CellCept®

Mycophenolate mofetil

COMPOSITION

Active substance: mycophenolate mofetil (MMF).

Excipients:

Capsules: croscarmellose sodium (produced from genetically modified cotton), colorant E132, excipients for capsules.

Film-coated tablets: croscarmellose sodium (produced from genetically modified cotton), colorant E132, excipients for coated tablets.

Lyophilized powder for solution for infusion:

Freeze-dried product: polysorbate 80 (produced from genetically modified maize), citric acid, sodium chloride, per vial.

PHARMACEUTICAL FORM AND QUANTITY OF ACTIVE SUBSTANCE PER UNIT

250 mg capsules.

500 mg film-coated tablets.

Lyophilized powder for solution for infusion: Vial containing 500 mg powder; the prepared infusion solution contains 6 mg/ml.

INDICATIONS AND POTENTIAL USES

CellCept is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

DOSAGE AND ADMINISTRATION

The first CellCept dose should be administered as soon as possible after renal, cardiac or hepatic transplantation.

The solution for infusion may be used in renal and hepatic transplantation instead of the oral forms over a period of up to 14 days. The administration of CellCept capsules or film-coated tablets should begin as soon as oral medication of the patient is possible.

Intravenous administration

Caution: CellCept i.v. solution must not be intravenously administered by rapid infusion or bolus injection.

Renal and hepatic transplant

Adults:

The recommended dose for renal and hepatic transplant patients is 1 g twice daily (daily dose 2 g).

The first dose of CellCept i.v. should be given within 24 hours after transplantation. After reconstitution as a 6 mg/ml solution, CellCept i.v. must be administered as a slow intravenous infusion over a 2-hour period. The suitable infusion rate is approximately 84 ml/hour.

Caution: The CellCept i.v. solution must never be administered intravenously by rapid infusion or bolus injection. The recommended infusion duration of 2 hours should be observed (infusion pump).

In renal transplant rejection, dose reduction or discontinuation is unnecessary. No pharmacokinetic data are available in hepatic transplant rejection.

Children and adolescents:

No data on intravenous administration are available for pediatric patients.

Oral administration

Renal transplant

Adults:

The best therapeutic benefit-risk ratio is observed with a daily dose of 2 g (4 capsules or 2 film-coated tablets twice daily). A daily dose of 2 g is generally recommended for renal transplant patients. Where a higher level of immunosuppression appears warranted in selected patients, a daily CellCept dose of 3 g (6 capsules or 3 film-coated tablets twice daily) can be given.

No dose adjustment is required in patients with delayed post-operative renal graft function. However, patients should be carefully monitored (see *Pharmacokinetics*). In renal transplant rejection, no changes occur in the pharmacokinetics of mycophenolic acid (MPA) that make it necessary to reduce the dose or discontinue administration.

Children and adolescents (age 3 months to 18 years):

The recommended dose of mycophenolate mofetil is 600 mg/m^2 administered orally twice daily (up to a maximum daily dose of 2 g).

When the solid oral dosage forms are used, patients with a body surface area of 1.25 to 1.5 m^2 may be treated with CellCept capsules at a dose of 750 mg twice daily (daily dose: 1.5 g). Patients with a body surface area >1.5 m^2 may be treated with CellCept capsules or film-coated tablets at a dose of 1 g twice daily (daily dose 2 g).

Cardiac transplant

Adults:

The recommended dose for cardiac transplant patients is 1.5 g twice daily (daily dose 3 g). In cardiac transplant rejection there is no reason for dose correction.

Children and adolescents:

No data are available for pediatric cardiac transplant patients.

Hepatic transplant

Adults:

The recommended dose for hepatic transplant patients is 1.5 g twice daily (daily dose 3 g). No pharmacokinetic data are available in hepatic transplant rejection.

Children and adolescents:

No data are available for pediatric hepatic transplant patients.

Directions for use

It is recommended that oral dosage forms of CellCept be taken on an empty stomach. Patients with a stable renal graft can take CellCept with food (see *Pharmacokinetics*).

Preparation of the infusion solution: see *Additional information.*

Special dosage instructions

Renal impairment

In cardiac or hepatic transplant patients with severe chronic renal failure, CellCept should be used only if the expected benefit outweighs the potential risk. No data are available in these patients.

Renal transplant recipients with severe chronic renal failure (glomerular filtration rate <25 ml/min/1.73 m^2) who were given single oral doses of CellCept had higher AUC values for plasma MPA and MPA glucuronide (MPAG) than patients with more minor renal impairment or healthy subjects. Such renal transplant recipients should not be treated with CellCept doses higher than 1 g twice daily and must be carefully monitored.

Hepatic impairment

Dose adjustment is unnecessary in renal transplant recipients with severe parenchymal liver disease.

No data are available on cardiac transplant recipients with severe parenchymal liver disease.

Myelosuppression

If neutropenia occurs (absolute neutrophil count [ANC] $<1.3\times10^3/\mu l$), CellCept must be discontinued or its dose reduced. Appropriate diagnostic tests should also be performed and treatment given, if required.

Elderly

In elderly patients the same dose is recommended as in adults. Patients in this age group are at increased risk of side effects (see *Undesirable effects*).

CONTRAINDICATIONS

Hypersensitivity to mycophenolate mofetil, mycophenolic acid or any of the constituents excipients; pregnancy.

WARNINGS AND PRECAUTIONS

Caution: CellCept i.v. solution must not be intravenously administered by rapid or bolus injection.

Neoplasms

Patients receiving CellCept as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to depend more on the intensity and duration of the immunosuppression than on the use of a particular drug. As in all patients at increased risk of skin cancer, sun and ultraviolet exposure should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Oversuppression of the immune system may also increase susceptibility to infection, including opportunistic infections, fatal infections and sepsis (see *Undesirable effects*).

In the three controlled studies of rejection prophylaxis after renal transplantation, the incidence of fatal infections was similar in patients receiving CellCept or the control treatment in combination with other immunosuppressants (<2%). In the controlled study on rejection prophylaxis following cardiac transplantation, fatal infections occurred in 1.7% of patients treated with CellCept and 3.8% treated with azathioprine in combination with other immunosuppressants.

In cardiac transplant patients treated with CellCept, herpes virus infections (*Herpes simplex*, *Herpes zoster* and cytomegalovirus [CMV]) were more frequent than in patients receiving azathioprine (see *Undesirable effects*).

Herpes simplex infections were also more frequent in hepatic patients treated with CellCept than in those treated with azathioprine.

Such infections include latent viral reactivation, such as hepatitis B or C reactivation, or infections caused by polyomaviruses. Cases of hepatitis due to hepatitis B or C reactivation have been reported in carrier patients treated with immunosuppressants. Cases of JC virus-associated progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with CellCept.

A causal relationship between PML and mycophenolate mofetil cannot be clarified because of other factors such as the underlying disease, immunosuppressant comedication and latency period. However, the possibility cannot be excluded that mycophenolate mofetil plays a role. In immunosuppressed patients who develop

neurological symptoms, physicians should therefore consider PML in the differential diagnosis.

BK virus nephropathy has been reported with the use of CellCept in renal transplant recipients. Such infection carries serious risks, resulting in some cases in loss of the renal graft. Appropriate patient monitoring can help to identify those at risk of developing BK virus nephropathy. In patients with evidence of BK virus nephropathy, a reduction in immunosuppressive effect should be considered.

Blood and immune system

A cumulative analysis of cases reported with CellCept included a small number of cases of pure red cell aplasia (PRCA), mainly in kidney or pancreas transplant recipients who had been treated with CellCept in combination with other immunosuppressants. In some patients the red cell count recovered after dose reduction or cessation of CellCept therapy. However, the immunosuppressive regimen should be modified only with great caution in transplant patients to avoid endangering the graft.

Patients treated with CellCept must be told to report immediately any evidence of infection or any unusual bruising, bleeding or other symptoms of bone marrow aplasia.

Up to 1.5% of renal transplant recipients treated with CellCept for rejection prophylaxis developed severe neutropenia (ANC <500/µl).

Up to 2.8% of cardiac transplant recipients receiving CellCept 3 g daily and no patients (0%) receiving azathioprine developed severe neutropenia.

Neutropenia may be caused by CellCept, concomitant medication, a viral infection or a combination of these factors.

In patients receiving CellCept the neutrophil count should be monitored and CellCept discontinued or its dose reduced as appropriate (see Special dosage instructions). Complete blood counts should be performed weekly during the first month of treatment, twice monthly in the second and third months, then once monthly for the first year.

Cases of hypogammaglobulinemia with recurrent infections have been reported in patients receiving CellCept in combination with other immunosuppressants. Patients showing recurrent infections should have their serum IgG levels measured and treatment adjusted, if required. In some cases, IgG levels returned to normal after a switch from CellCept to an alternative immunosuppressive therapy.

Patients should be advised that during treatment with CellCept, vaccinations may be less effective and that the use of live vaccines should be avoided (see *Interactions*).

Gastrointestinal tract

As CellCept has been implicated in an increased incidence of digestive system undesirable effects, including gastrointestinal ulcers, hemorrhage and perforation, it should be administered with caution in patients with severe gastrointestinal disease.

CellCept is an inosine monophosphate dehydrogenase (IMPDH) inhibitor, it should therefore be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine

phosphoribosyltransferase (HGPRT) such as Lesch-Nyhan or Kelley-Seegmiller syndrome.

Interactions

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants that interfere with MPA enterohepatic recirculation (e.g. ciclosporin) to others devoid of this effect (e.g. sirolimus or belatacept), or vice versa, as this might lead to changes in MPA exposure. Drugs of other classes which interfere with MPA's enterohepatic cycle (e.g. colestyramine) should be administered with caution due to their potential to reduce the plasma concentration and efficacy of CellCept.

It is recommended that CellCept not be coadministered with azathioprine since both products may cause bone marrow aplasia and their coadministration has not been studied.

Special patient populations

Elderly patients may have a higher risk of side effects than younger patients, for example an increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal hemorrhage and pulmonary edema (see *Undesirable effects*).

There have been reports of congenital malformations. For further information on use during pregnancy and lactation (see *Pregnancy and lactation*).

INTERACTIONS

Aciclovir, probenecid and other drugs subject to active tubular secretion: Aciclovir and its prodrugs (e.g. valaciclovir), probenecid and other drugs actively secreted by the tubules may compete with MPAG for tubular secretion. Coadministration of aciclovir and mycophenolate mofetil increases the AUC of MPAG by 8.6% and that of aciclovir by 17.4%. The presence of renal impairment may further increase the concentration of both substances.

Coadministration of probenecid and mycophenolate mofetil in monkeys results in a threefold increase in MPAG AUC.

Patients receiving mycophenolate mofetil in combination with other medicinal products subject to active tubular secretion must be closely supervised.

Ganciclovir: Based on the results of a single-dose administration study of recommended doses of oral mycophenolate mofetil and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of mycophenolate mofetil (MMF) (see *Pharmacokinetics*) and ganciclovir, it is anticipated that coadministration of these agents (which compete for renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is expected and MMF dose adjustment is not required. Patients with renal impairment cotreated with MMF and ganciclovir or its prodrugs (e.g. valganciclovir) must be carefully monitored.

Magnesium and aluminium hydroxide containing antacids and proton pump inhibitors (PPIs): Coadministration of CellCept with PPIs, including lansoprazole and pantoprazole, has been reported to decrease mycophenolic acid (MPA) exposure by up to

30% and Cmax by up to 60%. In a clinical trial of kidney transplant recipients and in an analysis of epidemiological data, the rates of acute rejection and graft loss were comparable between CellCept patients who were taking PPIs and those not taking PPIs.

This clinical observation can be extrapolated to magnesium and aluminium hydroxide antacids since the reduction in exposure is considerably less when CellCept is coadministered with these agents.

Colestyramine or other medicinal products that interfere with enterohepatic recirculation: Decreased absorption and interruption of enterohepatic recirculation by colestyramine reduces the mycophenolic acid AUC by 40%. Colestyramine or other medicinal products that interfere with enterohepatic recirculation, such as antibiotics, should be used only if mycophenolic acid levels are closely monitored, as the efficacy of CellCept may be reduced.

Ciclosporin A: The pharmacokinetics of ciclosporin A were unaffected by mycophenolate mofetil. However, ciclosporin A does interfere with enterohepatic recirculation of MPA. Thus, coadministration of CellCept with ciclosporin A in renal transplant patients reduced MPA exposures by 30–50% compared to patients receiving sirolimus or belatacept and comparable doses of CellCept.

Conversely, changes of MPA exposure should be expected when switching patients from ciclosporin A to one of the immunosuppressants that do not interfere with MPA's enterohepatic cycle.

Telmisartan: Concomitant administration of telmisartan and CellCept resulted in an approximately 30% decrease in mycophenolic acid (MPA) concentration. Telmisartan changes MPA 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 and loss or adverse event profiles between CellCept patients with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic drug-drug interaction were seen.

Oral contraceptives: The pharmacokinetics of oral contraceptives are unaffected by coadministration of CellCept. A study of coadministration 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 three 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 (see *Pregnancy and lactation*).

Rifampicin: A 70% decrease in mycophenolic acid exposure ($AUC_{0–12}$) was observed after dose-related correction in a single patient (a heart-lung transplant recipient) cotreated with rifampicin. It is therefore recommended that mycophenolic acid exposure be monitored and CellCept doses adjusted to maintain clinical efficacy when coadministering both medicinal products.

Tacrolimus: Coadministration of tacrolimus and 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 is not altered by CellCept.

However, in well-controlled hepatic transplant patients there was an increase of approximately 20% in tacrolimus AUC when multiple doses of CellCept (1.5 g twice daily) were administered to patients taking tacrolimus.

Trimethoprim/sulfamethoxazole, norfloxacin and metronidazole: 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: A 54% reduction in predose (trough) MPA concentrations has been observed in renal graft recipients during the period immediately after oral dosing with ciprofloxacin or amoxicillin plus clavulanic acid. This effect tends to decrease as the antibiotic treatment continues and it disappears after the antibiotic treatment is withdrawn. It is recommended that MPA exposure be monitored and CellCept doses adjusted to maintain clinical efficacy when the two products are coadministered.

Phosphate binders: Coadministration of sevelamer and CellCept decreased the MPA C_{max} and $AUC_{0–12}$ by 30% and 25%, respectively. Sevelamer and other phosphate binders should therefore preferably be given 2 hours after CellCept ingestion.

Live vaccines: Live vaccines should not be given to patients with an impaired immune response, as antibody production against vaccines could be decreased.

PREGNANCY AND LACTATION

CellCept is contraindicated in pregnancy.

Adverse effects on fetal development (including malformations) were observed in rats and rabbits at doses below those associated with maternal toxicity and below the recommended clinical dose.

No studies have been conducted in pregnant women.

Studies in rats have shown that mycophenolate mofetil is excreted in the milk. It is not known whether this is also true in humans. Breast-feeding should therefore be discontinued.

Congenital disorders: Congenital malformations including ear, facial, cardiac and nervous system malformations have been reported post-marketing in children of patients treated with MMF in combination with other immunosuppressants during pregnancy. Cases of spontaneous abortion have also been reported, particularly after first-trimester exposure to MMF.

Women of child-bearing age should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/ml within 1 week prior to beginning therapy. It is recommended that CellCept therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained.

Effective contraception must be used before beginning therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy (see *Interactions*).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

UNDESIRABLE EFFECTS

Clinical experience

The principal side effects associated with the administration of CellCept in the prevention of renal, cardiac and hepatic transplant rejection in combination with ciclosporin and corticosteroids are diarrhea, leukopenia, sepsis and vomiting. There is also evidence of an increased incidence of certain infections, e.g. opportunistic infections.

Controlled trials of mycophenolate mofetil in the prevention of rejection after renal transplantation showed an overall better tolerability profile with daily doses of 2 g rather than 3 g.

Malignancies

Patients receiving CellCept as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see *Warnings and precautions*).

Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g) with other immunosuppressants in controlled clinical trials of renal, cardiac and hepatic transplant patients followed for at least one year.

In controlled trials on the prophylaxis of rejection after renal transplantation the lymphoma rate was 3.9% in a mean follow-up of 42 months.

Non-melanoma skin cancers 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 incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year but less than 3 years.

Opportunistic infections

All transplant recipients are at increased risk of opportunistic infections, and this risk increases with total immunosuppressive load.

In renal and hepatic transplant patients the overall incidence of opportunistic infections was similar in patients treated with CellCept and azathioprine.

In cardiac transplant recipients the overall incidence of opportunistic infections on CellCept was about 10% higher than on azathioprine.

The most common opportunistic infections in renal, cardiac and hepatic transplant patients receiving CellCept (2 g or 3 g daily) and followed for at least 1 year were mucosal candidiasis, CMV viremia/syndrome and *Herpes simplex*. The proportion of patients with CMV viremia/syndrome was 13.5%.

Sepsis (generally due to CMV) occurred somewhat more often in renal transplant recipients treated with CellCept than in control patients, and was somewhat more frequent on treatment with 3 g daily than on 2 g daily. In the controlled cardiac transplantation study, no difference in the incidence of sepsis was observed between patients treated with CellCept and controls.

Among patients treated with CellCept to prevent renal transplant rejection, the incidence of fatal infections was similar to that on the comparison drug (<2%), the treatment in both cases being administered in combination with other immunosuppressants.

In the controlled study of cardiac transplant rejection prophylaxis, fatal infection or sepsis occurred in 1.7% of patients treated with CellCept and 3.8% of those receiving azathioprine, in each case combined with other immunosuppressants.

Urinary tract infections were frequently observed after renal transplantation in all treatment groups, though more often on CellCept than azathioprine or placebo.

Gastrointestinal side effects

In renal and cardiac transplant recipients, diarrhea occurred more commonly on treatment with CellCept than on azathioprine or placebo. Vomiting was also somewhat more frequent in these two patient groups. These gastrointestinal side effects occurred more often in renal transplant recipients receiving 3 g daily than in those on 2 g daily.

Myelosuppression

Leukopenia occurred more commonly in renal transplant recipients taking CellCept than in the control groups; it was most common in patients receiving 3 g mycophenolate mofetil per day.

By contrast, leukopenia in cardiac transplant recipients occurred more frequently on azathioprine than on treatment with CellCept.

Up to 1.5% of renal transplant recipients given CellCept to prevent graft rejection developed severe neutropenia (ANC <500/µl).

Following cardiac transplantation, severe neutropenia was observed in up to 2.8% of patients treated with CellCept 3 g daily to prevent graft rejection and in no patients treated with azathioprine.

Children and adolescents (3 months to 18 years)

In a clinical study with 100 pediatric patients aged 3 months to 18 years treated orally with mycophenolate mofetil 600 mg/m^2 twice daily, the side effects were generally similar in type to those observed in adult patients receiving CellCept 1 g twice daily.

However, the following treatment-related side effects occurred in children and adolescents at an incidence greater than 10% and were more frequent in children and adolescents, particularly in those under 6 years, than in adults: diarrhea, leukopenia, sepsis, infections, anemia.

Elderly patients (≥65 years)

Elderly patients may be at greater risk of developing certain infections (including tissue-invasive CMV disease), and possibly gastrointestinal hemorrhage and pulmonary edema, than younger patients, especially if they take CellCept as part of an immunosuppressive combination therapy.

Side effects observed distinctly more often in elderly renal transplant recipients were leukopenia, raised serum creatinine and dyspnea. However, their incidence was no greater on CellCept than in patients treated with azathioprine. Increased malignancy or mortality was not observed in this age group of renal transplant recipients.

Side effect profile of CellCept after oral administration

Adverse reactions reported in >10% and in 3%–<10% of patients treated with CellCept in the controlled trials on rejection prophylaxis after renal transplantation (3 trials, data for 2 g and 3 g), after cardiac transplantation (1 trial) and after hepatic transplantation (1 trial) are listed below.

Renal transplant studies with CellCept in combination with ciclosporin and corticosteroids (total: 1483 patients, 991 treated with CellCept)

Infections

Very common: Infections (20.9%), sepsis (19.7%).

Blood and lymphatic system

Very common: Anemia (25.8%), hypochromic anemia (11.5%), leukocytosis (10.9%), leukopenia (34.5%), thrombocytopenia (10.1%).

Common: Ecchymosis, polycythemia, hemorrhage.

Endocrine disorders

Common: Diabetes, parathyroid dysfunction.

Metabolic and nutritional disorders

Very common: Hypercholesterolemia (12.8%), hyperglycemia (12.4%), hyperkalemia (10.3%), hypokalemia (10.1%), hypophosphatemia (15.8%).

Common: Dehydration, hypervolemia, hypocalcemia, hypoglycemia, hypoproteinemia, acidosis, raised creatinine, hypercalcemia, hyperlipidemia, hyperuricemia, weight gain.

Psychiatric disorders

Common: Anxiety, depression.

Nervous system

Very common: Dizziness (11.2%), sleep disturbance (11.8%), tremor (11.8%), headache (21.1%).

Common: Paresthesia, somnolence.

Eyes

Common: Conjunctivitis, amblyopia, cataract.

Cardiovascular system

Very common: Hypertension (32.4%).

Common: Angina, atrial fibrillation, postural hypotension, hypotension, tachycardia, thrombosis, vasodilatation, palpitations.

Respiratory organs

Very common: Increased cough (15.5%), dyspnea (17.3%), pharyngitis (11.2%), bronchitis (11.9%), pneumonia (10.6%).

Common: Pulmonary edema, asthma, pleural effusion, rhinitis, sinusitis.

Gastrointestinal disorders

Very common: Constipation (22.9%), diarrhea (36.1%), dyspepsia (17.6%), oral candidiasis (12.1%), nausea (23.6%), vomiting (13.6%), abdominal pain (27.6%).

Common: Anorexia, gingivitis, gingival hyperplasia, gastroenteritis, esophagitis, stomatitis, flatulence, gastrointestinal hemorrhage, gastrointestinal candidiasis, obstruction, gastritis, hernia, enlarged abdomen.

Liver and biliary tract

Common: Hepatic impairment, hepatitis, raised alkaline phosphatase, elevated enzyme levels (γ-glutamyltransferase, lactate dehydrogenase, AST and ALT).

Skin

Very common: Acne (10.1%), *Herpes simplex* (18.2%).

Common: Benign skin neoplasms, skin cancer, fungal skin disease, skin hypertrophy, pruritus, sweating, skin ulcers, alopecia, *Herpes zoster*, hirsutism, rash.

Musculoskeletal system

Very common: Back pain (12.1%).

Common: Arthralgia, myalgia, leg cramps, myasthenia.

Kidneys and urinary tract

Very common: Urinary tract infections (45.5%), hematuria (14.0%), tubular necrosis (10.0%).

Common: Dysuria, urinary urgency, albuminuria, hydronephrosis, pyelonephritis.

Reproductive system and breast

Common: Impotence.

General disorders

Very common: Asthenia (16.1%), fever (23.3%), chest pain (13.4%), unspecified pain (33.0%), edema (12.2%).

Common: Cysts (including lymphocele and hydrocele), flu-like illness, facial edema, malaise, pelvic pain.

Cardiac transplant studies with CellCept in combination with ciclosporin and corticosteroids (total: 578 patients, 289 treated with CellCept)

Infections

Very common: Infections (25.6%), sepsis (18.7%).

Blood and lymphatic system

Very common: Anemia (42.9%), hypochromic anemia (24.6%), leukocytosis (40.5%), leukopenia (30.4%), thrombocytopenia (23.5%), ecchymosis (16.6%).

Common: Petechiae, increased prothrombin, increased thromboplastin time, hemorrhage.

Endocrine disorders

Common: Diabetes, Cushing's syndrome, hypothyroidism.

Metabolic and nutritional disorders

Very common: Hypercholesterolemia (41.2%), hyperglycemia (46.7%), hyperkalemia (14.5%), hypokalemia (31.8%), acidosis (14.2%), raised blood urea nitrogen (34.6%), raised creatinine (39.4%), hyperlipidemia (10.7%), hyperuricemia (16.3%), hypervolemia (16.6%), hypomagnesemia (18.3%), hyponatremia (11.4%), weight gain (15.6%).

Common: Dehydration, hypervolemia, hypocalcemia, hypoglycemia, hypoproteinemia, alkalosis, gout, hypochloremia, hypophosphatemia, hypoxia, respiratory acidosis, thirst, weight loss.

Psychiatric disorders

Very common: Anxiety (28.4%), agitation (13.1%), confusion (13.5%), depression (15.6%).

Common: Emotional lability, hallucinations, thought disturbances.

Nervous system

Very common: Dizziness (28.7%), sleep disturbances (40.8%), tremor (24.2%), paresthesia (20.8%), somnolence (11.1%), headache (54.3%).

Common: Seizures, neuropathy, vertigo.

Eyes

Very common: Amblyopia (14.9%).

Common: Conjunctivitis, visual disturbances, ocular hemorrhage.

Ear and inner ear

Common: Deafness, earache, tinnitus.

Cardiovascular system

Very common: Hypertension (77.5%), arrhythmias (19.0%), bradycardia (17.3%), hypotension (32.5%), acute heart failure (11.8%), pericardial effusion (15.9%).

Common: Angina, postural hypotension, supraventricular and ventricular extrasystoles, atrial flutter, atrial fibrillation, supraventricular and ventricular tachycardia, cardiac arrest, chronic heart failure, pulmonary hypertension, syncope, vasospasm, raised venous pressure.

Respiratory organs

Very common: Increased cough (31.1%), dyspnea (36.7%), pharyngitis (18.3%), asthma (11.1%), rhinitis (19.0%), pleural effusion (17.0%), sinusitis (26.0%), pneumonia (10.7%).

Common: Pulmonary edema, apnea, atelectasis, bronchitis, epistaxis, hemoptysis, singultus, neoplasms, pneumothorax, increased sputum, voice changes.

Gastrointestinal disorders

Very common: Constipation (41.2%), diarrhea (45.3%), dyspepsia (18.7%), oral candidiasis (11.4%), nausea (54.0%), vomiting (33.9%), flatulence (13.8%), abdominal pain (33.9%).

Common: Anorexia, gingivitis, gingival hyperplasia, gastroenteritis, esophagitis, stomatitis, dysphagia, melena, hernia, enlarged abdomen.

Liver and biliary tract

Very common: Increased enzyme levels (lactate dehydrogenase [23.2%], AST [17.3%], ALT [15.6%]), bilirubinemia (18.0%).

Common: Raised alkaline phosphatase, hepatic impairment, jaundice.

Skin

Very common: Acne (12.1%), *Herpes simplex* (20.4%), *Herpes zoster* (10.7%), rash (22.2%).

Common: Benign skin neoplasms, skin cancer, fungal skin disease, skin hypertrophy, pruritus, sweating, skin ulcers, hemorrhages, cellulitis, impaired wound healing.

Musculoskeletal system

Very common: Leg cramps (16.6%), muscle pain (12.5%), back pain (34.6%), myasthenia (12.5%).

Common: Arthralgia, neck pain.

Kidneys and urinary tract

Very common: Urinary tract infection (13.2%), renal impairment (21.8%), oliguria (14.2%).

Common: Dysuria, urinary urgency, hematuria, nocturia, renal failure, urinary incontinence, urinary retention.

Reproductive system and breasts

Common: Impotence.

General disorders

Very common: Asthenia (43.3%), fever (47.4%), chest pain (26.3%), unspecified pain (75.8%), edema (26.6%).

Common: Cysts (including lymphocele and hydrocele), flu-like illness, facial edema, malaise, pelvic pain, pallor.

Hepatic transplant studies with CellCept in combination with ciclosporin and corticosteroids (total: 564 patients, 277 treated with CellCept)

Infections

Very common: Infections (27.1%), sepsis (27.4%).

Blood and lymphatic system

Very common: Anemia (43.0%), hypochromic anemia (13.7%), leukocytosis (22.4%), leukopenia (45.8%), thrombocytopenia (38.3%).

Common: Ecchymosis, pancytopenia, increased prothrombin time, hemorrhage.

Endocrine disorders

Common: Diabetes mellitus.

Metabolic and nutritional disorders

Very common: Raised blood urea nitrogen (10.1%), raised creatinine (19.9%), hyperglycemia (43.7%), hyperkalemia (22.0%), hypocalcemia (30.0%), hypokalemia (37.2%), hypoglycemia (10.5%), hypomagnesemia (39.0%), hypophosphatemia (14.4%), hypoproteinemia (13.4%).

Common: Acidosis, dehydration, hypercholesterolemia, hyperlipidemia, hyperphosphatemia, hypervolemia, hyponatremia, hypoxia, hypovolemia, weight gain, weight loss.

Psychiatric disorders

Very common: Anxiety (19.5%), confusion (17.3%), depression (17.3%).

Common: Psychosis, abnormal thinking, delirium, excitation.

Nervous system

Very common: Dizziness (16.2%), insomnia (52.3%), paresthesia (15.2%), tremor (33.9%), headache (53.8%).

Common: Convulsions, dry mouth, hypesthesia, neuropathy, somnolence.

Eyes

Common: Visual disturbances, amblyopia, conjunctivitis.

Ear and inner ear

Common: Deafness.

Cardiovascular system

Very common: Hypertension (62.1%), hypotension (18.4%), tachycardia (22.0%).

Common: Arterial thrombosis, atrial fibrillation, arrhythmia, bradycardia, vasodilatation, syncope.

Respiratory organs

Very common: Atelectasis (13.0%), increased cough (15.9%), dyspnea (31.0%), pharyngitis (14.1%), pleural effusion (34.3%), pneumonia (13.7%), sinusitis (11.2%).

Common: Asthma, bronchitis, epistaxis, hyperventilation, pneumothorax, pulmonary edema, airway candidiasis, rhinitis.

Gastrointestinal disorders

Very common: Anorexia (25.3%), constipation (37.9%), diarrhea (51.3%), dyspepsia (22.4%), flatulence (12.6%), nausea (54.5%) and vomiting (32.9%), oral candidiasis (10.1%), hernia (11.6%), peritonitis (10.1%), ascites (24.2%), enlarged abdomen (18.8%), abdominal pain (62.5%).

Common: Dysphagia, gastritis, gastrointestinal bleeding, ileus, melena, mouth ulceration, esophagitis, rectal symptoms, gastric ulcer.

Liver and biliary tract

Very common: Cholangitis (14.1%), cholestatic jaundice (11.9%), hepatitis (13.0%), bilirubinemia (14.4%), abnormal liver function tests (24.9%).

Common: Jaundice, raised alkaline phosphatase, raised enzyme levels (AST and ALT).

Skin

Very common: Pruritus (14.1%), skin rash (17.7%), sweating (10.8%), abnormal wound healing (10.5%).

Common: Acne, fungal dermatitis, bleeding, *Herpes simplex*, *Herpes zoster*, hirsutism, benign skin tumors, skin ulcers, vesiculobullous rash, cellulitis, scrotal edema, abscess.

Musculoskeletal system

Very common: Back pain (46.6%).

Common: Joint, neck and muscle pain, leg cramps, myasthenia, osteoporosis.

Kidneys and urinary tract

Very common: Renal dysfunction (25.6%), oliguria (17.0%), urinary tract infection (18.1%).

Common: Acute renal failure, dysuria, hematuria, renal failure, urinary frequency, urinary incontinence.

General disorders

Very common: Asthenia (35.4%), chills (10.8%), fever (52.3%), chest pain (15.9%), undefined pain (74.0%), edema (28.2%).

Common: Cysts (including lymphocele and hydrocele), flu-like symptoms, malaise.

Side effect profile of CellCept i.v.

The adverse event profile of CellCept i.v. resembles that after oral administration of CellCept.

The tolerability profile of CellCept i.v. during the immediate post-transplant period was determined in a controlled double-blind tolerability study of daily dosing with 2 g compared to orally administered CellCept. The potential for venous irritation by CellCept i.v. was determined by comparison with placebo infusion.

Adverse reactions attributable to peripheral venous infusion were phlebitis and thrombosis, both observed in 4% of patients treated with CellCept i.v. These adverse events did not occur in patients in the control (placebo) group who were also treated intravenously. The incidence of other adverse events directly attributable to peripheral

venous infusion (e.g. pain at the infusion site, edema, inflammation) was similar in both treated groups.

Postmarketing experience

Infections

Severe life-threatening infections, such as meningitis and infective endocarditis, have occasionally been reported. There is also evidence of an increased incidence of certain infections, such as tuberculosis and atypical mycobacterial infections.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with CellCept (see *Warnings and precautions*). BK virus 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 (see *Warnings and precautions*).

Congenital disorders

Congenital malformations, including ear, facial, cardiac and nervous system malformations, have been reported in children of patients treated with MMF in combination with other immunosuppressants during pregnancy. Cases of spontaneous abortion have also been reported, particularly after first-trimester exposure to MMF.

Gastrointestinal disorders

Colitis (sometimes caused by CMV), 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, cardiac and hepatic transplant studies.

OVERDOSAGE

The experience with overdose of CellCept in humans is very limited. The cases of reported overdosage fall within the known safety profile of mycophenolate mofetil.

MPA and MPAG cannot be removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/ml), small amounts of MPAG are removed. MPA can be removed by bile acid sequestrants such as colestyramine.

PROPERTIES AND EFFECTS

ATC code: L04AA06

Mechanism of action and pharmacodynamics

MMF is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA is a selective, non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), which thus inhibits the *de novo* pathway of guanosine nucleotide synthesis. Since *de novo* purine synthesis is essential for T and B cell proliferation, while other cell types can use the salvage pathway, MPA has a more marked cytostatic effect on lymphocytes than on other cells.

Clinical efficacy

Renal transplant

Adults

Three studies on the prevention of acute rejection episodes compared two different dosages of oral CellCept (1 g twice daily and 1.5 g twice daily) with azathioprine (two studies) or placebo (one study), in each case in combination with ciclosporin and corticosteroids.

The primary efficacy endpoint was the proportion of patients in each treatment group with treatment failure within the first 6 months after transplantation (biopsy-proven acute rejection or death, graft loss or early termination from the study for other reasons).

CellCept in combination with corticosteroids and ciclosporin led to a statistically significant decrease ($p<0.05$) in the incidence of treatment failure within the first 6 months post-transplant compared to the active control with azathioprine:

USA study (N=499): (biopsy-proven) treatment failure on CellCept 2 g 31.1% (19.8%), CellCept 1 g 31.3% (17.5%), azathioprine 47.6% (38.0%).

Canada/Australia study (N=503): (biopsy-proven) treatment failure on CellCept 2 g 38.2% (19.7%), CellCept 1 g 34.8% (15.9%), azathioprine 50% (35.5%).

Europe study (N=491): (biopsy-proven) treatment failure on CellCept 2 g 30.3% (17.0%), CellCept 1 g 38.8% (13.8%), placebo 56% (46.4%).

No advantage could be shown for CellCept with regard to organ loss and patient death (12 months post-transplant).

Treatment of refractory rejection: In a randomized open comparative study, 150 renal transplant recipients with refractory acute organ rejection received either MMF 3 g or intravenous corticosteroids daily. This led to a lower incidence of graft loss or death at 6 months on CellCept than on intravenous corticosteroids (14.3% vs 26.0%; p=0.062).

Pediatrics

In a study in 100 pediatric patients aged 3 months to 18 years (33 patients <6 years, eight patients <2 years), the biopsy-proven rejection rate was similar across the age groups (3 months to <6 years, 6 years to <12 years, 12 years to 18 years) and comparable to that in adults. The combined incidence of graft loss (5%) and patient death (2%) at 12 months post-transplant was also similar to that in adult renal transplant patients.

Cardiac transplant

In a study in 650 patients (72 on placebo), patients received CellCept 1.5 g twice daily (N=289) or azathioprine 1.5–3 mg/kg body weight once daily (N=289), in each case in combination with ciclosporin and corticosteroids. No difference was observed between CellCept and azathioprine in either primary endpoint: (1) biopsy-proven rejection with hemodynamic compromise, retransplantation or death (32% on CellCept vs 35% on azathioprine), and (2) graft survival (death or retransplantation) in the first 12 months (6.2% on CellCept vs 11.4% on azathioprine).

Hepatic transplant

In a study in 565 patients, CellCept 1 g twice daily was given intravenously for up to 14 days followed by CellCept 1.5 g orally twice daily while the control arm received azathioprine 1–2 mg/kg body weight intravenously followed by azathioprine 1–2 mg/kg body weight orally once daily, in each case in combination with ciclosporin and corticosteroids. The primary efficacy endpoints were: (1) the proportion of patients who experienced one or more episodes of biopsy-proven and treated rejection or death/retransplantation in the first 6 months post-transplant, and (2) the proportion of patients who experienced graft loss (death/retransplantation) during the first 12 months post-transplant. Patients who prematurely discontinued treatment were followed for rejection episodes and organ loss (death/retransplantation) for one year.

Results: In the primary (intent-to-treat) analyses, CellCept in combination with corticosteroids and ciclosporin was more effective than azathioprine in preventing acute rejection (38.5% vs 47.7%; p=0.025) and equivalent to azathioprine for survival (death or retransplantation at 12 months: 14.7% vs 14.6%).

PHARMACOKINETICS

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

The pharmacokinetic profile of mycophenolic acid is similar in renal and cardiac transplant patients.

In hepatic transplant patients receiving a dose of mycophenolate mofetil 1.5 g orally or 1.0 g intravenously, mycophenolic acid blood levels are the same as in renal transplant patients receiving a dose of 1 g orally or intravenously.

In the early post-transplant period (<40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C_{max} approximately 40% lower compared to the late post-transplant period (3–6 months post-transplant).

Absorption

Following oral administration, mycophenolate mofetil is rapidly and extensively absorbed and undergoes complete presystemic metabolism to the active metabolite, MPA. Mycophenolate mofetil is not detectable in plasma after oral administration.

Because of enterohepatic recirculation a secondary MPA plasma peak is generally observed 6–12 hours after dosing. Some degree of enterohepatic recirculation is also anticipated following intravenous administration of CellCept.

The absolute bioavailability of mycophenolic acid after oral administration of mycophenolate mofetil is 94%.

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

Capsules and film-coated tablets are bioequivalent.

MPA AUC values in renal transplant patients receiving an intravenous infusion of CellCept 1 g twice daily in the immediate post-transplant period are similar to those observed after oral administration of CellCept 1 g twice daily.

Distribution

At clinically relevant concentrations, MPA is 97% bound to plasma albumin. Within the concentration range observed in stable patients following renal transplantation, MPAG (MPA glucuronide) is 82% bound to plasma albumin. However, at higher MPAG concentrations – as seen, for example, in patients with delayed graft function or severe renal failure – the bound dose fraction is reduced *in vitro* to 62%.

Metabolism

Following oral administration mycophenolate mofetil undergoes complete presystemic metabolism to active MPA. Similarly, following intravenous administration, mycophenolate mofetil is rapidly and completely converted to MPA.

MPA is chiefly converted in the liver by glucuronyltransferase.(UGT1A9 isoform) into inactive phenolic MPA glucuronide (MPAG). *In vivo*, MPAG is converted back to free MPA via enterohepatic recirculation; a smaller acylglucuronide (AcMPAG) fraction is also formed. AcMPAG is pharmacologically active and is suspected to be responsible for some side effects of MMF (diarrhea, leukopenia).

Elimination

Approximately 93% of the dose is excreted via the kidneys, mainly as MPAG, and about 5.5% in the feces. MPAG secreted into the bile undergoes enterohepatic recirculation.

Enterohepatic recirculation makes it difficult to determine the $t_{½}$ of MPA. The apparent half-life is approximately 16–18 hours.

MPA elimination depends on various transport proteins. Organic anion-transporting polypeptides (OATPs) and multidrug resistance protein 2 (MRP2) are involved in MPA elimination; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with biliary excretion of glucuronides. Multidrug resistance protein 1 (MRP1) is also able to transport MPA, but its contribution seems to be confined

to the absorption process. In the kidney, MPA and its metabolites interact strongly with renal organic anion transporters.

Pharmacokinetics in special patient populations

Renal impairment

In a single-dose study (6 subjects per group), MPA AUC in renal transplant recipients with severe chronic renal failure (glomerular filtration rate <25 ml/min/1.73 m^2) was 28–75% higher than in healthy subjects or patients with less severe renal impairment. MPAG AUC was also increased. The mean increase in MPA AUC in patients with severe renal failure was similar to that observed on increasing the dose of mycophenolate mofetil from 2 to 3 g daily.

Patients with delayed renal graft function: In patients with delayed renal graft function following transplantation, mean MPA $AUC_{0–12}$ was similar to that in patients without delayed graft function, although MPAG $AUC_{0–12}$ was two to three times higher in this group.

No data are available on cardiac or hepatic transplant recipients with severe chronic renal failure.

Hepatic impairment

Hepatic parenchymal disease did not affect the pharmacokinetics of MPA and MPAG in mild and moderate hepatic cirrhosis (Child-Pugh A and B). No studies are available in severe hepatic parenchymal disease and acute impairment.

Children and adolescents

Pharmacokinetic parameters were evaluated in 55 pediatric renal transplant patients (from 1 year to 18 years of age) given mycophenolate mofetil 600 mg/m^2 orally twice daily (up to a maximum of 1 g twice daily). This dose 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 in all age groups were similar in the early and late post-transplant period.

Elderly patients (≥ 65 years)

Pharmacokinetics have not been investigated in elderly patients.

PRECLINICAL DATA

In experimental models, mycophenolate mofetil was not tumorigenic. The highest dose tested in the animal carcinogenicity studies resulted in 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 studies (*in vitro* mouse lymphoma thymidine kinase assay and *in vivo* mouse bone marrow micronucleus test) suggested a potential of mycophenolate mofetil to cause chromosomal aberrations at high cytotoxic doses. Other genotoxicity studies

(bacterial mutagenicity test, mitotic gene conversion in yeast, chromosomal aberration test in Chinese hamster ovary cells) showed no evidence of mutagenic potential.

Mycophenolate mofetil had no effect on male rat fertility at oral doses up to 20 mg/kg/day. Systemic exposure at this dose represents 2–3 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 (F_1) in the absence of maternal toxicity. Systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. No effects on fertility or reproductive parameters were evident in treated females (P_1) or first generation descendants (F_2 females and males).

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

The hematopoietic and lymphoid systems were the primary organ systems affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels equivalent to or less than the clinical exposure at the recommended dose of 2 g/day in renal transplant recipients. Gastrointestinal undesirable effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended dose. Gastrointestinal and renal undesirable effects consistent with dehydration were observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The preclinical toxicity profile of mycophenolate mofetil appears to be consistent with the adverse events observed in human clinical trials which now provide a substantial volume of patient safety data (see *Undesirable effects*).

ADDITIONAL INFORMATION

Incompatibilities

CellCept i.v. infusion solution must not be mixed with other intravenous medicines or infusion admixtures or administered concurrently via the same infusion set.

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the container.

Special precautions for storage

CellCept capsules and film-coated tablets:

Do not store above 25 °C. Store in the original container in order to protect from light.

CellCept i.v preparation lyophilized powder for solution for infusion:

Do not store above 30 °C.

Instructions for use and handling

Capsules/film-coated tablets/lyophilized powder for solution for infusion

Because mycophenolate mofetil has demonstrated teratogenic effects (see *Pregnancy and lactation*), CellCept film-coated tablets should not be crushed and CellCept capsules should not be opened. The powder contained in CellCept capsules must not be inhaled or allowed to come into direct contact with the skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

Avoid direct contact of the 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.

Preparation of the infusion solution (6 mg/ml)

CellCept i.v. does not contain an antibacterial preservative. Reconstitution and dilution of the product must therefore be performed under aseptic conditions. CellCept i.v. must be reconstituted and diluted before use with 5% glucose infusion solution. Two vials of CellCept i.v. are required to prepare a 1 g dose.

1a. Reconstitute the content of each vial of CellCept i.v. by adding 14 ml of 5% glucose infusion solution.

b. Gently shake the vials to dissolve the medicinal product.

c. Check before diluting that the resulting solution is clear and colorless. Discard vials showing clouding or discoloration.

2a. Further dilute the reconstituted solutions of two vials with 140 ml 5% glucose infusion solution to a total volume of 168 ml, i.e. to a mycophenolate mofetil concentration of 6 mg/ml.

b. Check that the prepared solution is clear and colorless. Discard the infusion solution if it shows clouding or discoloration.

If the infusion solution is not prepared immediately prior to administration, it must be infused within 3 hours from reconstitution and dilution of the medicinal product. Store at 15–30 °C.

PACKS

Vials 500 mg 4

Capsules 250 mg	300 (3 x 100)
Film-coated tablets 500 mg	150 (3 x 50)

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Current at September 2015

Capsules and film-coated tablets:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Roche S.p.A., Milan; production site Segrate, Italy

Vials:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Roche Diagnostics GmbH, Mannheim, Germany