CELLCEPT®

1. Name of the medicinal product

CellCept®/CellCept® i.v.

2. Qualitative and quantitative composition

Active substances

Mycophenolate mofetil (MMF).

3. Pharmaceutical form and active substance quantity per unit

250 mg capsules.

500 mg film-coated tablets.

Powder for oral suspension: 35 g powder corresponding to 200 mg/ml after reconstitution.

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

4. Clinical particulars

4.1. Indications/Uses

CellCept is indicated in combination with corticosteroids and ciclosporin for the prophylaxis of acute transplant rejection in patients receiving allogeneic kidney, heart or liver transplants.

4.2 Dosage/administration

Please refer to the full prescribing information for corticosteroids and ciclosporin, which are used in combination with CellCept.

The first CellCept dose should be administered as soon as possible after kidney, heart or liver transplantation.

The solution for infusion may be used in kidney and liver transplantation instead of the oral forms over a period of up to 14 days. The administration of CellCept capsules, film-coated tablets or suspension 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.

Kidney and liver transplant

Adults

The recommended dose for kidney and liver 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 by slow intravenous infusion over at least 2 hours into a peripheral or central vein (infusion pump). The suitable infusion rate is 84 ml/hour.

In kidney transplant rejection, dose reduction or discontinuation is unnecessary. No pharmacokinetic data on liver transplant rejection are available.

Children and adolescents

No data on intravenous administration are available for paediatric patients.

Oral administration

Kidney transplant

Adults

The best therapeutic benefit-risk ratio is observed with a daily dose of 2 g (4 capsules or 2 film-coated tablets or 5 ml of suspension twice daily). A daily dose of 2 g is generally recommended for kidney 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 or 7.5 ml of suspension twice daily) can be given.

No dose adjustment is required in patients with delayed postoperative renal graft function. However, patients should be carefully monitored (see “Pharmacokinetics”). In kidney 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 (aged 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). The suspension is particularly suitable for treating children and adolescents.

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).

Heart transplant

Adults

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

Children and adolescents

No data are available for paediatric heart transplant patients.

Liver transplant

Adults

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

Children and adolescents

No data are available for paediatric liver 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”).

If necessary, the suspension can be administered via a nasogastric tube that is at least 8 French in diameter (minimum internal diameter 1.7 mm).

Preparation of the suspension and solution for infusion: see “Other information”.

Special dosage instructions

Patients with renal disorders

In heart or liver 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.

Kidney 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 mild renal impairment or healthy subjects. Such kidney transplant recipients should not be treated with CellCept doses higher than 1 g twice daily and must be carefully monitored (see "Interactions").

Patients with hepatic impairment

Dose adjustment is not recommended in kidney transplant recipients with severe parenchymal liver disease.

No data are available for heart transplant patients with severe hepatic parenchymal disease.

Myelosuppression

For patients who develop neutropenia (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 patients

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").

4.3. Contraindications

Known hypersensitivity to mycophenolate mofetil, mycophenolic acid or any of the excipients listed under "Composition".

CellCept is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see "Pregnancy, lactation").

CellCept is contraindicated in women of childbearing potential who are not using highly effective contraceptive methods (see “Pregnancy, lactation: Women and men of reproductive potential”).

CellCept is contraindicated in women who are breastfeeding (see “Pregnancy, lactation”).

4.4. 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 be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As in all patients at increased risk of skin cancer, exposure to sun 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 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 kidney 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 heart transplantation, fatal infections occurred in 1.7% of patients treated with CellCept and 3.8% treated with azathioprine in combination with other immunosuppressants.

In heart 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 reactivation of

hepatitis B or C 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 progressive multifocal leukoencephalopathy (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 ruled out that mycophenolate mofetil plays a role. Doctors should therefore consider PML in the differential diagnosis of immunosuppressed patients who develop neurological symptoms.

BK virus-associated nephropathy has been reported with the use of CellCept in kidney transplant recipients. This infection carries serious risks, resulting in some cases in loss of the renal graft. Appropriate patient monitoring can help to detect those at risk of developing BK virus-associated nephropathy. Due to the cytostatic effect of CellCept on B and T lymphocytes, COVID-19 may follow a more severe course. Dose reduction or discontinuation of CellCept should be considered in patients with evidence of BK virus-associated nephropathy or in cases of clinically significant COVID-19.

Blood and immune system

A cumulative analysis of cases reported with CellCept included a small number of cases of pure red cell aplasia (PRCA, erythroblastopenia), 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 kidney transplant recipients treated with CellCept for rejection prophylaxis developed severe neutropenia (ANC <500/µl).

Up to 2.8% of heart 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 and then once monthly for the first year.

Cases of hypogammaglobulinaemia with recurrent infections have been reported in patients receiving CellCept in combination with other immunosuppressants. Patients experiencing 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.

Blood donation

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

Vaccination

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, haemorrhage 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 phosphoribosyl-transferase (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.

Therapeutic drug monitoring of MPA may be appropriate when switching combination therapy or to ensure adequate immunosuppression in patients with high immunological risk (e.g. risk of rejection – treatment with antibiotics, anti-infective therapy with potential for interaction – see "Interactions").

Caution should be exercised when administering agents of other classes that affect MPA's enterohepatic cycle (e.g. cholestyramine, antibiotics), as they may reduce the plasma concentration and efficacy of CellCept (see "Interactions"). Sevelamer and other phosphate binders should be given two hours after CellCept intake to minimise impact on absorption.

Co-administration of CellCept with azathioprine is not recommended since both products may cause bone marrow aplasia and their co-administration has not been studied.

Specific patient groups

Use in elderly patients

Elderly patients may have a higher risk of side effects than younger patients, for example an increased risk of certain infections (including an invasive tissue attack by the cytomegalovirus) and possibly of gastrointestinal bleeding and pulmonary oedema (see "Adverse effects").

Use when pregnant/ breastfeeding

CellCept is contraindicated during pregnancy and breastfeeding (see "Pregnancy, lactation").

Use by semen donors

Men should not donate semen during treatment and for 90 days after stopping CellCept.

Use in renal impairment

Administration of doses greater than 1 g twice daily to kidney transplant patients with severe chronic renal impairment (glomerular filtration rate <25 ml/min/1.73 m^2) should be avoided except in the immediate post-transplant period or following treatment of acute refractory rejection (see "Pharmacokinetics" and "Special dosage instructions").

No dose adjustment is recommended for post-transplant patients with delayed renal graft function, but patients must be carefully monitored (see “Pharmacokinetics” and “Special dosage instructions”). No data are available on heart or liver transplant patients with severe renal impairment.

Use in patients with phenylketonuria

CellCept powder for oral suspension contains aspartame. Therefore, care should be taken in administering the suspension to patients with phenylketonuria.

4.5 Interactions

DNA polymerase inhibitors

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. Co-administration 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.

Co-administration 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 co-administration 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)

Co-administration of CellCept with PPIs, including lansoprazole and pantoprazole, has been reported to decrease mycophenolic acid (MPA) exposure by up to 30% and C_{max} 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 who were not.

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

Chelating agents

Cholestyramine or other medicinal products that interfere with enterohepatic recirculation

Decreased absorption and interruption of enterohepatic recirculation by cholestyramine reduces mycophenolic acid AUC by 40%. Cholestyramine 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.

Phosphate binders

Co-administration of sevelamer and CellCept decreased MPA C_{max} and AUC_{0-12} by 30% and 25%, respectively.

Immunosuppressant

Ciclosporin A

The pharmacokinetics of ciclosporin A were unaffected by mycophenolate mofetil.

However, ciclosporin A does interfere with enterohepatic recirculation of MPA. Thus, co-administration of CellCept with ciclosporin A in kidney transplant patients

reduced MPA exposures by 30-50% compared to patients receiving sirolimus or belatacept and comparable doses of CellCept.
Conversely, changes in 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 (see "Warnings and precautions").

Tacrolimus

Co-administration 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.

It has been shown that, in kidney transplant patients, tacrolimus concentration is not altered by CellCept.

However, in well-controlled liver 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.

Antibiotics

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 MPA exposure be monitored and CellCept doses adjusted to maintain clinical efficacy when co-administering both medicinal products.

Antibiotics eliminating β-glucuronidase-producing bacteria in the intestine (e.g. aminoglycosides, cephalosporin, fluoroquinolone and penicillin-class antibiotics) may affect MPAG/MPA enterohepatic recirculation. This may contribute to reduced systemic MPA exposure (see "Warnings and precautions", "Interactions").

Information is available on the following antibiotics:

Ciprofloxacin and amoxicillin plus clavulanic acid

A 54% reduction in pre-dose (trough) MPA concentrations has been reported 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 medicinal products are co-administered.

Norfloxacin and metronidazole

Norfloxacin in combination with metronidazole synergistically reduced MPA AUC_{0-48} by 30% following a single dose of CellCept. The effect on MPA systemic exposure was smaller when these antibiotics were administered separately.

Trimethoprim/sulfamethoxazole
No effect on systemic MPA exposure (AUC, C_{max}) was observed when using the trimethoprim/sulfamethoxazole combination.

Nystatin/tobramycin/cefuroxime

When a mixture of tobramycin, cefuroxime and nystatin is used orally for selective bowel decontamination after liver transplantation, approximately 30% lower MPA exposure must be expected during administration of the antibiotics.

Oral contraceptives

A study in which 18 women with psoriasis participated during 3 menstrual cycles and in which CellCept (1 g twice daily) and combination oral contraceptive preparations containing ethinylestradiol (0.02-0.04 mg) and levonorgestrel (0.05-0.20 mg), desogestrel (0.15 mg) or gestagen (0.05-0.10 mg) were administered concomitantly showed no clinically significant effect of CellCept on serum progesterone levels, LH and FSH. This suggests that CellCept does not affect the inhibitory effect on ovulation of oral contraceptives. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of CellCept (see “Pregnancy, lactation: Females and males of reproductive potential”).

Medicinal products that affect glucuronidation

Co-administration of medicinal products inhibiting glucuronidation of MPA may increase MPA exposure (e.g. a 35% increase in MPA $AUC_{0-\infty}$ was observed with concomitant use of isavuconazole). Caution is therefore required when administering these drugs concomitantly with CellCept.

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 and increases glucuronidation. When rates of transplant rejection and loss or adverse event profiles between CellCept patients with and without concomitant telmisartan medication were compared, no clinical consequences of the pharmacokinetic drug-drug interaction were seen.

Live vaccines

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

4.6. Pregnancy, lactation

Pregnancy

CellCept is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see “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 “Undesirable effects: Post-marketing experience”). In the medical literature, a risk of spontaneous abortion after mycophenolate mofetil exposure of 45% to 49% was reported. In comparison, a frequency of spontaneous abortions between 12% and 33% was reported in organ transplant patients treated with other immunosuppressants.

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

The following congenital malformations (including multiple malformations) were most frequently reported post-marketing in children of patients receiving 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, microphthalmia);
- 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 (e.g. spina bifida);
- Renal abnormalities.

In addition, there have been isolated reports of the following malformations

- Microphthalmia;
- Congenital choroid plexus cyst;
- Septum pellucidum agenesis;
- Olfactory nerve agenesis.

These results are consistent with the teratology studies in rats and rabbits, where foetal death (resorption) or malformations occurred in the absence of maternal toxicity (see "Preclinical data"). Labour and delivery: The safety of CellCept during labour and delivery has not been studied.

Lactation

Limited data show that mycophenolic acid passes into human breast milk. CellCept is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see "Contraindications").

Females and males of reproductive potential

Fertility

CellCept is contraindicated in women of childbearing potential who do not use highly effective contraceptive methods (see "Contraindications"). Mycophenolate mofetil was

found to be teratogenic in animal studies (see “Preclinical data”). No effects on fertility were observed in male and female rats treated with mycophenolate mofetil.

Pregnancy testing

Before starting CellCept treatment, women of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/ml to exclude unintended exposure of the embryo to mycophenolate. It is recommended that the second test be performed 8-10 days after the first test. In the case of transplants from deceased donors, if it is not possible to perform two tests 8-10 days apart before treatment starts (due to the unpredictable timing of organ availability), a pregnancy test must be performed immediately before starting treatment and a further test performed 8-10 days later. The results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their doctor immediately should pregnancy occur.

Contraception

Women

CellCept is contraindicated in women of childbearing potential who do not use highly effective contraceptive methods (see “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 counselled regarding pregnancy prevention and planning. Women of childbearing potential must use two reliable methods of contraception simultaneously, at least one of which must be highly effective, before starting CellCept therapy, during treatment and for six weeks after stopping treatment, unless abstinence is the chosen method of contraception.

Men

Limited clinical data are currently available on paternal exposure to CellCept. These data do not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate.

Non-clinical data show that the dose of mycophenolate that could be transferred via the seminal fluid to a potentially pregnant partner is 200-fold lower than the lowest teratogenic concentration in animals. Therefore, the risk of harm mediated via

seminal fluid is considered negligible. However, genotoxic effects have been observed in animal studies at exposures approximately 2.5-times human therapeutic exposure. Thus, the risk of genotoxic effects on sperm cells cannot completely be ruled out.

In the absence of sufficient data to rule out a risk of harm to a foetus conceived during or directly after treatment of the father, the following precautionary measure is recommended: Sexually active male patients and/or their female partners are advised to use an effective method of contraception (condoms) during treatment of the male patient and for at least 90 days after cessation of treatment. Condom use applies to both reproductively competent and vasectomised men, because the risks associated with the transfer of seminal fluid also exist in men who have had a vasectomy. Male patients of reproductive potential should be informed by a qualified healthcare professional about the potential risks of fathering a child and receive appropriate counselling.

4.7. Effects on ability to drive and use machines

No specific studies have been performed.
CellCept could affect the ability to drive and use machines. Patients should avoid driving or using machines if they experience adverse drug reactions such as somnolence, confusion, dizziness, tremor or hypotension during treatment with CellCept (see “Undesirable effects”).

4.8. Adverse effects

Clinical experience

An estimated total of 1557 patients received CellCept during pivotal clinical trials for the prevention of acute organ rejection. Of these, 991 were included in the pooled renal studies ICM1866, MYC022 and MYC023, 277 were in hepatic study MYC2646 and 289 in cardiac study MYC1864. Patients in all study arms also received ciclosporin and corticosteroids. The most common and/or severe adverse reactions in the pivotal trials included diarrhoea, leukopenia, sepsis and vomiting.

There was also evidence of an increased incidence of certain infections, e.g. opportunistic infections.

The three controlled trials of mycophenolate mofetil in the prevention of rejection after kidney transplantation showed a better safety profile overall with daily doses of 2 g rather than 3 g.

The safety profile of CellCept in patients treated for refractory kidney transplant rejection was similar to that observed in the pivotal studies for prevention of kidney transplant rejection at a daily dose of 3 g. The main adverse events reported more frequently in patients receiving CellCept than in patients on i.v. corticosteroids were diarrhoea and leukopenia, followed by anaemia, nausea, abdominal pain, sepsis, nausea with vomiting, and dyspepsia.

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

Children and adolescents (3 months to 18 years)

In a clinical study with 100 paediatric 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: diarrhoea, leukopenia, sepsis, infections, anaemia.

Elderly patients (≥65 years)

Elderly patients (≥65 years) may be at higher risk of adverse reactions due to immunosuppression, especially if they take CellCept as part of an immunosuppressive combination therapy. These patients may be at increased risk of certain infections (including tissue invasive cytomegalovirus [CMV] disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger persons.

Side effect profile of CellCept in pivotal clinical trials

The adverse drug reactions (ADRs) observed in clinical trials are listed by MedDRA system organ class and their frequency. The frequency categories of the individual ADRs are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Due to the great differences observed in the frequency of certain ADRs in different transplant-related indications, frequencies are listed separately for kidney, liver and heart transplant patients.

Kidney transplant studies with CellCept in combination with ciclosporin and corticosteroids (991 patients treated with CellCept)

Infections and infestations

Very common: Bacterial infections (39.9%), viral infections (16.3%).

Common: Fungal infections.

Benign, malignant and unspecified neoplasms (incl. cysts and polyps)

Common: Benign neoplasm of skin, skin cancer, neoplasm.

Blood and lymphatic system disorders

Very common: Leukopenia (28.6%), anaemia (20.0%).

Common: Thrombocytopenia, leukocytosis, ecchymosis, pancytopenia.

Uncommon: Pseudolymphoma.

Metabolism and nutrition disorders

Very common: Hypercholesterolaemia (11.0%), hypophosphataemia (10.8%).

Common: Hyperglycaemia, hypokalaemia, hyperlipidaemia, hyperkalaemia, acidosis, hypocalcaemia, hypomagnesaemia, weight loss.

Psychiatric disorders

Common: Insomnia, depression, confusion.

Nervous system disorders

Very common: Headache (14.8%).

Common: Tremor, dizziness, paraesthesia, hypertonia, somnolence.

Cardiac disorders

Common: Tachycardia.

Vascular disorders

Very common: Hypertension (27.5%).

Common: Hypotension, venous thrombosis (i.v. only).

Respiratory, thoracic and mediastinal disorders

Very common: Dyspnoea (12.2%), cough (11.4%).

Common: Pleural effusion.

Gastrointestinal disorders

Very common: Diarrhoea (30.4%), abdominal pain (22.4%), nausea (18.4%), constipation (18.0%), dyspepsia (13.0%), vomiting (10.6%).

Common: Flatulence, oesophagitis, loss of appetite, gastritis, gastrointestinal ulcer, gastrointestinal haemorrhage, ileus, colitis, stomatitis.

Hepatobiliary disorders

Common: Blood lactate dehydrogenase increased, hepatic enzymes increased, blood alkaline phosphatase increased, hepatitis.

Skin and subcutaneous tissue disorders

Common: Rash, alopecia.

Musculoskeletal and connective tissue disorders

Common: Arthralgia, muscle weakness.

Renal and urinary disorders

Very common: Haematuria (10.0%).

Common: Blood creatinine increased.

Uncommon: Blood urea increased.

General disorders and administration site conditions

Very common: Oedema (21.0%), pyrexia (18.6%), asthenia (10.8%).

Common: Pain, hernia, malaise, chills.

Heart transplant study with CellCept in combination with ciclosporin and corticosteroids (289 patients treated with CellCept)

Infections and infestations

Very common: Viral infections (31.1%), bacterial infections (19.0%), fungal infections (13.1%).

Benign, malignant and unspecified neoplasms (incl. cysts and polyps)

Common: Benign neoplasm of skin, skin cancer, neoplasm.

Blood and lymphatic system disorders

Very common: Anaemia (45.0%), leukocytosis (42.6%), leukopenia (34.4%), thrombocytopenia (24.2%), ecchymosis (20.1%).

Common: Pseudolymphoma.

Uncommon: Pancytopenia.

Metabolism and nutrition disorders

Very common: Hyperglycaemia (48.4%), hypercholesterolaemia (46.0%), hypokalaemia (32.5%), hypomagnesaemia (20.1%), hyperkalaemia (16.3%), acidosis (14.9%), hyperlipidaemia (13.8%).

Common: Hypophosphataemia, hypocalcaemia, weight loss.

Psychiatric disorders

Very common: Insomnia (43.3%), depression (20.1%), confusion (14.2%).

Nervous system disorders

Very common: Headache (58.5%), dizziness (34.3%), tremor (26.3%), hypertonia (17.3%), paraesthesia (15.6%), somnolence (12.8%).

Cardiac disorders

Very common: Tachycardia (22.8%).

Vascular disorders

Very common: Hypertension (78.9%), hypotension (34.3%).

Common: Venous thrombosis (i.v. only).

Respiratory, thoracic and mediastinal disorders

Very common: Dyspnoea (44.3%), cough (40.5%), pleural effusion (18%).

Gastrointestinal disorders

Very common: Nausea (56.1%), diarrhoea (52.6%), constipation (43.6%), abdominal pain (41.9%), vomiting (39.1%), dyspepsia (22.1%), flatulence (18.0%), loss of appetite (14.2%).

Common: Gastritis, oesophagitis, gastrointestinal haemorrhage, gastrointestinal ulcer, stomatitis, colitis, ileus.

Hepatobiliary disorders

Very common: Blood lactate dehydrogenase increased (23.5%), hepatic enzymes increased (17.3%).

Common: Alkaline phosphatase increased.

Uncommon: Hepatitis.

Skin and subcutaneous tissue disorders

Very common: Rash (26.0%).

Common: Alopecia.

Musculoskeletal and connective tissue disorders

Very common: Muscle weakness (13.8%), arthralgia (10.0%).

Renal and urinary disorders

Very common: Blood creatinine increased (42.2%), blood urea increased (36.7%).

Common: Haematuria.

General disorders and administration site conditions

Very common: Oedema (67.5%), pyrexia (56.4%), asthenia (49.1%), pain (42.2%), chills (13.5%), hernia (12.1%).

Common: Malaise.

Liver transplant study with CellCept in combination with ciclosporin and corticosteroids (277 patients treated with CellCept)

Infections and infestations

Very common: Bacterial infections (27.4%), viral infections (14.1%), fungal infections (10.1%).

Benign, malignant and unspecified neoplasms (incl. cysts and polyps)

Common: Benign neoplasm of skin, neoplasm.

Uncommon: Skin cancer.

Blood and lymphatic system disorders

Very common: Leukopenia (45.8%), anaemia (43.0%), thrombocytopenia (38.3%), leukocytosis (22.4%).

Common: Ecchymosis, pancytopenia.

Uncommon: Pseudolymphoma.

Metabolism and nutrition disorders

Very common: Hyperglycaemia (43.7%), hypomagnesaemia (39.0%), hypokalaemia (37.2%), hypocalcaemia (30.0%), hyperkalaemia (22.0%), hypophosphataemia (14.4%).

Common: Hyperlipidaemia, acidosis, weight loss, hypercholesterolaemia.

Psychiatric disorders

Very common: Insomnia (52.3%), depression (17.3%), confusion (17.3%).

Nervous system disorders

Very common: Headache (53.8%), tremor (33.9%), dizziness (16.2%), paraesthesia (15.2%).

Common: Somnolence, hypertonia.

Cardiac disorders

Very common: Tachycardia (22.0%).

Vascular disorders

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

Common: Venous thrombosis (i.v. only).

Respiratory, thoracic and mediastinal disorders

Very common: Pleural effusion (34.3%), dyspnoea (31.0%), cough (15.9%).

Gastrointestinal disorders

Very common: Abdominal pain (62.5%), nausea (54.5%), diarrhoea (51.3%), constipation (37.9%), vomiting (32.9%), loss of appetite (25.3%), dyspepsia (22.4%), flatulence (18.8%).

Common: Gastrointestinal haemorrhage, gastrointestinal ulcer, oesophagitis, gastritis, ileus, colitis, stomatitis.

Hepatobiliary disorders

Very common: Hepatic enzymes increased (24.9%), hepatitis (13.0%).

Common: Blood alkaline phosphatase increased.

Uncommon: Blood lactate dehydrogenase increased.

Skin and subcutaneous tissue disorders

Very common: Rash (17.7%).

Common: Alopecia.

Musculoskeletal and connective tissue disorders

Common: Arthralgia, muscle weakness.

Renal and urinary disorders

Very common: Blood creatinine increased (19.9%), blood urea increased (10.1%).

Common: Haematuria.

General disorders and administration site conditions

Very common: Pyrexia (52.3%), oedema (48.4%), pain (46.6%), asthenia (35.4%), hernia (11.6%), chills (10.8%).

Common: Malaise.

Further information on selected undesirable effects

Infections

All patients treated with immunosuppressants are at increased risk of bacterial, viral and fungal infections (some with potentially fatal outcome), including infections by opportunistic pathogens and reactivation of latent viral infections. The risk increases with total immunosuppressive load.

The most serious infections were sepsis and peritonitis.

The most common opportunistic infections in kidney, heart and liver transplant patients receiving CellCept (2 g or 3 g daily) and followed for at least 1 year were mucosal candidiasis, CMV viraemia/syndrome and herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%.

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").

Three-year safety data in kidney and heart transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. Liver transplant patients were followed for at least 1 year but less than 3 years.

In supportive clinical trials on the prophylaxis of rejection after kidney transplant, the lymphoma rate was 3.9% in a mean follow-up of 42 months.

Blood and lymphatic system disorders

Cytopenias, including leukopenia, anaemia, thrombocytopenia and pancytopenia, are a known risk associated with mycophenolate and may lead or contribute to the occurrence of infections and haemorrhages.

Gastrointestinal undesirable effects

The most serious gastrointestinal disorders were ulceration and haemorrhage, which are known risks associated with mycophenolate. Oral, oesophageal, gastric or intestinal ulcers, often complicated by haemorrhage, as well as haematemesis,

melaena and haemorrhagic forms of gastritis and colitis, were commonly reported in the pivotal trials. However, the most common gastrointestinal disorders were diarrhoea, nausea and vomiting. Endoscopic examinations of patients with CellCept-related diarrhoea revealed isolated cases of intestinal villous atrophy.

General disorders and administration site conditions

Oedema, including peripheral, facial and scrotal oedema, has been reported very frequently in the pivotal studies. Musculoskeletal pain, such as myalgia, neck and back pain, has also been reported very frequently.

Post-marketing experience

Side effect profile of CellCept in post-marketing experience

The adverse drug reactions (ADRs) are listed by MedDRA system organ class and their frequency. The frequency categories of the individual ADRs are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Infections and infestations

Uncommon: Protozoal infections.

Benign, malignant and unspecified neoplasms (incl. cysts and polyps)

Uncommon: Lymphoma, lymphoproliferative disease.

Blood and lymphatic system disorders

Uncommon: Pure red cell aplasia (PRCA, erythroblastopenia), bone marrow failure.

Gastrointestinal disorders

Common: Pancreatitis.

Immune system disorders

Common: Hypersensitivity.

Uncommon: Hypogammaglobulinaemia.

Respiratory, thoracic and mediastinal disorders

Uncommon: Pulmonary fibrosis, interstitial lung disease, bronchiectasis, lymphocele.

General disorders and administration site conditions

Uncommon: De novo purine synthesis inhibitor-associated acute inflammatory syndrome.

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.

Progressive multifocal leukoencephalopathy (PML) and BK virus-associated nephropathy have been reported in patients treated with CellCept.

Congenital disorders and pregnancy, puerperium and perinatal conditions

See “Pregnancy, lactation”.

General disorders and administration site conditions

De novo purine synthesis inhibitor-associated acute inflammatory syndrome is a newly described paradoxical pro-inflammatory reaction associated with mycophenolate and other purine synthesis inhibitors and characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. According to isolated literature reports, rapid improvement was observed after discontinuation of the drug.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS)https://pv.pharmacyboardkenya.org.

4.9. Overdose

Experience with overdose of CellCept in humans is very limited. The cases of reported overdose fall within the known safety profile of mycophenolate mofetil.
MPA and MPAG cannot be removed by haemodialysis. However, at high MPAG plasma concentrations (>100 µg/ml), small amounts of MPAG can be eliminated. MPA can be removed by bile acid sequestrants such as cholestyramine.

5. Properties/Effects

5.1. Pharmacodynamic properties

ATC code

L04AA06

Mechanism of action/Pharmacodynamics

Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA is a selective, non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis.
Two isoforms of IMPDH have been identified: type I isoform, which is present in most known cells (including resting human lymphocytes), and type II isoform, which is highly and predominantly expressed in activated human B and T lymphocytes. The type II isoform is almost five times more sensitive to inhibition by MPA than the type I isoform.
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 potent cytostatic effect on lymphocytes than on other cells.
In addition to IMPDH inhibition, MPA also influences the intracellular signalling pathways responsible for metabolic programming of lymphocytes. It has been shown, using human CD4+ cells, that MPA (partially) reversibly shifts lymphocyte transcriptional activity from a proliferative state to an anergic state, in which they no longer respond to their growth factor (IL-2).

Clinical efficacy

Kidney 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 3 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 3 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 3 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 randomised, open, comparative study, 150 kidney 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).

Paediatrics

In a study conducted in 100 paediatric patients aged 3 months to 18 years (33 patients <6 years, 8 patients <2 years), the biopsy-proven rejection rate was similar across all 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 kidney transplant patients.

Heart transplant

In a study conducted in 650 patients (of which 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 haemodynamic 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).

Liver 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%).

5.2. Pharmacokinetics

The pharmacokinetics of mycophenolate mofetil have been studied in kidney, heart and liver transplant patients.

The pharmacokinetic profile of mycophenolic acid is similar in kidney and heart transplant patients.

In liver 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 kidney transplant patients receiving a dose of 1 g orally or intravenously.

In the early post-transplant period (<40 days post-transplant), kidney, heart and liver transplant patients had mean MPA AUCs approximately 30% lower and C_{max} approximately 40% lower than the equivalent values in the late post-transplant period (3-6 months post-transplant). This is described as non-stationarity in MPA pharmacokinetics.

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 the 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 kidney transplant patients in doses of 1.5 g twice daily. However, peak concentration (C_{max}) of MPA decreased by 40% in the presence of food.

Capsules, film-coated tablets and suspension are bioequivalent.

MPA AUC values in kidney 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. This value depends on renal function. Changes in albumin binding after the start of treatment may explain the variability of MPA pharmacokinetics. Within the concentration range observed in stable patients following kidney 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 principally metabolised in the liver by glucuronyl transferase (UGT1A9 isoform) into inactive phenolic glucuronide of MPA (MPAG). In vivo, MPAG is converted back to free MPA via enterohepatic recirculation; a smaller acyl glucuronide (AcMPAG) fraction is also formed. AcMPAG is pharmacologically active and is suspected to be responsible for some side effects of MMF (diarrhoea, leukopenia).

Elimination

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

Enterohepatic recirculation makes it difficult to determine the $t_{½}$ of MPA, hence only approximate values can be given. In healthy volunteers and patients with autoimmune diseases, clearance values of approximately 10.6 l/h and 8.27 l/h, respectively, and half-lives of 17 h were observed. In transplant patients, mean clearance values were higher (range: 11.9-34.9 l/h) and mean half-lives shorter (5-11 h), with little difference between kidney, liver and heart transplant patients. For each individual patient, these elimination parameters depend, among other things, on the type of any concomitant treatment with other immunosuppressants, time elapsed since transplantation, plasma albumin concentration and renal function. These cofactors may explain why lower exposure is observed when CellCept is co-

administered with ciclosporin (see “Warnings and precautions”) and why plasma concentrations tend to increase with time compared to the values observed immediately after transplantation (see “Pharmacokinetics – Absorption”).
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.

Kinetics in specific patient groups

Renal impairment

In a single-dose study (6 subjects per group), MPA AUC in kidney 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 2-3 times higher compared to the latter.

No data are available on heart or liver 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 paediatric kidney 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 kidney 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)
Based on limited study data, the pharmacokinetics of mycophenolate mofetil and its metabolites were not altered in elderly transplant patients compared to younger transplant patients.

5.3. Preclinical data

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in rats, mice, dogs and monkeys. These effects occurred at systemic exposure corresponding to or less than the recommended clinical dose of 2 g/day for kidney transplant recipients. Gastrointestinal undesirable effects were observed in dogs at systemic exposure equivalent to or less than the recommended dose. Gastrointestinal and renal undesirable effects in association with dehydration were also observed in monkeys at the highest dose (systemic exposure equivalent to or greater than the clinical dose). The preclinical toxicity profile of mycophenolate mofetil is consistent with the undesirable effects observed in human clinical trials.

Carcinogenicity

In experimental models, mycophenolate mofetil was not tumorigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2-3 times the systemic exposure (AUC or C_{max}) observed in kidney 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 heart transplant patients at the recommended clinical dose of 3 g/day.

Genotoxicity

Two genotoxicity studies (*in vitro* mouse lymphoma thymidine kinase assay and *in vivo* mouse bone marrow micronucleus test) suggested that mycophenolate mofetil had the potential 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.

Impaired fertility

Mycophenolate mofetil had no effect on rat fertility at oral doses up to 20 mg/kg/day. Systemic exposure (C_{max}) at this dose represents 2-3 times (C_{max}) the clinical exposure at the recommended clinical dose of 2 g/day in kidney transplant patients and 1.3-2 times (C_{max}) the clinical exposure at the recommended clinical dose of 3 g/day in heart 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 (C_{max}) the clinical exposure at the recommended clinical dose of 2 g/day in kidney transplant patients and approximately 0.3 times (C_{max}) the clinical exposure at the recommended clinical dose of 3 g/day in heart transplant patients. No effects on fertility or reproductive parameters were evident in treated females (P_1females) or first-generation descendants (F_2 females and males).

Reproductive toxicity

In teratology studies in rats and rabbits, foetal 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 (C_{max}) 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 kidney transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day in heart transplant patients (see “Pregnancy, lactation”).

Pharmaceutical particulars

6.1. List of excipients

Capsules

Croscarmellose sodium (produced from genetically modified cotton), colouring: E132, excipients per capsule.

Film-coated tablets

Croscarmellose sodium (produced from genetically modified cotton), colouring E132, excipients per coated tablet.

Powder for oral suspension

Soybean lecithin (produced from genetically modified soybean oil), flavouring agents: vanillin and others, aspartame, sorbitol (produced from genetically modified maize), preservative E218, excipients for powder q.s. 1 ml reconstituted suspension.

Lyophilisate for solution for infusion

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

6.2. Incompatibilities

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

6.3. Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

6.4. Special precautions for storage

CellCept, capsules and CellCept, film-coated tablets

Do not store above 25°C. Store in the original pack to protect the contents from moisture.

CellCept, powder for oral suspension and CellCept i.v., lyophilised powder for solution for infusion

Do not store above 30°C.

Keep out of the sight and reach of children.

Instructions for handling

Capsules/film-coated tablets/powder for oral suspension/lyophilised powder for solution for infusion

Since mycophenolate mofetil has been shown to have a teratogenic effect (see "Pregnancy"), CellCept film-coated tablets and capsules should not be crushed or opened. Patients should 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.

Preparation of the suspension

It is recommended that CellCept suspension be prepared by a professional before it is dispensed to the patient. It is recommended that disposable gloves be worn during reconstitution and when wiping the outside of the bottle/lid and table after reconstitution.

1. Shake the closed bottle several times to loosen the powder.
2. Add 94 ml of purified water (aqua purificata) to a measuring cylinder.
3. Pour about half the purified water into the bottle. Then close the bottle and shake carefully for about 1 minute.
4. Add the rest of the water to the bottle and again shake the closed bottle for about 1 minute.
5. Take off the childproof cap. Insert the bottle adapter into the neck of the bottle.
6. Reclose the bottle tightly with the childproof cap. This ensures childproof closure of the bottle and correct positioning of the adapter.
7. Write the expiry date of the reconstituted suspension on the bottle label. The reconstituted suspension can be stored for up to 60 days.

Preparation of the solution for infusion (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 solution for infusion. Two vials of CellCept i.v. are required to prepare a 1 g dose.

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

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

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

2. a. Further dilute the reconstituted solutions of two vials with 140 ml 5% glucose solution for infusion 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 colourless. Discard the solution for infusion if it shows clouding or discolouration.

If the solution for infusion 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.

6.5. Packs

CellCept capsules 250 mg: 100, 3*100 and 300 [B]

CellCept film-coated tablets 500 mg: 50, 3*50 and 150 [B]

CellCept powder for oral suspension, 35 g bottle*:* 1 (with adapter and 2 oral dispensers) [B]

CellCept i.v. lyophilised powder for solution for infusion, 500 mg vials: 4 [B]

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

7. Marketing authorisation holder and Manufacturing Site Address

Capsules and film-coated tablets:

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

by Delpharm Milano S.R.L Via Carnevale, 1 20090 Segrate (Milano) Italy

Vials:

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

by Roche Diagnostics GmbH Germany, Sandhofer Strasse 116, Mannheim, D-68305

8. Marketing Authorisation number:

9. Date of first registration / Renewal of the registration:

10. Date of revision of the text

April 2024