-sindroom of ’n ander seldsame oorerflike tekort hipoxantien-guanien fosforibosiel-transferase (HGFRT) het nie. U moenie CellCept neem indien u enige van hierdie afwykings het nie.

Neem spesiale voorsorg met CellCept I.V.:

U moet u dokter onmiddellik inlig:

- Indien u enige tekens van infeksie ervaar (bv. koors, seerkeel), onverwagse kneusing en/of bloeding.
- Indien u enige probleme met u verteringstelsel ervaar of ervaar het, bv. maagsere.
- Indien u beplan om swanger te raak of indien u swanger raak terwyl u CellCept neem.

CellCept verlaag u liggaam se verdedigingsmeganisme. As gevolg hiervan, is daar ’n groter risiko van velkanker. Daarom moet u dus u blootstelling aan sonlig en UV lig beperk deur toepaslike beskermende klere te dra en sonskermmiddel met ’n hoë beskermingsfaktor te gebruik.

Neem van CellCept met voedsel en drank:

Om voedsel en drank te neem, het geen invloed op u behandeling met CellCept nie.

Swangerskap en borsvoeding:

Moenie CellCept neem indien u swanger is of borsvoed nie.

Die gebruik van CellCept gedurende swangerskap kan dalk miskraam of skade aan ongebore baba veroorsaak (byvoorbeeld abnormale ontwikkeling van ore).

Indien u beplan om swanger te raak, bespreek alternatiewe medisyne met u dokter om verwerping van u oorgeplante orgaan die beste te verhoed. In sekere gevalle kan u en u dokter dalk besluit dat die voordele om CellCept vir u gesondheid te neem belangriker is as die moontlike risiko's aan u ongebore baba.

Vertel dadelik u dokter indien:

- U dink dat u dalk swanger is
- U borsvoed
- U van plan is om binnekort met ’n gesin te begin

U moet ten minste twee verskillende tipes betroubare geboortebeperking gelyktydig gebruik –

- vier weke voor CellCept begin gebruik
- gedurende u hele behandeling met CellCept
- vir ses weke nadat u met CellCept opgehou het

tensy u kies om seksuele omgang te vermy (geheelonthouding)

U moet met u dokter praat oor die mees gepaste metodes van geboortebeperking vir u gebaseer op u individuele situasie.

Indien u moontlik kan swanger raak, moet u ’n negatiewe swangerskaptoets hê VOOR u behandeling met CellCept begin.
Indien u swanger is of borsvoed, bespreek dit asseblief met u dokter, apteker of ander gesondheidsorgdeskundige voordat u CellCept neem.

Motorbestuur en gebruik van masjinerie:

- Moenie bestuur nie, want CellCept kan u vermoë raak om veilig te bestuur.
- Moenie enige apparate of masjiene hanteer nie.

Om ander middels saam met CellCept I.V. te neem:

Vertel altyd u gesondheidsorgdeskundige indien u enige ander middels neem. (Dit sluit komplementêre of tradisionele middels in.) Die rede hiervoor is omdat CellCept dalk die manier wat sommige middels werk, kan beïnvloed. Sommige ander middels kan dalk ook die manier wat CellCept werk, beïnvloed.
Neem u enige middels wat die volgende bevat:

- azathioprien of enige ander immuun-onderdrukkende middel (wat soms aan pasiënte gegee word na ’n oorplantingsoperasie);
- cholestiramien (wat gebruik word om pasiënte met hoë bloedcholesterol te behandel);
- rifampsien (wat gebruik word om TB te behandel);
- orale siprofloksasien of amoksisillien plus klavulaansuur (antibiotika); teensuurmiddels, protonpompinhibtors (PPI's), insluitend lansoprasool en pantoprasool;
- fosfaatbinders (gebruik by pasiënte met chroniese nierversaking om die absorpsie van fosfaat te verlaag)

of enige ander medisyne (insluitende dié wat u sonder ‘n voorskrif kan koop) wat u dokter nie van weet nie?
Indien u vaksiene moet kry (lewendige vaksiene)? U doktor sal u moet adviseer
wat vir u toepaslik sal wees.

Indien enige van die bogenoemde op u van toepassing is, praat met u dokter, verpleegkundige, vroedvrou of apteker voordat u CellCept ontvang.

HOE CellCept I.V. TOEGEDIEN SAL WORD

Daar sal nie van u verwag word om CellCept self te neem nie. Dit sal deur ’n opgeleide persoon aan u toegedien word.

Moenie medisyne wat vir u voorgeskryf is met ander deel nie.

U moet by u dokter of apteker seker maak indien u nie seker is nie. U dokter sal bestuur hoe u CellCept sal ontvang.

Die gewone dosis is:

Metode en roete van toediening

Cellcept word gewoonlik deur ’n dokter of verpleegkundige in die hospitaal gegee. Dit word as ’n stadige drip (infusie) in ’n aar gegee.

Hoeveel sal u ontvang

Die hoeveelheid wat u benodig hang af van die oorplanting wat u gehad het. Die gewone dosisse word hieronder aangedui. Behandeling sal voortduur solank as wat u dokter van mening is u u liggaam moet verhoed om u oorplantingsorgaan te verwerp.

Sodra u kan sluk, sal u u medisyne oraal ontvang.

U dokter sal u inlig hoe lank u behandeling met CellCept sal duur. Moenie behandeling vroeg staak nie. Indien u van mening is dat die effek van CellCept te sterk of te swak is, vertel u dokter of apteker.

Indien u meer CellCept I.V. ontvang het as wat u moes:

Aangesien ’n gesondheidsorgdeskundige CellCept sal toedien, sal hy/sy die dosis beheer. In die geval van oordosering sal u dokter egter die oordosering bestuur.

Indien u vergeet om CellCept te neem:

U dokter sal die tyd bestuur wat u u dripinfusie ontvang.

Indien u ophou om CellCept I.V. te neem:

Effekte wanneer behandeling met CellCept gestaak word

Staking van behandeling met CellCept kan die kanse vir verwerping van u oorgeplante orgaan verhoog.

Indien u enige verdere vrae oor die gebruik van hierdie produk het, vra u dokter.

MOONTLIKE NEWE-EFFEKTE

CellCept kan newe-effekte hê.

Nie alle newe-effekte wat vir CellCept aangemeld is, word by hierdie inligtingstuk ingesluit nie. Indien u algemene gesondheid verswak of u enige ongewenste effekte ervaar terwyl u CellCept neem, raadpleeg u dokter, apteker of ander gesondheidsorgdeskundige vir advies.

Dikwels:

Sommige van die meer algemene probleme is diarree, minder witselle en/of rooiselle in die bloed, infeksie en braking. U dokter sal gereeld bloedtoetse doen om die aantal bloedselle of veranderings in die vlakke van enige van die ander stowwe wat in bloed voorkom, bv. suiker, vet, cholesterol te moniteer.

Kinders kan meer vatbaar wees vir newe-effekte soos diarree, infeksies, minder witselle en minder rooiselle in die bloed.

CellCept verlaag u liggaam se eie verdedigingsmeganisme om u te verhoed om u oorgeplante nier, hart of lewer te verwerp. Gevolglik sal u liggaam nie so goed in staat wees soos normaalweg om infeksies te beveg nie. Dus, as u CellCept neem kan u meer infeksie opdoen as gewoonlik, soos infeksies van die brein, vel, mond, maag en ingewande, longe en urienweg**.**

Minder dikwels:

’n Baie klein aantal CellCept pasiënte het kanker van die limfoïede weefsel en vel ontwikkel.

Algemene newe-effekte wat u liggaam as geheel kan affekteer kan **hipersensitiwiteit** (soos anafilakse, angioedeem), koors, lusteloosheid, probleme met slaap, pyne (soos abdominale, borskas, gewrig/spier, pyn tydens urinering), hoofpyn, griepsimptome en swelling insluit.

Ander ongewenste effekte sluit in:

Afwykings van die vel soos aknee, koorssere, shingles, velgroeisels, haarverlies, uitslag, jeuk.

Urienwegafwykings soos nierprobleme of die dringende nood om urien te passeer.

Afwykings van die ingewande en mond soos hardlywigheid, naarheid, slegte spysvertering, inflammasie van die pankreas, ingewandsafwykings insluitende bloeding, inflammasie van die maag, lewer probleme, inflammasie van die kolon, verlies van eetlus, winderigheid en mondsere.

Afwykings van die senuwees en sintuie soos konvulsies, bewing, duiseligheid, depressie, lomerigheid, gevoelloosheid, spierspasmas, angstigheid, veranderinge in gedagtes en gemoedstemming.

Metaboliese, bloed- en aarafwykings soos gewigsverlies, jig, hoë bloedsuiker, bloeding, klonte en kneusings, veranderinge in bloeddruk, abnormale hartklop en verwyding van bloedvate kan voorkom.

Afwykings van die longe soos longontsteking, brongitis, kortasemheid, hoes, vog op die longe/borsholte, sinusprobleme.

Indien u oor dié of enige ander ongewenste effek(te) bekommerd is, praat met u dokter. Indien u enige newe-effekte ondervind wat nie in hierdie pamflet gelys is nie, vertel asseblief u dokter of apteker.

BEWARING EN WEGDOENING VAN CellCept I.V.

Bêre alle medisyne buite bereik van kinders.

CellCept I.V.: Bêre teen of benede 30 °C.

Hou houer dig toe.

Moet nie CellCept gebruik ná die vervaldatum wat op die houer aangebring is nie.

Verdunde infusie-oplossing

Bêre tussen 15 – 30 °C.

Neem alle ongebruikte medisyne terug na u apteker.

Moenie ongebruikte medisyne in dreine of rioolstelsels (bv. toilette) wegdoen nie.

AANBIEDING VAN CellCept I.V.

CellCept I.V. : Pakke wat 4 flessies bevat.

IDENTIFIKASIE VAN CellCept I.V.

CellCept I.V.: 20 mℓ glas flessie met ’n grys butielrubber prop en aluminiumseël en met ’n plastiese flip-af doppie. Die flessies bevat ’n steriele wit tot naas-wit geliofiliseerde poeier.

REGISTRASIENOMMER

CellCept I.V. Infusie (Parenteraal): 33/34/0201

NAAM EN ADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE

Roche Products (Edms) Bpk

24 Frickerweg

Illovo

Gauteng

Suid-Afrika

Roche Ethical Assistance Line (REAL) tolvry: 0800 21 21 25

DATUM VAN PUBLIKASIE

Registrasie: 2 April 2004 (33/34/0201)

Laaste hersiening: 23 November 2017