PROFESSIONAL INFORMATION

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 tachycardias), atrial	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) *****
			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/ Nutritional	3 – < 10 %	acidosis (metabolic or respiratory), alkaline phosphatase	abnormal healing, alkaline phosphatase increased, alkalosis,	acidosis (metabolic or respiratory), alkaline phosphatase

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) *****
		increased, dehydration, elevated enzyme levels (gamma glutamyl transpeptidase, lactic dehydrogenase, AST and ALT, elevated creatinine, hypercalcaemia, hyperlipaemia, hypervolaemia, hypocalcaemia, hypoglycaemia, hypoproteinaemia, hyperuricaemia, weight gain	dehydration, gout, hypocalcaemia, hypochloraemia, hypoglycaemia, hypoproteinaemia, hypophosphataemia, hypovolaemia, hypoxia, respiratory acidosis, thirst, weight loss	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, gastroenteritis, gastrointestinal haemorrhage,	elevated liver function tests (incl. AST, ALT), anorexia, dysphagia, gastroenteritis, gingivitis, gum hyperplasia, jaundice,	dysphagia, gastritis, gastrointestinal haemorrhage, ileus, jaundice, melaena, mouth ulceration,

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) *****
		gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, oesophagitis, stomatitis	melaena, oesophagitis, stomatitis	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, hirsutism, pruritus, skin carcinoma, skin hypertrophy (incl.	benign neoplasm of skin, fungal dermatitis, haemorrhage, pruritus, skin carcinoma, skin hypertrophy, skin	acne, fungal dermatitis, haemorrhage, herpes simplex, herpes zoster, hirsutism, skin benign neoplasm, skin ulcer,

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) *****
		actinic keratosis), sweating, skin ulcer, rash	ulcer, sweating	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
Special Senses	≥ 10 %	–	amblyopia	–
Special Senses	3 – < 10 %	amblyopia, cataract, conjunctivitis	abnormal vision, conjunctivitis,	abnormal vision, amblyopia,

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) *****
			deafness, ear pain, eye haemorrhage, tinnitus	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 °C.

CellCept I.V. and CellCept OS powder for oral suspension: Store at or below 30 °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

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

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CellCept 250 mg capsules:

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