

CellCept®

Mycophenolate mofetil

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Immunosuppressant; inosine monophosphate dehydrogenase (IMPDH) inhibitor.

1.2 Type of Dosage Form

CellCept is supplied as film-coated caplets.

1.3 Route of Administration

Oral administration.

1.4 Sterile/Radioactive Statement

No information.

1.5 Qualitative and Quantitative Composition

Active ingredient: mycophenolate mofetil.

Each film-coated caplets contains 500 mg mycophenolate mofetil.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

CellCept is indicated for the prophylaxis of acute organ rejection and increased graft and patient survival in patients receiving allogeneic cardiac transplants. CellCept should be used concomitantly with ciclosporin and corticosteroids.

CellCept is indicated for induction and maintenance therapy of adult patients with WHO Class III, IV, V lupus nephritis. This indication is based on the evidence in literature reports of studies of treatment in patients with lupus nephritis, the majority of whom were ISN/RPS (2003) Class IV. The evidence for efficacy was based on surrogate endpoints.

2.2 Dosage and Administration

Transplant patients

Standard dosage for prophylaxis of renal rejection

The initial dose of CellCept should be given orally within 72 hours following transplantation. 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 compared to patients receiving 3 g per day of CellCept.

Standard dosage for prophylaxis of cardiac rejection

The initial dose of CellCept should given orally within 5 days following transplantation. A dose of 1.5 g administered twice a day (daily dose of 3 g) is recommended for use in cardiac transplant patients.

Oral administration (see 3.2.1 Pharmacokinetic Properties, Absorption)

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

Lupus nephritis patients

Standard Dosage for Induction Therapy

Adults: A dose of 750 mg–1.5 g administered orally twice a day (daily dose of up to 3 g) is recommended.

Standard Dosage for Maintenance Therapy

Adults: A dose of 500 mg–1 g administered orally twice a day is recommended.

CellCept should be used in combination with corticosteroids. Doses should be introduced gradually and adjusted according to clinical response. Therapeutic drug monitoring could help prevent sub-therapeutic exposure ($C_{\min} \geq 3.0$ mg/L or inter-dose AUC ≥ 35 h*mg/L).

2.2.1 Special Dosage Instructions

Patients with neutropenia

If neutropenia develops (absolute neutrophil count $< 1.3 \times 10^3/\mu\text{L}$), dosing with CellCept should be interrupted or the dose should be reduced (see 2.4 *Warnings and Precautions*).

Physician should perform appropriate diagnostic test, manage the patients appropriately.

Patients with severe renal impairment

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 mL/min/1.73 m²), outside of the immediate post-transplant period or after treatment of acute or refractory rejection, doses greater than 1 g administered twice a day should be avoided (see 2.4 *Warnings and Precautions*).

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

Patients with delayed renal graft function post-transplant

No dose adjustments are needed for renal patients experiencing delayed renal graft function post-operatively (see 3.2 *Pharmacokinetics Properties*).

Patients with severe hepatic impairment

No dose adjustments are needed for renal patients with severe hepatic parenchymal disease (see 3.2 *Pharmacokinetics Properties*).

For cardiac transplant patients and lupus nephritis patients with severe hepatic parenchymal disease, no data are available.

Elderly (≥ 65 years)

The recommended oral doses of 1 g b.i.d. for renal transplant patients and 1.5 g b.i.d. for cardiac transplant patients are appropriate for elderly patients (see 2.4 *Warnings and Precautions*).

For lupus nephritis patients, no recommendation is available.

Children

Safety and efficacy in pediatric patients have not been established. Very limited pharmacokinetic data are available for pediatric renal transplant patients. No data are available for pediatric patients receiving cardiac transplants.

2.3 Contraindications

Allergic reactions to CellCept have been observed. Therefore, CellCept is contraindicated in patients with hypersensitivity to mycophenolate mofetil or mycophenolic acid (MPA).

CellCept is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see 2.5.2 *Pregnancy*).

CellCept is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see 2.5.1 *Females and Males of Reproductive Potential*).

CellCept is contraindicated in women who are breastfeeding (see 2.5.3 *Lactation*).

2.4 Warnings and Precautions

2.4.1 General

Neoplasms

As in all patients receiving immunosuppressive regimens involving combinations of drugs, patients receiving CellCept as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see 2.6 *Undesirable Effects*). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

As with all patients at an increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections and sepsis (see 2.6 *Undesirable Effects*). Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation, or infections caused by polyomaviruses. Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. Cases of Progressive Multifocal Leukoencephalopathy (PML) associated with the JC virus, sometimes fatal, have been reported in CellCept treated patients. The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms 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. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

Blood and immune system

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; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also 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 instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Patients on CellCept should have complete blood counts weekly during the first month of treatment, twice monthly for the second and third months, then monthly through the first year. In particular, patients receiving CellCept should be monitored for neutropenia. The development of neutropenia may be related to CellCept, concomitant medications, viral infection or some

combination of these causes (see 2.2.1 *Special Dosage Instructions*). If neutropenia develops (absolute neutrophil count $< 1.3 \times 10^3/\mu\text{L}$), dosing with CellCept should be interrupted or the dose should be reduced and the patient carefully observed (see 2.2.1 *Special Dosage Instructions*).

Patients should not donate blood during therapy and for at least 6 weeks following discontinuation of CellCept.

Patients should be advised that during treatment with CellCept vaccinations may be less effective and the use of live attenuated vaccines should be avoided (see 2.4.5 *Interactions with Other Medicinal Products and Other Forms of Interaction*). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Gastro-intestinal

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 digestive system disease.

CellCept is an inosine monophosphate dehydrogenase (IMPDH) inhibitor; therefore it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Interactions

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation e.g. ciclosporin to others devoid of this effect e.g. sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Drugs which interfere with MPA's enterohepatic cycle (e.g. cholestyramine, antibiotics) should be used with caution due to their potential to reduce the plasma levels and efficacy of CellCept (see 2.4.5 *Interactions with Other Medicinal Products and Other Forms of Interaction*).

It is recommended that CellCept should not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied.

Special Populations

Elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary edema, compared with younger individuals (see 2.6 *Undesirable Effects*).

CellCept is contraindicated in pregnancy and during breastfeeding (see 2.5.2 *Pregnancy* and 2.5.3 *Lactation*).

Men should not donate semen during therapy and for 90 days following discontinuation of CellCept.

Administration of doses greater than 1 g twice daily to renal transplant patients with severe chronic renal impairment should be avoided (see 3.2 *Pharmacokinetic Properties* and 2.2.1 *Special Dosage Instructions*).

No dose adjustment is recommended for post-transplant patients with delayed renal graft function, but patients should be carefully monitored (see 3.2 *Pharmacokinetic Properties* and 2.2.1 *Special Dosage Instructions*). No data are available for cardiac transplant patients with severe renal impairment.

2.4.2 Drug Abuse and Dependence

No information.

2.4.3 Ability to Drive and Use Machines

No information.

2.4.4 Laboratory Tests

No information.

2.4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

Acyclovir: Higher MPAG (the phenolic glucuronide of MPA) and acyclovir plasma concentrations were observed when mycophenolate mofetil was administered with acyclovir than when the drugs were administered alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate and acyclovir or its prodrugs e.g. valacyclovir to compete for tubular secretion, further increasing the concentrations of both drugs.

Antacids and proton pump inhibitors (PPIs): Decreased mycophenolic acid (MPA) exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole were administered with CellCept. When comparing rates of transplant rejection or rates of graft loss between CellCept patients taking PPIs vs. CellCept patients not taking PPIs, no significant differences were seen. These data support extrapolation of this finding to all antacids because the reduction in exposure when CellCept was co-administered with magnesium and aluminium hydroxides is considerably lower than when CellCept was co-administered with PPIs. PPIs and antacids should be used with caution when co-administered with CellCept.

Cholestyramine: Following single-dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g three times daily of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA. Caution should be used during concomitant administration of drugs that interfere with enterohepatic circulation (see 2.4 *Warnings and Precautions*).

Ciclosporin A: Ciclosporin A (CsA) pharmacokinetics were unaffected by mycophenolate mofetil. However, CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30-50% in renal transplant patients treated with CellCept and CsA compared with patients receiving sirolimus or belatacept and similar doses of CellCept. Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which do not interfere with MPA's enterohepatic cycle (see 2.4 *Warning and Precautions*).

Drugs affecting glucuronidation

Concomitant administration of drugs inhibiting glucuronidation of MPA may increase MPA exposure (e.g. increase of MPA AUC_{0-∞} by 35% was observed with concomitant administration of isavuconazole). Caution is therefore recommended when administering these drugs concomitantly with CellCept.

Telmisartan: Concomitant administration of telmisartan and CellCept resulted in an approximately 30% decrease of mycophenolic acid (MPA) concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression which in turn results in an enhanced UGT1A9 expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between CellCept patients with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic DDI were seen. However, caution should be exercised when

CellCept is co-administered with telmisartan and monitoring of CellCept levels may be considered.

Ganciclovir: Based on the results of a single dose administration study of recommended doses of oral mycophenolate and i.v. ganciclovir and the known effects of renal impairment on the pharmacokinetics of MMF (see 3.2 *Pharmacokinetic Properties* and 2.4 *Warnings and Precautions*) and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and MMF dose adjustment is not required. In patients with renal impairment in which MMF and ganciclovir or its prodrugs e.g. valganciclovir are co-administered, patients should be monitored carefully.

Oral contraceptives: A study of co-administration of CellCept (1 g twice daily) and combined oral contraceptives containing ethinylestradiol (0.02-0.04 mg) and levonorgestrel (0.05-0.20 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. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of CellCept (see 2.5.1 *Female and Males of Reproductive Potential*).

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 drugs are administered concomitantly. Alternatively a change in antimycobacterial therapy might have to be considered.

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: Stable renal transplant patients receiving cyclosporin and CellCept (1 g twice daily) showed about a 30% increase in MPA plasma AUC and about a 20% decrease in MPAG plasma AUC when cyclosporin was replaced with tacrolimus. MPA C_{max} was not affected, while MPAG C_{max} was reduced by approximately 20%. The mechanism of this finding is not well understood. Increased biliary secretion of MPAG accompanied with increased enterohepatic recirculation of MPA may be partly responsible for the finding, since the elevation of MPA concentrations associated with tacrolimus administration was more pronounced in the later portions of the concentration-time profile (4-12 hours after dosing). For patients on tacrolimus, the dose of CellCept should not exceed 1 g twice a day. Patients should be carefully observed and managed appropriately.

In another study in renal transplant patients it was shown that the tacrolimus concentration did not appear to be altered by CellCept.

Antibiotics eliminating β -glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone, and penicillin classes of antibiotics) may interfere with MPAG/MPA enterohepatic recirculation thus leading to reduced systemic MPA exposure (see 2.4.1 *Warning and Precautions, Interactions*).

Information concerning the following antibiotics is available:

Ciprofloxacin or amoxicillin plus clavulanic acid: Reductions in pre-dose (trough) MPA concentrations of 54% have been reported in renal transplant recipients in the 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.

Norfloxacin and metronidazole: Norfloxacin in combination with metronidazole reduced the MPA AUC_{0-48} by 30% following a single dose of CellCept. No such effect on the systemic exposure of MPA with either of these antibiotics occurred when they were administered separately.

Trimethoprim/sulphamethoxazole: No effect on the systemic exposure of MPA (AUC , C_{max}) was seen with the combination trimethoprim/sulfamethoxazole.

Other interactions: Co-administration of probenecid with mycophenolate mofetil in monkeys raises the plasma AUC of MPAG 3-fold. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

Concomitant administration of sevelamer and CellCept in adults and pediatric patients decreased the MPA C_{max} and AUC_{0-12} by 30% and 25%, respectively. This data suggest 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 2.4 *Warnings and Precautions*).

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Fertility

CellCept is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see 2.3 *Contraindications*). Malformations (including anophthalmia, agnathia, and hydrocephaly) occurred in the first generation offspring of female rats treated with oral doses of mycophenolate mofetil in the absence of maternal toxicity (see 3.3.3 *Impairment of Fertility*). No effect was seen on the fertility of male rats treated with mycophenolate mofetil.

Pregnancy Testing

Prior to starting therapy with CellCept, female patients of childbearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL. A second test should be performed 8-10 days later.

Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Contraception

Females

CellCept is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see 2.3 *Contraindications*).

Before the start of treatment, female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning. Women of childbearing potential should use two reliable forms of contraception simultaneously, at least one of which must be highly effective, before beginning CellCept therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Males

Limited clinical evidence is currently available on paternal exposure to CellCept. This evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate.

Non-clinical evidence shows that the dose of mycophenolate that could be transferred via the seminal fluid to a potentially pregnant partner is 30-fold lower than the concentration without teratogenic effects in animals and 200-fold lower than the lowest teratogenic concentration in animals. However, genotoxic effects have been observed in animal studies at exposures exceeding the human therapeutic exposures by approximately 2.5-times. Thus, the risk of genotoxic effects on sperm cells cannot completely be excluded.

In absence of sufficient data to exclude a risk of harm to the fetus conceived during or directly after the treatment of the father, the following precautionary measure is recommended: sexually active male patients and/or their female partners are recommended to use effective contraception during treatment of the male patient and for at least 90 days after cessation of treatment.

2.5.2 Pregnancy

CellCept is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see 2.3 *Contraindications*). CellCept is a human teratogen, with an increased risk of spontaneous abortions (mainly in the first trimester) and congenital malformations in case of maternal exposure during pregnancy (see 2.6.2 *Undesirable Effects, Post Marketing*). In the medical literature, the risk of spontaneous abortions has been reported as 45 to 49% following mycophenolate mofetil exposure, compared to a reported rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants.

Congenital malformations (including multiple malformations in individual newborns) have been reported in 23 to 27% of live births in mycophenolate mofetil exposed pregnancies in published literature. For comparison the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4 to 5% in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.

The following malformations were most frequently reported postmarketing, in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants during pregnancy:

- 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).

These findings were consistent with teratology studies performed in rats and rabbits where fetal resorptions and malformations occurred in absence of maternal toxicity (see 3.3.4 *Teratogenicity*).

Labor and delivery: The safe use of CellCept during labor and delivery has not been established.

2.5.3 Lactation

It is not known whether the drug is excreted in human milk. Due to the potential for serious adverse reactions in nursing infants, CellCept is contraindicated during breastfeeding (see section 2.3 *Contraindication*).

Although the relevance to humans is unknown, studies in rats have shown mycophenolate mofetil to be excreted in milk.

2.5.4 Paediatric Use

See 2.2 *Dosage and Administration* and 3.2.6 *Pharmacokinetics in Special Populations*.

2.5.5 Geriatric Use

See 2.2 *Dosage and Administration* and 3.2.6 *Pharmacokinetics in Special Populations*.

2.5.6 Renal Impairment

See 2.2 *Dosage and Administration* and 3.2.6 *Pharmacokinetics in Special Populations*.

2.5.7 Hepatic Impairment

See 2.2 *Dosage and Administration* and 3.2.6 *Pharmacokinetics in Special Populations*.

2.6 Undesirable Effects

The safety profile presented in this section is based on data from both clinical trials and post marketing experience and has been shown to be consistent across transplant and lupus nephritis patient populations.

2.6.1 Clinical Trials

The principal adverse reactions associated with the administration of CellCept in the prevention of renal and cardiac transplant rejection in combination with cyclosporin and corticosteroids include diarrhea, leukopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infection, e.g. opportunistic infections (see 2.4 *Warnings and Precautions* and 3.1.2 *Clinical/Efficacy Studies*).

The safety profile of CellCept in patients treated for refractory renal transplant rejection was similar to that observed in three controlled trials for prevention of renal rejection at doses of 3 g per day. Diarrhea and leukopenia, followed by anemia, nausea, abdominal pain, sepsis, nausea and vomiting, and dyspepsia were the predominant adverse events reported more frequently in patients receiving CellCept in comparison to patients receiving i.v. corticosteroids.

Malignancies

As in patients receiving immunosuppressive regimens involving combinations of drugs, patients receiving CellCept as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see 2.4 *Warnings and Precautions*). Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g daily) in combination with other immunosuppressants in controlled clinical trials of renal and cardiac transplant patients followed for at least 1 year. Non-melanoma skin carcinoma occurred in 1.6% to 4.2% of patients; other types of malignancy occurred in 0.7% to 2.1% of patients. Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in the incidence of malignancy compared to the 1-year data.

In controlled trials of treatment of refractory renal rejection the lymphoma rate was 3.9% at an average follow-up of 42 months.

Opportunistic infections

All transplant patients are at increased risk of opportunistic infections, the risk increased with total immunosuppressive load (see 2.4 *Warnings and Precautions*). The most common opportunistic infections in patients receiving CellCept (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials of renal (2 g data) and cardiac transplant patients followed for at least 1 year were candida mucocutaneous, CMV viremia/syndrome and Herpes simplex. The proportion of patients with CMV viremia/syndrome was 13.5%.

Elderly patients (≥ 65 years)

Elderly patients (≥ 65 years), 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 hemorrhage and pulmonary edema, compared to younger individuals (see 2.4 *Warnings and Precautions*).

Safety profile of CellCept following oral administration

Adverse events reported in ≥ 10% and in 3–< 10% of patients treated with CellCept in controlled trials for prevention of renal transplant rejection (3 trials, 2 g and 3 g data) and one controlled cardiac transplant trial are listed in the following table.

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

Body System		Adverse Events Reported in Renal Transplant Patients (n=991)*	Adverse Events Reported in Cardiac Transplant Patients (n=289)**
Body as a whole	≥ 10%	asthenia, fever, headache, infection, pain (includes abdominal, back, and chest), edema, sepsis	asthenia, fever, chills, headache, infection, pain (includes abdominal, back, and chest), edema, sepsis
	3–< 10%	cysts (including lymphocele and hydrocele), enlarged abdomen, facial edema, flu syndrome, hemorrhage, hernia, malaise, pelvic pain	cellulitis, cysts (including lymphocele and hydrocele), enlarged abdomen, facial edema, flu syndrome, hemorrhage, hernia, malaise, neck pain, pallor, pelvic pain
Blood and lymphatic	≥ 10%	anemia (including hypochromic anemia), leucocytosis, leucopenia, thrombocytopenia	anemia (including hypochromic anemia), ecchymosis, leucocytosis, leucopenia, thrombocytopenia
	3–< 10%	ecchymosis, polycythemia	petechia, prothrombin time increased, thromboplastin time increased
Urogenital	≥ 10%	hematuria, renal tubular necrosis, urinary tract infection	abnormal kidney function (decrease in renal function, elevated serum creatinine), oliguria, urinary tract infection
	3–< 10%	albuminuria, dysuria, hydronephrosis, impotence, pyelonephritis, urinary frequency	dysuria, hematuria, impotence, nocturia, renal failure, urinary frequency, urinary incontinence, urinary retention
Cardio-vascular	≥ 10%	hypertension	arrhythmia, bradycardia, cardiac failure, hypertension, hypotension, pericardial effusion
	3–< 10%	angina pectoris, atrial fibrillation, hypotension, postural hypotension, tachycardia, thrombosis, vasodilatation	angina pectoris, arrhythmias (including supraventricular and ventricular extrasystoles, atrial flutter, supraventricular and ventricular tachycardias), atrial

Body System		Adverse Events Reported in Renal Transplant Patients (n=991)*	Adverse Events Reported in Cardiac Transplant Patients (n=289)**
			fibrillation, cardiac arrest, congestive heart failure, postural hypotension, pulmonary hypertension, syncope, vasospasm, venous pressure increased
Metabolic/ Nutritional	≥ 10%	hypercholesterolemia, hyperglycemia, hyperkalemia, hypokalemia, hypophosphatemia	acidosis (metabolic or respiratory), bilirubinemia, elevated BUN, elevated creatinine, elevated enzyme levels (lactic dehydrogenase, SGOT and SGPT), hypercholesterolemia, hyperglycemia, hyperkalemia, hyperlipemia, hyperuricemia, hypervolemia, hypokalemia, hypomagnesemia, hyponatremia, weight gain
	3-< 10%	acidosis (metabolic or respiratory), alkaline phosphatase increased, dehydration, elevated enzyme levels (gamma glutamyl transpeptidase, lactic dehydrogenase, SGOT and SGPT), elevated creatinine, hypercalcemia, hyperlipemia, hypervolemia, hypocalcemia, hypoglycemia, hypoproteinemia, hyperuricemia, weight gain	abnormal healing, alkaline phosphatase increased, alkalosis, dehydration, gout, hypocalcemia, hypochloremia, hypoglycemia, hypoproteinemia, hypophosphatemia, hypovolemia, hypoxia, respiratory acidosis, thirst, weight loss
Gastro-intestinal	≥ 10%	constipation, diarrhea, dyspepsia, nausea and vomiting, oral moniliasis	constipation, diarrhea, dyspepsia, flatulence, nausea and vomiting, oral moniliasis
	3-< 10%	elevated liver function tests (incl. AST, ALT), anorexia, flatulence, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, esophagitis, stomatitis	elevated liver function tests (incl. AST, ALT), anorexia, dysphagia, gastroenteritis, gingivitis, gum hyperplasia, jaundice, melena, esophagitis, stomatitis
Respiratory	≥ 10%	cough increased, dyspnea, pharyngitis, pneumonia, bronchitis	asthma, cough increased, dyspnea, pharyngitis, pleural effusion, pneumonia, rhinitis, sinusitis
	3-< 10%	asthma, pleural effusion, pulmonary edema, rhinitis, sinusitis	apnoea, atelectasis, bronchitis, epistaxis, hemoptysis, hiccup, neoplasm, pneumothorax, pulmonary edema, sputum increased, voice alteration
Skin and Appendages	≥ 10%	acne, herpes simplex	acne, herpes simplex, herpes zoster, rash
	3-< 10%	alopecia, benign neoplasm of skin, fungal dermatitis, herpes zoster, hirsutism, pruritus, skin carcinoma, skin hypertrophy (incl. actinic keratosis), sweating, skin ulcer, rash	benign neoplasm of skin, fungal dermatitis, hemorrhage, pruritus, skin carcinoma, skin hypertrophy, skin ulcer, sweating
Nervous	≥ 10%	dizziness, insomnia, tremor	agitation, anxiety, confusion, depression, dizziness, hypertonia, insomnia, paresthesia, somnolence, tremor
	3-< 10%	anxiety, depression, hypertonia,	convulsion, emotional lability,

Body System		Adverse Events Reported in Renal Transplant Patients (n=991)*	Adverse Events Reported in Cardiac Transplant Patients (n=289)**
		paresthesia, somnolence	hallucinations, neuropathy, thinking abnormal, vertigo
Musculo-skeletal	≥ 10%	–	leg cramps, myalgia, myasthenia
	3–< 10%	arthralgia, leg cramps, myalgia, myasthenia	arthralgia
Special Senses	≥ 10%	–	amblyopia
	3–< 10%	amblyopia, cataract, conjunctivitis	abnormal vision, conjunctivitis, deafness, ear pain, eye hemorrhage, tinnitus
Endocrine	≥ 10%	–	–
	3–< 10%	diabetes mellitus, parathyroid disorder (elevated PTH level)	diabetes mellitus, Cushing's syndrome, hypothyroidism

*(total n=1483) ** (total n=578)

In the three controlled trials for prevention of renal transplant rejection, patients receiving 2 g per day of CellCept demonstrated an overall better safety profile than did patients receiving 3 g CellCept.

2.6.1.1 Laboratory Abnormalities

No information.

2.6.2 Post Marketing

Infections:

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

Cases of Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, have been reported in CellCept treated patients. The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune function.

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.

Blood and Immune System:

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

Congenital disorders:

Congenital malformations have been reported post marketing in children of female patients exposed to CellCept in combination with other immunosuppressants during pregnancy (see 2.5.2 Pregnancy).

Pregnancy, puerperium and perinatal conditions:

Cases of spontaneous abortions have been reported in patients exposed to mycophenolate mofetil, mainly in the first trimester (see 2.5.2 Pregnancy).

Gastro-intestinal:

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

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

2.6.2.1 Laboratory Abnormalities

No information.

2.7 Overdose

Reports of overdoses with mycophenolate mofetil have been received from clinical trials and during post-marketing experience. In many of these cases no adverse events were reported. In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the drug.

It is expected that an overdose of mycophenolate mofetil could possibly result in over-suppression of the immune system and increase susceptibility to infections and bone marrow suppression (see 2.4 *Warnings and Precautions*). If neutropenia develops, dosing with CellCept should be interrupted or the dose reduced (see 2.4 *Warnings and Precautions*).

MPA cannot be removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 µg/mL), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, can remove MPA by increasing excretion of the drug (see 3.2 *Pharmacokinetic Properties*).

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. 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. CellCept is effective in the prophylaxis of organ rejection in patients receiving allogeneic renal transplants and in the prophylaxis of organ rejection in patients receiving allogeneic cardiac transplants.

3.1.2 Clinical/Efficacy Studies

Transplant studies

CellCept has been administered in combination with the following agents in clinical trials for the prevention of renal and cardiac rejection episodes: antithymocyte globulin, OKT3, ciclosporin and corticosteroids. CellCept has also been administered in combination with ciclosporin and corticosteroids for the treatment of refractory renal rejection episodes. Prior to treatment with CellCept, patients may have also received antilymphocyte globulin, antithymocyte globulin and OKT3. CellCept has further been used in clinical trials together with daclizumab and tacrolimus.

Prevention of organ rejection

The safety and efficacy of CellCept in combination with corticosteroids and ciclosporin for the prevention of organ rejection were assessed in renal transplant patients in three randomised, double-blind, multicentre trials and in cardiac patients in one randomised double-blind, multicentre trial.

Renal transplant

The three studies compared two dose levels of oral CellCept (1 g twice daily and 1.5 g twice daily) with azathioprine (2 studies) or placebo (1 study) when administered in combination with ciclosporin and corticosteroids to prevent acute rejection episodes.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced treatment failure within the first 6 months after transplantation (defined as biopsy-proven acute rejection on treatment or the occurrence of death, graft loss or early termination from the study for any reason without prior biopsy-proven rejection). CellCept was studied in the following three therapeutic regimens: (1) antithymocyte globulin induction/MMF or azathioprine/ciclosporin/corticosteroids, (2) MMF or azathioprine/ciclosporin/corticosteroids, and (3) MMF or placebo/ciclosporin/corticosteroids.

CellCept, in combination with corticosteroids and ciclosporin reduced (statistically significant at the < 0.05 level) the incidence of treatment failure within the first 6 months following transplantation. The following tables summarise the results of these studies. Patients who prematurely discontinued treatment were followed for the occurrence of death or graft loss, and the cumulative incidence of graft loss and patient death are summarised separately. Patients who prematurely discontinued treatment were not followed for the occurrence of acute rejection after termination. More patients receiving CellCept discontinued (without prior biopsy-proven rejection, death or graft loss) than discontinued in the control groups, with the highest rate in the CellCept 3 g/day group. Therefore, the acute rejection rates may be underestimates, particularly in the CellCept 3 g/day group.

**Renal Transplant Studies
Incidence of Treatment Failure
(Biopsy-proven Rejection or Early Termination for Any Reason)**

USA Study* (n=499 patients)	CellCept 2 g/day (n=167 patients)	CellCept 3 g/day (n=166 patients)	Azathioprine 1 to 2 mg/kg/day (n=166 patients)
All treatment failures	31.1%	31.3%	47.6%
Early termination without prior acute rejection**	9.6%	12.7%	6.0%
Biopsy-proven rejection episode on treatment	19.8%	17.5%	38.0%

* antithymocyte globulin induction/MMF or azathioprine/ciclosporin/corticosteroids

Europe/Canada/ Australia Study* (n=503 patients)	CellCept 2 g/day (n=173 patients)	CellCept 3 g/day (n=164 patients)	Azathioprine 100 to 150 mg/day (n=166 patients)
All treatment failures	38.2%	34.8%	50.0%
Early termination without prior acute rejection**	13.9%	15.2%	10.2%
Biopsy-proven rejection episode on treatment	19.7%	15.9%	35.5%

* MMF or azathioprine/ciclosporin/corticosteroids

Europe Study* (n=491 patients)	CellCept 2 g/day (n=165 patients)	CellCept 3 g/day (n=160 patients)	Placebo (n=166 patients)
All treatment failures	30.3%	38.8%	56.0%
Early termination without prior acute rejection**	11.5%	22.5%	7.2%
Biopsy-proven rejection episode on treatment	17.0%	13.8%	46.4%

* MMF or placebo/ciclosporin/corticosteroids

** Does not include death and graft loss as reason for early termination.

Cumulative incidence of 12-month graft loss and patient death are presented below. No advantage of CellCept with respect to graft loss and patient death was established. Numerically, patients receiving CellCept 2 g/day and 3 g/day experienced a better outcome than controls in all three studies; patients receiving CellCept 2 g/day experienced a better outcome than CellCept 3 g/day in two of the three studies. Patients in all treatment groups who terminated treatment early were found to have a poor outcome with respect to graft loss and patient death at 1 year.

Renal Transplant Studies Cumulative Incidence of Combined Graft Loss and Patient Death at 12 Months

Study	CellCept 2 g/day	CellCept 3 g/day	Control (Azathioprine or Placebo)
USA	8.5%	11.5%	12.2%
Europe/Canada/Australia	11.7%	11.0%	13.6%
Europe	8.5%	10.0%	11.5%

Cardiac transplant

A double-blind, randomised, comparative, parallel-group, multicentre study was performed in primary cardiac transplant recipients. The total number of patients enrolled was 650; 72 never received study drug and 578 received study drug. Patients received CellCept 1.5 g b.i.d. (n=289) or azathioprine 1.5 to 3 mg/kg/day (n=289), in combination with ciclosporin and corticosteroids as maintenance immunosuppressive therapy. The two primary efficacy endpoints were: (1) the proportion of patients who, after transplantation, had at least one endomyocardial biopsy-proven rejection with haemodynamic compromise, or were re-transplanted or died, within the first 6 months, and (2) the proportion of patients who died or were transplanted during the first 12 months following transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection for up to 6 months and for the occurrence of death for 1 year.

1. *Rejection*: No difference was established between CellCept and azathioprine (AZA) with respect to biopsy-proven rejection with haemodynamic compromise, as presented below.

	Rejection at 6 Months			
	All Patients		Treated Patients	
	AZA n=323	CellCept n=327	AZA n=289	CellCept n=289
Biopsy-proven rejection with haemodynamic compromise*	121 (38%)	120 (37%)	100 (35%)	92 (32%)

* Haemodynamic compromise occurred if any of the following criteria were met: pulmonary capillary wedge pressure ≥ 20 mm or a 25% increase; cardiac index < 2.0 L/min/m² or a 25% decrease; ejection fraction $\leq 30\%$; pulmonary artery oxygen saturation $\leq 60\%$ or a 25% decrease; presence of new S₃ gallop; fractional shortening was $\leq 20\%$ or a 25% decrease; inotropic support required to manage the clinical condition.

2. *Survival*: In the enrolled patients, there were no statistically significant differences between patients randomised to MMF and patients randomised to AZA for death and re-transplantation. In patients who received study drug, the lower limit of the 97.5% confidence interval of the difference of death and re-transplantation was 0.9 at 1 year, indicating that MMF was superior to AZA in these patients, as presented below.

	Death or Re-transplantation at 1 Year			
	All Patients		Treated Patients	
	AZA n=323	CellCept n=327	AZA n=289	CellCept n=289
Death or Re-transplantation	49 (15.2%)	42 (12.8%)	33 (11.4%)	18 (6.2%)
Weighted Treatment Difference	2.6%		5.3%	
Lower Limit of 97.5% one-sided Confidence Interval	-2.5%		+0.9%	

Lupus nephritis studies

Studies comparing the use of mycophenolate mofetil with intravenous cyclophosphamide (IVC) and azathioprine (AZA) in patients with proliferative lupus nephritis have been reported in the literature and a Cochrane review including over 5000 patients supports the use of MMF for induction and maintenance therapy (Tunncliffe D., 2018). Results from the two pivotal published studies with MMF in induction and maintenance therapy are given below:

The ALMs study (Appel et al., 2009) compared MMF and IVC as induction treatment for active lupus nephritis in a 24-week open-label parallel group multicenter study. 370 patients with Class III to V lupus nephritis were randomly assigned to a target dose of 3 g/day MMF or 0.5 to 1.0 g/m² IVC. Both groups received prednisone, tapered from a maximum starting dose of 60 mg/day. The primary endpoint was a pre-specified decrease in urine protein/creatinine ration and stabilization or improvement in serum creatinine. Secondary endpoints included complete renal remission, systemic disease activity and damage, and safety. No significant difference in response rate between the two groups was detected. The primary efficacy endpoint was achieved in 104 (56.2%) patients receiving MMF, compared with 98 (53.0%) patients receiving IVC. No significant differences were detected between the MMF and IVC groups with regards to the rates of adverse events, serious adverse events or infections.

Dooley et al., 2011 conducted a 36-month randomized, double-blind, double dummy study comparing MMF (2 g per day) plus placebo and AZA (2 mg per kg per day) plus placebo for the maintenance of remission in 227 patients who met the response criteria during the ALMS 6-month induction trial with either MMF or IVC. 116 patients were randomly assigned to MMF and 111 to AZA. The primary endpoint was the time to treatment failure measured as the time until the first event defined as death, end-stage renal disease, sustained doubling of the serum creatinine level, renal flare, or the need for rescue therapy. Secondary assessment included the time to the individual components of treatment failure and adverse events. MMF was superior to AZA with respect to the primary end point, time to treatment failure (hazard ratio, 0.04; 95% confidence interval, 0.25 to 0.77; p=0.003), and with respect to time to renal flare and time to rescue therapy (hazard ratio, < 1.00; p < 0.05). Observed rates of treatment failure were 16.4% (19 of 116 patients) in the MMF group and 32.4% (36 of 111) in the AZA. Adverse events, most commonly minor infections and gastrointestinal disorders, occurred in more than 95% of the patients in both groups (p=0.68). Serious adverse events occurred in 33.3% of the patients in the AZA group and in 23.5% of those in the MMF group (p=0.11), and the rate of withdrawal due to adverse events was higher with AZA than with MMF (39.6% vs. 25.2%, p=0.02).

3.2 Pharmacokinetic Properties

The pharmacokinetics of MMF have been studied in renal and cardiac transplant patients and in patients with lupus nephritis.

In general, the pharmacokinetic profile of MPA is similar in renal and in cardiac transplant patients.

The pharmacokinetic profile of MPA in lupus nephritis is similar to that reported in transplantation (including the high variability in exposure to active drug observed) but is complicated by more unpredictable changes in renal function in lupus nephritis patients.

3.2.1 Absorption

Following oral and intravenous administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic 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 quantitation (0.4 µg/mL).

Immediately post-transplant (< 40 days), renal and cardiac 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 values obtained following administration of 1 g twice daily intravenous CellCept at the recommended infusion rate to renal patients in the immediate post-transplant phase are comparable to those observed following oral dosing.

Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil administered at doses of 1.5 g twice daily to renal transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food.

Equivalence of oral dosage forms

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 has been shown to be bioequivalent to four 250 mg capsules (see 2.2 *Dosage and Administration*).

3.2.2 Distribution

Secondary increases in plasma MPA concentrations are usually observed at approximately 6-12 hours post-dose, consistent with enterohepatic recirculation. A reduction of approximately 40% in the AUC of MPA is associated with co-administration of cholestyramine (4 g three times daily), consistent with interruption of enterohepatic recirculation.

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

3.2.3 Metabolism

MPA is conjugated primarily by glucuronyltransferase (isoform UGT1A9) to form the inactive phenolic glucuronide of MPA (MPAG). *In vivo*, MPAG is converted back to free MPA via enterohepatic recirculation. A minor acylglucuronide (AcMPAG) is also formed. AcMPAG is pharmacologically active and is suspected to be responsible for some of MMF's side effects (diarrhea, leukopenia).

3.2.4 Elimination

Oral administration of radiolabelled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the dose recovered in the urine and 6% recovered in the faeces. Most (about 87%) of a dose is excreted in the urine as MPAG. A negligible amount of drug (< 1% of dose) is excreted as MPA in the urine.

At clinically encountered concentrations, MPA and MPAG are not removed by haemodialysis. However, at high MPAG concentrations (> 100 µg/mL), small amounts of MPAG are removed. By interfering with enterohepatic circulation of the drug, bile acid sequestrants, such as cholestyramine, reduce MPA AUC (see 2.7 *Overdose*).

MPA's disposition depends on several transporters. Organic anion-transporting polypeptides (OATPs) and multidrug resistance-associated protein 2 (MRP2) are involved in MPA's disposition; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with the glucuronides' biliary excretion. Multidrug resistance protein 1 (MDR1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney MPA and its metabolites potentially interact with renal organic anion transporters.

3.2.5 Pharmacokinetics in Special Populations

Patients with severe renal impairment

In a single-dose study (6 subjects per group), mean plasma MPA AUCs observed after oral dosing in subjects with severe chronic renal impairment (glomerular filtration rate < 25 mL/min/1.73m²)

were 28-75% higher than those observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single-dose MPAG AUC was 3- to 6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment and normal healthy subjects, consistent with the known renal elimination of MPAG.

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

There is also a paucity of information available for lupus nephritis patients with severe renal impairment. Therapeutic drug monitoring in lupus nephritis patients with GFR < 30 mL/min is advisable.

Patients with delayed renal graft function post-transplant

In patients with delayed renal graft function post-transplant, mean MPA AUC₀₋₁₂ was comparable to that seen in post-transplant patients without delayed renal graft function. There may be a transient increase in the free-fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of CellCept does not appear to be necessary (see 2.2.1 *Special Dosage Instructions*). Mean plasma MPAG AUC₀₋₁₂ was 2- to 3-fold higher than in post-transplant patients without delayed renal graft function.

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

Patients with hepatic impairment

Overall, the pharmacokinetics of MPA and MPAG were relatively unaffected by hepatic parenchymal disease in volunteers with alcoholic cirrhosis dosed with oral or intravenous MMF. Effects of hepatic disease on these processes probably depend on the particular disease. Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Elderly (≥ 65 years)

Pharmacokinetics in the elderly has not been formally evaluated.

3.3 Preclinical Safety

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended doses. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The nonclinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials which now provide safety data of more relevance to the patient population (see 2.6 *Undesirable Effects*).

3.3.1 Carcinogenicity

No information.

3.3.2 Mutagenicity

No information.

3.3.3 Impairment of Fertility

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 to 3 times the clinical exposure at the

recommended clinical dose of 2 g/day in renal transplant patients and 1.3–2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

3.3.4 Teratogenicity

In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels are approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients.

Refer to section 2.5.2 *Pregnancy*.

3.3.5 Other

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2–3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3–2 times the systemic exposure (AUC or C_{max}) observed in cardiac transplant patients at the recommended clinical dose of 3 g/day. Two genotoxicity assays (the mouse lymphoma/thymidine kinase assay and the mouse micronucleus aberration assay) indicated a potential of mycophenolate mofetil to cause chromosomal instability at severely cytotoxic dose levels. Other genotoxicity tests (the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay) did not demonstrate mutagenic activity.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage and shelf life

Store below 30°C, store in the original package.

This medicine should not be used after the expiry date (EXP) shown on the pack. See also outer pack for storage remark.

4.2 Special Instructions for Use, Handling and Disposal

CellCept oral administration

Mycophenolate mofetil has demonstrated teratogenic effects (see 2.5.2 *Pregnancy*), therefore CellCept tablets and capsules should not be crushed or opened. Patients should also avoid inhalation or contact of the skin or mucous membranes with the powder contained in CellCept capsules and oral suspension (before reconstitution). If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

Packs

Caplets 500 mg

Box, 5 blisters @ 10 film-coated caplets

Reg No. **DKIXXXX**

Medicine: keep out of reach of children

Obat: Jauhkan dari jangkauan anak-anak

On medical prescription only

Harus dengan resep dokter

Made by:

Delpharm Milano S.r.l.,

Segrate, Italy

Released by:

F. Hoffmann-La Roche Ltd.

Basel, Switzerland

Imported by:

PT **Menarini Indria Laboratories**

Bekasi, Indonesia

Distributed by:

PT Roche Indonesia

Jakarta, Indonesia

(This PI draft has been reviewed and approved for submission by Pramelita on 29-Apr-2021)

INFORMASI PRODUK UNTUK PASIEN

CELLCEPT **Mikofenolat mofetil** **Kaplet salut selaput** **500 mg**

Bacalah seluruh brosur ini dengan saksama sebelum Anda mulai menggunakan obat ini karena brosur ini berisi informasi yang penting bagi Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, apoteker atau perawat Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka serupa dengan penyakit Anda.
- Jika Anda mengalami efek samping, bicarakanlah dengan dokter, apoteker atau perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi di luar dari apa yang tercantum pada brosur ini. Lihat bagian 4.

Apa yang terdapat di dalam brosur ini

1. Apa itu CellCept dan kegunaannya
2. Apa yang perlu Anda ketahui sebelum mengonsumsi CellCept
3. Cara mengonsumsi CellCept
4. Efek samping yang mungkin terjadi
5. Cara penyimpanan CellCept
6. Isi kemasan dan informasi lainnya

1. Apa itu CellCept dan kegunaannya

Nama lengkap obat Anda adalah CellCept kaplet salut selaput 500 mg.

- Pada brosur ini digunakan nama singkat yaitu CellCept.

CellCept mengandung mikofenolat mofetil.

- Kandungan tersebut termasuk ke dalam golongan “imunosupresan”.

CellCept digunakan untuk:

- mencegah tubuh Anda menolak organ transplan (jantung)
- induksi dan pemeliharaan pada pengobatan penyakit lupus nefritis, pada orang dewasa

CellCept sebaiknya digunakan bersama obat lainnya:

- bersama siklosporin dan kortikosteroid untuk pencegahan penolakan transplan jantung
- bersama kortikosteroid untuk pengobatan lupus nefritis

2. Apa yang perlu Anda ketahui sebelum mengonsumsi CellCept

PERINGATAN

Mikofenolat menyebabkan cacat lahir dan keguguran. Jika Anda adalah perempuan yang memiliki potensi untuk hamil, Anda harus menunjukkan hasil tes kehamilan yang negatif sebelum memulai pengobatan dan harus menggunakan kontrasepsi seperti yang disarankan oleh dokter Anda.

Jangan mengonsumsi CellCept:

- Jika Anda alergi (memiliki hipersensitivitas) terhadap mikofenolat mofetil, asam mikofenolat, atau kandungan lain yang terdapat dalam obat ini (tercantum di bagian 6)
- Jika Anda adalah perempuan yang memiliki potensi untuk hamil dan tidak menunjukkan hasil negatif dari tes kehamilan sebelum menerima resep pertama, karena mikofenolat dapat menyebabkan cacat lahir dan keguguran
- Jika Anda sedang hamil atau sedang merencanakan kehamilan atau berpikir Anda sedang hamil
- Jika Anda tidak menggunakan kontrasepsi yang efektif (lihat bagian Kehamilan, kontrasepsi, dan menyusui)
- Jika Anda sedang menyusui

Jangan mengonsumsi obat ini jika salah satu kondisi di atas berlaku untuk Anda. Jika Anda tidak yakin, hubungi dokter, apoteker atau perawat Anda sebelum mengonsumsi CellCept.

Peringatan dan perhatian

Segera hubungi dokter Anda sebelum mengonsumsi CellCept:

- Jika Anda memiliki tanda infeksi, seperti demam atau sakit tenggorokan
- Jika Anda memiliki memar atau perdarahan yang tidak terduga
- Jika Anda pernah memiliki permasalahan dengan sistem pencernaan seperti tukak lambung
- Jika Anda berencana untuk hamil atau mengalami kehamilan ketika mengonsumsi CellCept

Jika salah satu kondisi di atas berlaku pada Anda (atau Anda tidak yakin), segera hubungi dokter Anda sebelum mengonsumsi CellCept.

Efek sinar matahari

CellCept menurunkan daya tahan tubuh Anda. Sebagai akibatnya, terdapat peningkatan risiko kanker kulit. Batasi jumlah sinar matahari dan sinar UV dengan cara:

- Memakai pakaian pelindung yang menutupi kepala, leher, lengan, dan tungkai
- Menggunakan tabir surya dengan faktor proteksi (SPF) yang tinggi

Obat lainnya dan CellCept

Segera hubungi dokter, apoteker atau perawat Anda jika Anda sedang menggunakan, belum lama telah menggunakan, atau mungkin akan menggunakan obat-obatan lainnya; termasuk obat yang didapat tanpa resep dan obat herbal. Hal ini karena CellCept dapat memengaruhi cara kerja obat lainnya. Selain itu, obat lain mungkin dapat memengaruhi cara kerja CellCept.

Secara khusus, hubungi dokter, apoteker atau perawat Anda jika Anda sedang mengonsumsi obat di bawah ini sebelum mulai mengonsumsi CellCept:

- azathioprin atau obat lainnya yang menekan sistem imun Anda – diberikan setelah operasi transplantasi
- kolestiramin – digunakan untuk menangani kolesterol tinggi
- rifampisin – antibiotik yang digunakan untuk mencegah dan mengobati infeksi seperti tuberkulosis (TBC)
- antasida atau penghambat pompa proton – digunakan untuk masalah asam lambung seperti gangguan pencernaan
- pengikat fosfat – digunakan pada pasien dengan gagal ginjal kronik untuk menurunkan kadar fosfat yang diserap darah
- antibiotik – digunakan untuk mengobati infeksi bakteri
- isavuconazol – digunakan untuk mengobati infeksi jamur
- telmisartan – digunakan untuk mengobati tekanan darah tinggi

Vaksin

Jika Anda membutuhkan vaksin (vaksin hidup) ketika mengonsumsi CellCept, hubungi dokter, apoteker atau perawat Anda terlebih dahulu. Dokter Anda yang akan menentukan vaksin yang dapat Anda gunakan.

Anda tidak boleh mendonorkan darah selama dalam pengobatan dengan CellCept dan paling tidak 6 (enam) minggu setelah penghentian pengobatan. Pasien laki-laki tidak boleh mendonasikan sperma atau air mani selama pengobatan dengan CellCept dan paling tidak 90 hari setelah penghentian pengobatan.

Konsumsi CellCept dengan makanan dan minuman

Konsumsi makanan dan minuman tidak memberikan pengaruh terhadap pengobatan CellCept Anda.

Kehamilan, kontrasepsi, dan menyusui

Kontrasepsi pada perempuan yang mengonsumsi CellCept

Jika Anda adalah perempuan yang memiliki potensi untuk hamil, Anda harus menggunakan metode kontrasepsi yang efektif selama pengobatan dengan CellCept. Hal tersebut termasuk:

- Sebelum Anda mulai mengonsumsi CellCept
- Selama masa pengobatan dengan CellCept
- Selama 6 minggu setelah menghentikan pengobatan CellCept

Konsultasikan dengan dokter Anda tentang kontrasepsi yang paling sesuai untuk Anda. Hal ini tergantung dari situasi individual Anda. Penggunaan dua jenis kontrasepsi lebih dianjurkan karena dapat menurunkan kemungkinan kehamilan yang tidak diinginkan. **Hubungi dokter Anda sesegera mungkin jika Anda berpikir bahwa kontrasepsi Anda mungkin tidak efektif atau Anda lupa mengonsumsi pil kontrasepsi.**

Anda dikategorikan sebagai perempuan yang tidak dapat hamil apabila kondisi berikut ada pada Anda:

- Anda sudah mengalami menopause, yaitu berusia paling tidak 50 tahun dan menstruasi terakhir Anda terjadi lebih dari 1 tahun lalu (jika menstruasi Anda berhenti karena pengobatan kanker, maka masih ada kemungkinan bagi Anda untuk dapat hamil)
- Kedua tuba falopi dan ovarium Anda sudah diangkat melalui operasi (salpingo-ooforektomi bilateral)
- Uterus/rahim Anda sudah diangkat melalui operasi (histerektomi)
- Kedua ovarium Anda sudah tidak berfungsi (kegagalan ovarium dini, yang sudah dikonfirmasi oleh spesialis ginekologi)
- Anda dilahirkan dengan kondisi langka dimana kehamilan tidak mungkin terjadi: genotipe XY, sindrom Turner, atau agensis uterus
- Anda adalah anak-anak atau remaja yang belum menstruasi

Kontrasepsi pada laki-laki yang mengonsumsi CellCept

Bukti yang saat ini ada tidak mengindikasikan terjadinya peningkatan risiko malformasi atau keguguran jika sang ayah yang mengonsumsi CellCept. Namun, risiko tidak dapat sepenuhnya diabaikan. Sebagai pencegahan, Anda atau pasangan perempuan Anda sebaiknya menggunakan metode kontrasepsi yang efektif selama pengobatan dan selama 90 hari setelah Anda berhenti dari pengobatan CellCept.

Jika Anda berencana untuk mempunyai anak, diskusikan dengan dokter Anda mengenai potensi risikonya.

Kehamilan dan menyusui

Jika Anda sedang hamil atau menyusui, berpikir bahwa Anda mungkin hamil atau sedang merencanakan kehamilan, hubungi dokter atau apoteker Anda sebelum memulai pengobatan. Dokter Anda akan memaparkan risiko jika terjadi kehamilan dan alternatif yang dapat Anda lakukan untuk pengobatan Anda jika:

- Anda merencanakan kehamilan
- Menstruasi Anda terlambat atau Anda merasa menstruasi Anda terlambat, atau Anda mengalami perdarahan menstruasi yang tidak biasa, atau Anda curiga bahwa Anda hamil
- Anda melakukan hubungan seksual tanpa menggunakan metode kontrasepsi yang efektif

Jika Anda menjadi hamil pada saat pengobatan dengan CellCept, Anda harus segera memberitahukan dokter Anda. Namun, tetaplah mengonsumsi CellCept sampai dengan jadwal Anda berkonsultasi.

Kehamilan

Mikofenolat sangat sering menyebabkan keguguran (50%) dan cacat lahir yang parah (23-27%) pada janin. Cacat lahir yang telah dilaporkan mencakup kelainan telinga, mata, wajah (bibir sumbing atau celah langit-langit), serta kelainan pada perkembangan jari, jantung, kerongkongan, ginjal, dan sistem saraf (contohnya spina bifida; ketika tulang pada tulang belakang tidak berkembang dengan baik). Bayi Anda mungkin dapat mengalami satu atau lebih dari kelainan tersebut.

Jika Anda perempuan yang memiliki potensi untuk hamil, Anda harus memberikan hasil tes kehamilan yang negatif sebelum memulai pengobatan dan harus mengikuti saran kontrasepsi yang diberikan dokter Anda. Dokter Anda mungkin meminta lebih dari satu tes untuk memastikan Anda tidak hamil sebelum memulai pengobatan.

Menyusui

Jangan mengonsumsi CellCept jika Anda sedang menyusui. Karena sejumlah kecil obat ini dapat tersalurkan ke air susu ibu (ASI).

Mengemudi dan menggunakan mesin

CellCept tidak memengaruhi kemampuan Anda untuk mengemudi ataupun menggunakan alat atau mesin.

3. Cara mengonsumsi CellCept

Selalu konsumsi CellCept sama seperti instruksi dokter. Anda harus memastikan kepada dokter, apoteker atau perawat Anda jika tidak yakin.

Jumlah yang harus dikonsumsi

Berikut adalah dosis yang lazim digunakan. Pengobatan akan berlanjut selama diperlukan untuk mencegah penolakan organ transplantasi.

Transplantasi ginjal

- Dosis pertama diberikan dalam rentang waktu 3 hari setelah operasi transplantasi
- Dosis harian adalah 4 kaplet (2 gram obat) yang dikonsumsi dalam 2 dosis terpisah
- Minum 2 kaplet di pagi hari dan 2 kaplet di malam hari.

Transplantasi jantung

- Dosis pertama diberikan dalam rentang waktu 5 hari setelah operasi transplantasi
- Dosis harian adalah 6 kaplet (3 gram obat) yang dikonsumsi dalam 2 dosis terpisah.
- Minum 3 kaplet di pagi hari dan 3 kaplet di malam hari.

Lupus nefritis

- Dosis harian untuk induksi adalah hingga 3-6 kaplet (dosis harian maksimum 3 gram) yang dikonsumsi dalam 2 dosis terpisah (minum 2 atau 3 kaplet di pagi hari dan 1 atau 3 kaplet di malam hari)
- Dosis harian untuk pemeliharaan adalah 2-4 kaplet (dosis harian maksimum 2 gram) yang dikonsumsi dalam 2 dosis terpisah (minum 1 atau 2 kaplet di pagi hari dan 1 atau 2 kaplet di malam hari)

Dosis untuk anak

Belum terdapat data keamanan dan khasiat yang cukup terkait penggunaan CellCept pada anak.

Cara minum obat

- Telan kaplet secara utuh dengan segelas air
- Jangan membelah atau menggerus kaplet tersebut

Jika Anda mengonsumsi CellCept lebih dari yang seharusnya

Jika Anda mengonsumsi CellCept lebih dari yang seharusnya, segera hubungi dokter atau pergi ke rumah sakit. Lakukan hal yang sama ketika ada seseorang yang tidak sengaja menelan obat tersebut. Selalu bawa kemasan obat bersama Anda.

Jika Anda lupa mengonsumsi CellCept

Jika Anda lupa mengonsumsi obat ini, segeralah konsumsi begitu Anda ingat. Lalu, lanjutkan konsumsi pada waktu biasa. Jangan mengonsumsi dosis dua kali lipat untuk mengganti dosis yang terlupakan.

Jika Anda berhenti mengonsumsi CellCept

Jangan berhenti mengonsumsi CellCept kecuali jika dokter meminta Anda untuk berhenti.

Untuk pasien penerima transplant: Jika Anda menghentikan pengobatan, Anda dapat meningkatkan risiko penolakan organ transplantasi.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan produk ini, tanyakan pada dokter, apoteker, atau perawat Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat, CellCept dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya.

Segera hubungi dokter jika Anda mengetahui atau merasakan adanya efek samping serius seperti di bawah ini – Anda mungkin memerlukan pengobatan segera:

- Anda mengalami tanda infeksi seperti demam atau sakit tenggorokan
- Anda mengalami memar atau perdarahan yang tidak terduga
- Anda mengalami ruam, bengkak pada wajah, bibir, lidah, atau tenggorokan dengan kesulitan bernafas – Anda mungkin memiliki reaksi alergi serius pada obat ini (seperti anafilaksis, angioedema)

Masalah yang umum terjadi

Masalah yang lebih umum terjadi antara lain diare, penurunan jumlah sel darah putih atau sel darah merah, infeksi, nyeri pada perut, mual, muntah, dan gangguan asam lambung. Dokter Anda akan melakukan tes darah rutin untuk memeriksa perubahan pada:

- Jumlah sel darah Anda
- Jumlah zat lain pada darah Anda, seperti kadar gula, lemak, atau kolesterol

Melawan infeksi

CellCept menurunkan sistem pertahanan tubuh Anda. Untuk pasien penerima transplant, hal ini untuk mencegah tubuh Anda menolak organ transplantasi. Sebagai akibatnya, tubuh Anda tidak dapat melawan infeksi sebaik biasanya. Hal ini memungkinkan Anda mendapat infeksi lebih sering daripada biasanya. Hal ini termasuk infeksi pada otak, kulit, mulut, lambung dan usus, paru-paru, dan saluran kemih.

Kanker kelenjar getah bening dan kulit

Seperti yang dapat terjadi pada pasien yang mengonsumsi obat jenis ini (imunosupresan), terdapat pasien CellCept dengan jumlah yang sangat sedikit yang mengalami kanker pada kelenjar getah bening dan kulit.

Efek samping umum yang tidak diinginkan

Anda mungkin mengalami efek samping umum di seluruh tubuh Anda, termasuk reaksi alergi serius (seperti anafilaksis, angioedema), demam, merasa sangat lelah, sakit kepala, nyeri (misalnya pada perut, dada, sendi dan punggung), sakit kepala, gejala seperti flu, dan bengkak.

Efek lain yang tidak diinginkan meliputi:

Masalah kulit misalnya:

- jerawat, herpes mulut/oral, sinanaga (herpes zoster), pertumbuhan kulit, kerontokan rambut, ruam, gatal.

Masalah saluran kemih seperti:

- masalah ginjal atau rasa sangat ingin berkemih.

Masalah sistem pencernaan dan mulut seperti:

- pembengkakan gusi dan luka pada mulut (seriawan),
- radang pada pankreas, usus besar, atau lambung,
- masalah usus termasuk perdarahan, masalah hepar/hati,
- konstipasi, mual, gangguan pencernaan, kehilangan nafsu makan, kembung/sering buang gas.

Masalah sistem saraf seperti:

- merasa pusing, mengantuk, atau mati rasa,
- gemetar (tremor), spasme otot, kejang,
- merasa cemas atau depresi, perubahan suasana hati atau pikiran.

Masalah jantung dan pembuluh darah seperti:

- perubahan tekanan darah, detak jantung yang tidak biasa, pelebaran pembuluh darah.

Masalah paru-paru seperti:

- pneumonia, bronkitis,
- sesak napas, batuk, yang bisa disebabkan oleh bronkiektasis (kondisi dimana saluran napas dalam paru-paru melebar secara abnormal) atau fibrosis paru (luka pada paru-paru). Hubungi dokter Anda jika Anda mengalami batuk terus-menerus atau sulit bernapas;
- cairan dalam paru-paru atau rongga dada,
- masalah sinus.

Masalah lainnya seperti:

- penurunan berat badan, asam urat (gout), peningkatan gula darah, perdarahan, memar.

Pelaporan efek samping

Apabila Anda mengalami efek samping apapun, hubungi dokter, apoteker, atau perawat Anda. Hal ini termasuk semua efek samping lainnya yang tidak tercantum dalam brosur ini. Dengan melaporkan efek samping, Anda dapat membantu menyediakan informasi tambahan terkait keamanan obat ini.

Anda juga dapat melaporkan efek samping secara langsung melalui:

PT Roche Indonesia – Local Safety Unit

Email: Indonesia.safety@roche.com

Tel: 0-800-140-1579 (bebas pulsa)

Pusat Farmakovigilans

c.q. Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor, dan Zat Adiktif

Badan Pengawas Obat dan Makanan Republik Indonesia

Melalui pos: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: pv-center@pom.go.id

Tel: +62-21-4244691 Ext. 1079

Website: <https://e-meso.pom.go.id/>

5. Cara penyimpanan CellCept

- Jauhkan dari pandangan dan jangkauan anak-anak
- Jangan minum kaplet setelah melewati tanggal kedaluwarsa yang tertera pada dus setelah tulisan “EXP”. Tanggal kedaluwarsa tersebut mengacu pada hari terakhir pada bulan tersebut.
- Jangan simpan pada suhu lebih dari 30°C.
- Simpan di dalam dus untuk mencegah obat terpapar cahaya
- Obat tidak boleh dibuang melalui sistem pembuangan limbah rumah tangga. Tanyakan pada apoteker Anda bagaimana cara pembuangan obat yang sudah tidak digunakan lagi. Upaya-upaya ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

CellCept kaplet salut selaput mengandung

- Zat aktif berupa mikofenolat mofetil.
- Bahan-bahan lainnya yaitu:
 - ✓ Inti kaplet: selulosa mikrokristalin, polividon (K-90), natrium kroskarmelosa, magnesium stearat
 - ✓ Selaput kaplet: hidroksipropil metilselulosa, hidroksipropil selulosa, titanium dioksida (E171), polietilen glikol 400, *indigo carmine aluminium lake* (E132), *red iron oxide* (E172).

Tampilan CellCept dan isi dalam kemasan

- Kaplet CellCept berwarna lavender (ungu) dan berbentuk kaplet. Terdapat tulisan “CellCept 500” yang terukir pada satu sisi dan “Roche” pada sisi lainnya
- Tersedia dalam kemasan 50 kaplet (dikemas dalam blister masing-masing berisi 10 kaplet)

Kemasan

Dus, 5 blister @ 10 kaplet

Nomor izin edar: **DKIXXXXXX**

Obat: jauhkan dari jangkauan anak-anak
Harus dengan Resep Dokter

Diproduksi oleh:

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Segrate, Italia

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Basel, Swiss

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PT **Menarini Indria Laboratories**
Bekasi, Indonesia

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Jakarta, Indonesia

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