SCHEDULE H PRESCRIPTION DRUG- CAUTION
WARNING: To be sold by retail on the prescription, shall be supplied against the prescription of a Specialist/Nephrologist only

Mycophenolate Mofetil Capsules I.P. 250mg
Mycophenolate Mofetil Tablets I.P. 500mg
Mycophenolate Mofetil Oral Suspension I.P. 200mg/ml

CellCept®

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1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Selective Immunosuppressive agent – Mycophenolic acid (ATC Code – L04AA06).

1.2 Type of Dosage Form and strengths

Dosage form: CellCept is supplied as capsules, tablets and powder for oral suspension.

Strength:

Capsules: 250mg

Tablets: 500mg

Powder for oral suspension: 1g/5ml [200mg/ml]

1.3 Route of Administration

Oral.

1.4 Qualitative and Quantitative Composition

Active ingredient: Mycophenolate Mofetil I.P.

Each capsule contains 250 mg Mycophenolate Mofetil I.P.;
Each tablet contains 500 mg Mycophenolate Mofetil I.P.;
Each 5 mL of the constituted suspension contains 1 g of Mycophenolate Mofetil I.P. (200mg/ml).

Excipients:

Capsules: Starch (pregelatinised), Croscarmellose sodium, Povidone K90, Magnesium Stearate, Titanium dioxide I.P., Yellow Oxide of iron, Red Oxide of iron, Gelatin, Printing

ink [shellac (NF), Black Oxide of iron CI 77499 E 172 (NF), dehydrated alcohol (USP), propylene glycol (USP), N-butyl alcohol (NF), isopropyl alcohol (USP), strong ammonia solution (NF), potassium hydroxide (NF) and water purified (USP)], Indigo Carmine.

Tablets: Microcrystalline Cellulose, Croscarmellose sodium, Povidone K 90, Magnesium stearate, Hypromellose, Hydroxypropyl cellulose, Titanium dioxide I.P., Macrogol 400, Indigo Carmine, Red Oxide of Iron.

Powder for oral suspension: Silica (colloidal anhydrous), Xanthan gum, Soybean lecithin powder, Sorbitol, Aspartame, Citric acid (anhydrous), Sodium citrate (dihydrate), Methyl parahydroxybenzoate and Mixed fruit flavor.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

CellCept is indicated for the prophylaxis of acute organ rejection and for the treatment of refractory organ rejection in patients receiving allogeneic renal transplants.

CellCept increases graft and patient survival in patients receiving allogeneic cardiac transplants.

CellCept is indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic hepatic transplantation.

CellCept should be used concomitantly with cyclosporin and corticosteroids.

CellCept is indicated for induction and maintenance therapy of patients with Class III-V lupus nephritis (diagnosed according to International Society of Nephrology/Renal Pathology Society classification).

2.2 Dosage and Administration

Transplant patients

Standard dosage for prophylaxis of renal rejection

Adults: A dose of 1 g administered orally twice a day (daily dose of 2 g) is recommended for use in renal transplant patients. Although a dose of 1.5 g administered twice daily (daily dose of 3 g) was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established for renal transplant patients. Patients receiving 2 g/day of CellCept demonstrated an overall better safety profile compared to patients receiving 3 g/day of CellCept.

Children (aged 3-months to 18 years): the recommended dose of CellCept powder for oral suspension is 600 mg/m^2 administered twice daily (up to a maximum of 2 g daily). Patients with a body surface area of 1.25 to 1.5 m^2 may be prescribed CellCept capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area > 1.5 m^2 may be prescribed CellCept tablets at a dose of 1 g twice daily (2 g daily dose).

Standard dosage for prophylaxis of cardiac rejection

Adults: A dose of 1.5 g administered orally twice a day (daily dose of 3 g) is recommended for use in cardiac transplant patients.

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

Standard dosage for prophylaxis of hepatic rejection

Adults: A dose of 1.5 g orally twice a day (daily dose of 3 g) is recommended for use in hepatic transplant patients.

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

Standard dosage for treatment of first or refractory renal rejection

Adults: A dose of 1.5 g administered orally twice a day (daily dose of 3 g) is recommended for management of first or refractory rejection.

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

Oral administration (see 3.2.1 *Pharmacokinetic Properties, Absorption*).

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

Lupus nephritis patients

Standard Dosage for Induction Therapy

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

Children: A dose of 600 mg/m^2 administered orally twice a day (up to a maximum of 2g daily) is recommended.

Standard Dosage for Maintenance Therapy

Adults: A dose of 500mg – 1g administered orally twice a day is recommended.
Children: A dose of 300 mg/m^2 administered orally twice a day is recommended CellCept should be used in combination with corticosteroids. Doses should be introduced gradually and adjusted according to clinical response. Therapeutic drug monitoring could help prevent sub-therapeutic exposure (C_{min} ≥3.0 mg/L or inter-dose AUC ≥35 h*mg/L).

2.2.1 Special Dosage Instructions

Pediatric use
See 2.2 *Dosage and administration* and *3.2.5 Pharmacokinetics in Special Populations.*

Geriatric use
For transplant patients, no oral dosage adjustment is recommended (see 2.4 *Warnings and Precautions*).

For lupus nephritis patients, no recommendation is available.

Renal impairment

For renal transplant patients with severe chronic renal impairment (glomerular filtration rate <25 mL/min/1.73m^2) outside of the immediate post-transplant period or after treatment of acute or refractory rejection, administration of doses greater than 1g twice daily should be avoided (see 3.2 *Pharmacokinetic Properties).*

For post-transplant patients with delayed renal graft function, no dose adjustment is recommended but patients should be carefully monitored (see 3.2 *Pharmacokinetic Properties*).

For cardiac or hepatic transplant patients with severe renal impairment, no data are available.

For lupus nephritis patients with GFR <30mL/min, therapeutic drug monitoring is advised.

Hepatic impairment

For renal transplant patients with severe hepatic parenchymal disease, no dose adjustments are recommended (see 3.2 *Pharmacokinetic Properties*).

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

Patients with neutropenia

For patients that develop neutropenia (absolute neutrophil count <1.3 x 10^3/µl), dosing with CellCept should be interrupted or the dose should be reduced (see 2.4 *Warnings and Precautions*).

2.3 Contraindications

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

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

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

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

2.4 Warnings and Precautions

2.4.1 General

Neoplasms

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

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

Infections

Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections and sepsis (see 2.6 *Undesirable Effects*) Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation, or infections caused by polyomaviruses. Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants.

Cases of Progressive Multifocal Leukoencephalopathy (PML) associated with the JC virus, sometimes fatal, have been reported in CellCept treated patients. The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

BK virus-associated nephropathy has been observed during the use of CellCept in patients post renal transplant. This infection can be associated with serious outcomes, sometimes leading to renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Due to the cytostatic effect of CellCept on B- and T-lymphocytes, increased severity of COVID-19 may occur. Dose reduction or discontinuation of CellCept should be considered for patients who develop evidence of BK virus-associated nephropathy, or in cases of clinically significant COVID-19.

Blood and immune system

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

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

Patients on CellCept should have complete blood counts weekly during the first month of treatment, twice monthly for the second and third months, then monthly through the first year. In particular, patients receiving CellCept should be monitored for neutropenia. The development of neutropenia may be related to CellCept, concomitant medications, viral infection or some combination of these causes (see 2.2.1 *Special Dosage Instructions*). If neutropenia develops (absolute neutrophil count $<1.3 \times 10^3/\mu L$), dosing with CellCept should be interrupted or the dose should be reduced and the patient carefully observed (see 2.2.1 *Special Dosage Instructions*).

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 the use of live attenuated vaccines should be avoided (see 2.8 *Interactions with other Medicinal Products and other Forms of Interaction*). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Gastro-intestinal

CellCept has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, CellCept should be administered with caution in patients with active digestive system disease.

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

phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Interactions

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation e.g. ciclosporin to others devoid of this effect e.g. tacrolimus,sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure (see 2.8 *Interactions with other Medicinal Products and other Forms of Interaction*). Therapeutic drug monitoring of MPA may be appropriate when switching combination therapy (e.g. from ciclosporin to tacrolimus or vice versa) or to ensure adequate immunosuppression in patients with high immunological risk (e.g. risk of rejection, treatment with antibiotics, addition or removal of an interacting medication).

Drugs which interfere with MPA's enterohepatic cycle (e.g. cholestyramine, sevelamer, antibiotics) should be used with caution due to their potential to reduce the plasma levels and efficacy of CellCept (see 2.8 *Interactions with other Medicinal Products and other Forms of Interaction*). Sevelamer and other calcium free phosphate binders should be taken 2 hours after CellCept intake to minimise the impact on the absorption of MPA.

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

Special Populations

Geriatric population

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

Pregnancy and breastfeeding

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

Semen Donation

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

Patients with phenylketonuria

CellCept oral suspension contains aspartame, a source of phenylalanine (equivalent to 2.78 mg per 5mL of oral suspension). Therefore, care should be taken if CellCept oral suspension is administered to patients with phenylketonuria.

2.4.2 Drug Abuse and Dependence

There is no data available to show that CellCept has the potential for drug abuse or dependence.

2.4.3 Ability to Drive and Use Machines

CellCept may have a moderate influence on the ability to drive and use machines. Patients should be advised to use caution when driving or using machines if they experience adverse drug reactions such as somnolence, confusion, dizziness, tremor or hypotension during treatment with CellCept (see *2.6 Undesirable Effects*).

2.5 Use in Special Populations

2.5.1 FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Fertility

CellCept is contraindicated in women of childbearing potential not using highly effective contraceptive methods. (see section *2.3 Contraindications).* Malformations (including anophthalmia, agnathia, and hydrocephaly) occurred in the first generation offspring of female rats treated with oral doses of mycophenolate mofetil in the absence of maternal toxicity (see 3.3.1 *Impairment of Fertility*). No effect was seen on the fertility of male rats treated with mycophenolate mofetil.

Pregnancy Testing

Prior to starting therapy with CellCept female patients of childbearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/ml. A second test should be performed 8-10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Contraception

Females

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

Before the start of treatment, female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning.

Women of child bearing potential should use two reliable forms of contraception simultaneously, at least one of which must be highly effective, before beginning CellCept therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Males

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

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

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

2.5.2 PREGNANCY

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

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

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

- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos);
- Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly);
- Cardiac abnormalities such as atrial and ventricular septal defects;
- Esophageal malformations (e.g. esophageal atresia);
- Nervous system malformations (such as spina bifida).

These findings were consistent with teratology studies performed in rats and rabbits where fetal resorptions and malformations occurred in absence of maternal toxicity (see *3.3.2 Reproductive Toxicity*).

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

2.5.3 LACTATION

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

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

2.5.4 Paediatric Use

See section 2.2 *Dosage and Administration, 2.6 Undesirable effects,* and 3.2.5 section *Pharmacokinetics in Special Populations.*

2.5.5 Geriatric Use

See 2.2 *Dosage and Administration,* 2.4 *Warnings and Precautions, 2.6 Undesirable effects,* and 3.2.5 *Pharmacokinetics in Special Populations.*

2.5.6 Renal Impairment

See 2.2 *Dosage and Administration* and 3.2 *Pharmacokinetic Properties.*

2.5.7 Hepatic Impairment

See 2.2 *Dosage and Administration* and 3.2.5 *Pharmacokinetics in Special Populations.*

2.6 Undesirable Effects

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

2.6.1 Clinical Trials

An estimated total of 1557 patients received CellCept during pivotal clinical trials in the prevention of acute organ rejection. Of these, 991 were included in the pooled renal studies ICM1866, MYC022, MYC023, 277 were included in the hepatic study MYC2646, and 289 were included in the cardiac study MYC1864. Patients in all study arms also received ciclosporin and corticosteroids

Diarrhea, leukopenia, sepsis, and vomiting were among the most common and/or serious adverse drug reactions associated with the administration of CellCept in the pivotal trials. There was also evidence of a higher frequency of certain types of infection, e.g. opportunistic infections (see section 2.4 *Warnings and Precautions*).

In the three pivotal trials for prevention of renal transplant rejection, patients receiving 2 g per day of CellCept demonstrated an overall better safety profile than patients receiving 3 g CellCept. The safety profile of CellCept in patients treated for refractory renal transplant rejection was similar to that observed in the pivotal trials for prevention of renal rejection at doses of 3 g per day. Diarrhea and leukopenia, followed by anemia, nausea, abdominal pain, sepsis, nausea and vomiting, and dyspepsia were the predominant adverse events reported more frequently in patients receiving CellCept in comparison to patients receiving i.v. corticosteroids.

The adverse event profile associated with the administration of CellCept i.v. has been shown to be similar to that observed after oral administration.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class along with their incidence. The corresponding frequency category for each adverse drug reaction is based on the following convention: 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 large differences observed in the frequency of certain ADRs across the different transplant indications, the frequency is presented separately for renal, hepatic and cardiac transplant patients.

Table 1 Summary of adverse drug reactions occurring in patients treated with CellCept in pivotal clinical trials

Adverse drug reaction **(MedDRA)** **System Organ Class**	**Renal transplant n = 991**		**Hepatic transplant n = 277**		**Cardiac transplant n = 289**	
	Incidence (%)	Frequency	Incidence (%)	Frequency	Incidence (%)	Frequency
Infections and infestations						
Bacterial infections	39.9	Very Common	27.4	Very Common	19.0	Very Common
Fungal infections	9.2	Common	10.1	Very Common	13.1	Very Common
Viral infections	16.3	Very Common	14.1	Very Common	31.1	Very Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Benign neoplasm of skin	4.4	Common	3.2	Common	8.3	Common
Neoplasm	1.6	Common	2.2	Common	4.2	Common
Skin cancer	3.2	Common	0.7	Uncommon	8.0	Common
Blood and lymphatic system disorders						
Anemia	20.0	Very Common	43.0	Very Common	45.0	Very Common
Ecchymosis	3.6	Common	8.7	Common	20.1	Very Common
Leukocytosis	7.6	Common	22.4	Very Common	42.6	Very Common
Leukopenia	28.6	Very Common	45.8	Very Common	34.3	Very Common
Pancytopenia	1.0	Common	3.2	Common	0.7	Uncommon
Pseudolymphoma	0.6	Uncommon	0.4	Uncommon	1.0	Common
Thrombocytopenia	8.6	Common	38.3	Very Common	24.2	Very Common
Metabolism and nutrition disorders						
Acidosis	3.4	Common	6.5	Common	14.9	Very Common

Hypercholesterolemia	11.0	Very Common	4.7	Common	46.0	Very Common
Hyperglycemia	9.0	Common	43.7	Very Common	48.4	Very Common
Hyperkalemia	7.3	Common	22.0	Very Common	16.3	Very Common
Hyperlipidemia	7.6	Common	8.7	Common	13.8	Very Common
Hypocalcemia	3.2	Common	30.0	Very Common	8.0	Common
Hypokalemia	7.8	Common	37.2	Very Common	32.5	Very Common
Hypomagnesemia	1.8	Common	39.0	Very Common	20.1	Very Common
Hypophosphatemia	10.8	Very Common	14.4	Very Common	8.7	Common
Weight decreased	1.0	Common	4.7	Common	6.2	Common
Psychiatric disorders						
Confusional state	1.4	Common	17.3	Very Common	14.2	Very Common
Depression	3.7	Common	17.3	Very Common	20.1	Very Common
Insomnia	8.4	Common	52.3	Very Common	43.3	Very Common
Nervous system disorders						
Dizziness	7.8	Common	16.2	Very Common	34.3	Very Common
Headache	14.8	Very Common	53.8	Very Common	58.5	Very Common
Hypertonia	3.3	Common	7.6	Common	17.3	Very Common
Paresthesia	6.3	Common	15.2	Very Common	15.6	Very Common
Somnolence	2.6	Common	7.9	Common	12.8	Very Common
Tremor	9.2	Common	33.9	Very Common	26.3	Very Common
Cardiac disorders						
Tachycardia	4.3	Common	22.0	Very Common	22.8	Very Common
Vascular disorders						
Hypertension	27.5	Very Common	62.1	Very Common	78.9	Very Common

Hypotension	4.9	Common	18.4	Very Common	34.3	Very Common
Venous thrombosis*	4.4	Common	2.5	Common	2.4	Common
Respiratory, thoracic and mediastinal disorders						
Cough	11.4	Very Common	15.9	Very Common	40.5	Very Common
Dyspnea	12.2	Very Common	31.0	Very Common	44.3	Very Common
Pleural effusion	2.2	Common	34.3	Very Common	18.0	Very Common
Gastrointestinal disorders						
Abdominal pain	22.4	Very Common	62.5	Very Common	41.9	Very Common
Colitis	1.6	Common	2.9	Common	2.8	Common
Constipation	18.0	Very Common	37.9	Very Common	43.6	Very Common
Decreased appetite	4.7	Common	25.3	Very Common	14.2	Very Common
Diarrhea	30.4	Very Common	51.3	Very Common	52.6	Very Common
Dyspepsia	13.0	Very Common	22.4	Very Common	22.1	Very Common
Esophagitis	4.9	Common	4.3	Common	9.0	Common
Flatulence	6.4	Common	18.8	Very Common	18.0	Very Common
Gastritis	4.4	Common	4.0	Common	9.3	Common
Gastrointestinal hemorrhage	2.7	Common	8.3	Common	7.6	Common
Gastrointestinal ulcer	3.1	Common	4.7	Common	3.8	Common
Ileus	2.4	Common	3.6	Common	2.4	Common
Nausea	18.4	Very Common	54.5	Very Common	56.1	Very Common
Stomatitis	1.4	Common	1.4	Common	3.5	Common
Vomiting	10.6	Very Common	32.9	Very Common	39.1	Very Common
Hepatobiliary disorders						
Blood alkaline phosphatase increased	5.2	Common	5.4	Common	9.3	Common
Blood lactate dehydrogenase increased	5.8	Common	0.7	Uncommon	23.5	Very Common

Hepatic enzyme increased	5.6	Common	24.9	Very Common	17.3	Very Common
Hepatitis	2.2	Common	13.0	Very Common	0.3	Uncommon
Skin and subcutaneous tissues disorders						
Alopecia	2.2	Common	2.2	Common	2.1	Common
Rash	6.4	Common	17.7	Very Common	26.0	Very Common
Musculoskeletal and connective tissue disorders						
Arthralgia	6.4	Common	6.1	Common	10.0	Very Common
Muscular weakness	3.0	Common	4.0	Common	13.8	Very Common
Renal and urinary disorders						
Blood creatinine increased	8.2	Common	19.9	Very Common	42.2	Very Common
Blood urea increased	0.8	Uncommon	10.1	Very Common	36.7	Very Common
Hematuria	10.0	Very Common	5.1	Common	5.2	Common
General disorders and administration site conditions						
Asthenia	10.8	Very Common	35.4	Very Common	49.1	Very Common
Chills	2.0	Common	10.8	Very Common	13.5	Very Common
Edema	21.0	Very Common	48.4	Very Common	67.5	Very Common
Hernia	4.5	Common	11.6	Very Common	12.1	Very Common
Malaise	2.4	Common	5.1	Common	9.0	Common
Pain	9.8	Common	46.6	Very Common	42.2	Very Common
Pyrexia	18.6	Very Common	52.3	Very Common	56.4	Very Common

* Reported following intravenous administration.

Description of selected adverse drug reactions

Infections

All patients treated with immunosuppressants are at increased risk of bacterial, viral, and fungal infections (some of which may lead to a fatal outcome), including those caused by opportunistic agents and latent viral reactivation (see *2.4.1 Warning and Precautions)*. The risk increases with total immunosuppressive load (see 2.4 *Warnings and Precautions*). The most serious infections were sepsis and peritonitis. The most common opportunistic infections in patients receiving CellCept with other immunosuppressants were mucocutaneous candida, CMV viremia/syndrome, and herpes simplex. The proportion of patients with CMV viremia/syndrome was 13.5%.

Malignancies

Patients receiving CellCept as part of an immunosuppressive regime are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see 2.4 *Warnings and Precautions*).

Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in the incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year, but less than 3 years. In supportive clinical trials of treatment of refractory renal rejection, the lymphoma rate was 3.9% at an average follow-up of 42 months.

Blood and lymphatic disorders

Cytopenias, including leukopenia, anemia, thrombocytopenia and pancytopenia, are a known risk associated with mycophenolate and may lead or contribute to the occurrence of infections and hemorrhages (see *2.4 Warnings and Precautions*).

Gastrointestinal
The most serious gastrointestinal disorders were ulceration and hemorrhage which are known risks associated with CellCept. Mouth, esophageal, gastric, duodenal, and intestinal ulcers often complicated by hemorrhage, as well as hematemesis, melena, and hemorrhagic forms of gastritis and colitis were commonly reported during the pivotal clinical trials. The most common gastrointestinal disorders however, were diarrhea, nausea and vomiting. Endoscopic investigation of patients with CellCept-related diarrhea have revealed isolated cases of intestinal villous atrophy (see *2.4 Warnings and Precautions*).

General disorders and administration site conditions
Edema, including peripheral, face and scrotal edema, was reported very commonly during the pivotal trials. Musculoskeletal pain such as myalgia, and neck and back pain were also very commonly reported

Special Populations

Children (aged 3 months to 18 years)

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

Elderly patients (≥ 65 years)

Elderly patients, particularly those who are receiving CellCept as part of a combination immunosuppressive regimen, may be at greater increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal hemorrhage and pulmonary edema, compared to younger individuals (see 2.4 *Warnings and Precautions*).

2.6.2 Post Marketing

Adverse drug reactions in Table 2 are listed according to system organ class in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: 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).

Table 2 Adverse drug reactions identified from post-marketing experience

Adverse drug reaction (MedDRA) System Organ Class	**Incidence (%)**	**Frequency category**
Infections and infestations		
Protozoal infections	N/A	Uncommon[2]
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Lymphoma	N/A	Uncommon[2]
Lymphoproliferative disorder	N/A	Uncommon[2]
Blood and lymphatic system disorders		
Aplasia pure red cell	N/A	Uncommon[2]
Bone marrow failure	N/A	Uncommon[2]
Gastrointestinal disorders		
Pancreatitis	1.80[1]	Common
Immune system disorders		
Hypersensitivity	3.10[1]	Common
Hypogammaglobulinemia	0.40[1]	Uncommon
Respiratory, thoracic and mediastinal disorders		

Bronchiectasis	N/A	Uncommon[2]
Interstitial lung disease	0.20[1]	Uncommon
Pulmonary fibrosis	0.40[1]	Uncommon
Vascular disorders		
Lymphocele	N/A	Uncommon[2]
General disorders and administration site conditions		
De novo purine synthesis inhibitors-associated acute inflammatory syndrome	N/A	Uncommon[2]

[1] Highest incidence observed during the pivotal clinical trials
[2] The frequency category for ADRs observed only in the post marketing setting is defined as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to CellCept in pivotal trials.

Infections

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

Progressive Multifocal Leukoencephalopathy (PML) and BK virus-associated nephropathy have been reported in CellCept treated patients (see *2.4 Warnings and Precautions*).

Congenital disorders and Pregnancy, puerperium, and perinatal conditions:

See *2.5.2 Pregnancy* for further information.

General disorders and administration site conditions:

De novo purine synthesis inhibitors-associated acute inflammatory syndrome is a newly described paradoxical pro-inflammatory reaction associated with mycophenolate and other purine synthesis inhibitors, characterized by fever, arthralgias, arthritis, muscle pain and elevated inflammatory markers. Anecdotal literature reports showed rapid improvements following discontinuation of the drug.

2.7 OVERDOSE

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

It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone

marrow suppression (see section 2.4 *Warnings and Precautions*). If neutropenia develops, dosing with CellCept should be interrupted or the dose reduced (see section 2.4 *Warnings and Precautions*).

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

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

DNA Polymerase Inhibitors (acyclovir, ganciclovir)

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

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

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

Sequestrants
Cholestyramine: Following single-dose administration of 1.5 g of Mycophenolate mofetil to normal healthy subjects pretreated with 4 g three times daily of cholestyramine for 4

days, there was a 40% reduction in the AUC of MPA. Caution should be used during concomitant administration of drugs that interfere with enterohepatic circulation (see 2.4 *Warnings and Precautions*).

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

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

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

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

However, in 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.

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

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

Information concerning the following antibiotics is available:

Ciprofloxacin or amoxicillin plus clavulanic acid: Reductions in pre-dose (trough) MPA concentrations of 54% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. Effects tended to diminish with continued antibiotic use and cease after

discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure, therefore clinical relevance of these observations is unclear.

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

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

Oral contraceptives
A study of coadministration of CellCept (1g twice daily) and combined oral contraceptives containing ethinylestradiol (0.02 - 0.04 mg) and levonorgestrel(0.05 - 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 - 0.10 mg) conducted in 18 women with psoriasis over 3 menstrual cycles showed no clinically relevant influence of CellCept on serum levels of progesterone, LH and FSH, thus indicating no influence of CellCept on the ovulation-suppressing action of the oral contraceptives. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by coadministration of CellCept (see 2.5.1 *Female and Males of Reproductive Potential*).

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

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

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

Live vaccines: live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished (see 2.4 *Warnings and Precautions*).

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

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

3.1.2 Clinical / Efficacy Studies

Transplant studies

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

Prevention of organ rejection

Adults

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

Children

The safety, pharmacokinetics and efficacy of CellCept in combination with corticosteroids and ciclosporin for the prevention of organ rejection in paediatric renal transplant patients were assessed in an open-label, multicentre study in 100 patients (aged 3-months to 18 years).

Renal transplant

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

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

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

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

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

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

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

* MMF or azathioprine/ciclosporin/corticosteroids

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

*MMF or placebo/ciclosporin/corticosteroids

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

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

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

Study	CellCept 2 g/day	CellCept 3 g/day	Control (Azathioprine or Placebo)
USA	8.5%	11.5%	12.2%

Europe/Canada/Australia	11.7%	11.0%	13.6%
Europe	8.5%	10.0%	11.5%

*Children (aged 3 months to 18 years)**:***
One open-label, safety, pharmacokinetics and efficacy study of CellCept powder for oral suspension in combination with ciclosporin and corticosteroids for the prevention of renal allograft rejection was performed in 100 paediatric patients (aged 3 months to 18 years) at centres in the US (9), Europe (5) and Australia (1). CellCept was dosed at 600 mg/m^2 twice daily (up to 1 g twice daily) in all age groups.

The primary efficacy endpoint was the proportion of patients experiencing an acute rejection episode in the first 6 months posttransplant. The rate of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6 years to <12 years, 12 years to 18 years). The overall biopsy-proven rejection rate at 6 months was comparable to adults. The combined incidence of graft loss (5%) and patient death (2%) at 12 months posttransplant was similar to that observed in adult renal transplant patients.

Cardiac transplant

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

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

Rejection at 6 Months

	All Patients		Treated Patients	
	AZA N = 323	CellCept N = 327	AZA N = 289	CellCept N = 289

Biopsy-proven rejection with hemodynamic compromise*	121 (38%)	120 (37%)	100 (35%)	92 (32%)

* Hemodynamic compromise occurred if any of the following criteria were met: pulmonary capillary wedge pressure ≥20 mm or a 25% increase; cardiac index <2.0 l/min/m^2 or a 25% decrease; ejection fraction ≤30%; pulmonary artery oxygen saturation ≤60% or a 25% decrease; presence of new S_3 gallop; fractional shortening was ≤20% or a 25% decrease; inotropic support required to manage the clinical condition.

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

Death or Retransplantation at 1 year

	All Patients		Treated Patients	
	AZA N = 323	CellCept N = 327	AZA N = 289	CellCept N = 289
Death or retransplantation	49 (15.2%)	42 (12.8%)	33 (11.4%)	18 (6.2%)
Weighted Treatment Difference	2.6%		5.3%	
Lower Limit of 97.5% one-sided confidence interval	-2.5%		+0.9%	

Hepatic transplant

A double-blind, randomized, comparative, parallel-group, multicenter study in primary hepatic transplant recipients was performed at 16 centers in the United States, 2 in Canada, 4 in Europe and 1 in Australia. The total number of patients enrolled was 565 and 564 received study drug. Patients either received CellCept 1g twice daily intravenously for up to 14 days followed by CellCept 1.5 g twice daily orally or azathioprine 1-2 mg/kg/day intravenously followed by azathioprine 1-2 mg/kg/day orally, in combination with ciclosporin and corticosteroids as maintenance immunosuppressive therapy. The two primary endpoints were: (1) the proportion of patients who experienced, in the first 6 months post transplantation, one or more episodes of biopsy-proven and treated rejection or death/retransplantation, and (2) the proportion of patients who experienced graft loss (death/retransplantation) during the first 12 months post transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection and for the occurrence of graft loss (death/retransplantation) for 1 year. Results: In the primary (intent-to-treat) analyses CellCept in combination with corticosteroids and

ciclosporin was superior to azathioprine for prevention of acute rejection (p = 0.025) and equivalent to azathioprine for survival.

Rejection at 6 Months / Death or Retransplantation at 1 Year

	AZA N = 287	CellCept N = 278
Biopsy proven, treated rejection at 6 months	137 (47.7%)	107 (38.5%)
Death or retransplantation at 1 year	42 (14.6%)	41 (14.7%)

Treatment of refractory organ rejection

A randomized, open-label comparison study of MMF 3 g per day against intravenous corticosteroids was conducted in 150 renal transplant recipients with refractory, acute, cellular allograft rejection. The primary endpoint was the proportion of patients who were still alive with a functioning graft at 6 months after study entry.

Results: The incidence of graft loss in the control group was unexpectedly low and the primary analysis, based on the sequential probability ratio test, showed a trend toward improved graft survival in the MMF group (p = 0.081). A secondary analysis, using the Cochran-Mantel-Haenzel test (not adjusted for sequential monitoring), suggested a 45% reduction in the incidence of graft loss or death at 6 months after study entry in the MMF arm (p = 0.062).

Graft Loss or Death at 6 Months

	i.v. Steroids N = 73	CellCept N = 77
Graft loss or death at 6 months	19 (26.0%)	11 (14.3%)

Lupus nephritis studies

Many studies have investigated the use of CellCept for induction and maintenance therapy of lupus nephritis. Two large meta-analyses provide the most robust evidence to support the use of MMF in the management of lupus nephritis:

- The Cochrane Collaboration reviewed 50 randomised controlled trials including 2846 adults and children with biopsy-proven lupus nephritis Class III-V receiving immunosuppressive therapy. MMF with corticosteroids was found to be as effective as IV cyclophosphamide with corticosteroids in preventing death,

inducing complete remission in proteinuria and achieving stable kidney function at six months with lower rates of toxicity. In maintenance therapy, MMF with corticosteroids was more effective than AZA with corticosteroids at preventing relapse with no difference in clinically important side effects.

- The National Kidney Foundation reviewed 53 randomised trials including 4,222 adults and children (from 10 years of age) with proliferative lupus nephritis receiving immunosuppressive therapy. Thirty-eight of the trials in the Cochrane review were also included in this meta-analysis. MMF with corticosteroids was as effective as IV cyclophosphamide with corticosteroids for inducing remission in lupus nephritis with improved tolerability. MMF with corticosteroids was superior to AZA with corticosteroids for maintaining disease remission.

The results of these meta-analyses are in line with the results of the largest randomised controlled study in lupus nephritis, the Aspreva Lupus Management Study (ALMS), which was a two-phase study investigating the efficacy of CellCept in induction and maintenance therapy of patients with Class III-V lupus nephritis. In the induction phase of the study, patients were randomly assigned to a target dose of 3g/day CellCept or 0.5 to 1.0 g/m^2/month IV cyclophosphamide for 6 months. Both groups received prednisone, tapered from a maximum starting dose of 60mg/day. There was no significant difference in the number of patients who met the primary endpoint of a pre-specified decrease in urine protein/creatinine ratio and stabilization or improvement in serum creatinine, supporting the finding of the meta-analyses that CellCept is as effective as IV cyclophosphamide for induction therapy. In the 36-month maintenance phase of the study, the primary endpoint was the time to treatment failure measured as the time until the first event which was defined as death, end-stage renal disease, sustained doubling of the serum creatinine level, renal flare, or the need for rescue therapy. CellCept (2g/day) was superior to AZA (2mg/kg/day) in time to treatment failure (hazard ratio, 0.44; 95% confidence interval, 0.25 to 0.77; P = 0.003), supporting the finding of the meta-analyses that MMF is more effective than azathioprine at preventing relapse.

3.1.3 IMMUNOGENICITY

No data available.

3.2 Pharmacokinetic Properties

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

In general, the pharmacokinetic profile of MPA is similar in renal and in cardiac transplant patients. In the early transplant period, hepatic transplant patients receiving a 1.5 g oral MMF dose have similar MPA levels compared to renal transplant patients receiving 1 g oral MMF. The pharmacokinetic profile of MPA in lupus nephritis is similar to that reported in transplantation (including the high variability in exposure to active drug observed) but is complicated by more unpredictable changes in renal function in lupus nephritis patients.

3.2.1 Absorption

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94% relative to i.v. mycophenolate mofetil. Mycophenolate mofetil can be measured systemically during intravenous infusion; however, after oral administration it is below the limit of quantitation (0.4 µg/ml).

Immediately post-transplant (<40 days) renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C_{max} approximately 40% lower compared to the late transplant period (3-6 months post-transplant). This is referred to as non-stationarity of MPA pharmacokinetics. MPA AUC values obtained following administration of 1 g twice daily intravenous CellCept at the recommended infusion rate to renal patients in the immediate post-transplant phase are comparable to those observed following oral dosing. In hepatic transplant patients, administration of 1 g twice daily intravenous CellCept followed by 1.5 g twice daily oral CellCept resulted in MPA AUC values similar to those found in renal transplant patients administered 1 g CellCept twice daily.

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

Equivalence of oral dosage forms

Bioequivalence of CellCept oral dosage forms have been evaluated. Two 500 mg tablets have been shown to be bioequivalent to four 250mg capsules. Likewise, 1g/5mL of CellCept constituted powder for oral suspension has been shown to be bioequivalent to four 250mg capsules (see section 2.2 *Dosage and Administration*).

3.2.2 Distribution

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

At clinically relevant concentrations, MPA is 97% bound to plasma albumin. This value is dependent on renal function; changes in albumin binding after initiating therapy may explain the non-stationarity in the pharmacokinetics of MPA.

3.2.3 Metabolism

MPA is conjugated primarily by glucuronyl transferase (isoform UGT1A9) to form the inactive phenolic glucuronide of MPA (MPAG). *In vivo*, MPAG is converted back to free MPA via enterohepatic recirculation. A minor acylglucuronide (AcMPAG) is also formed.

AcMPAG is pharmacologically active and is suspected to be responsible for some of MMF's side effects (diarrhoea, leucopenia).

3.2.4 Elimination

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

Enterohepatic recirculation interferes with accurate determination of MPA's disposition parameters; only apparent values can be indicated. In healthy volunteers and patients with autoimmune disease approximate clearance values of 10.6 L/h and 8.27 L/h respectively and half-life values of 17 h were observed. In transplant patients mean clearance values were higher (range 11.9-34.9 L/h) and mean half-life values shorter (5-11 h) with little difference between renal, hepatic or cardiac transplant patients. In the individual patients, these elimination parameters vary based on type of co-treatment with other immunosuppressants, time post-transplantation, plasma albumin concentration and renal function. These factors explain why reduced exposure is seen when CellCept is co-administered with cyclosporine (see section 2.8) and why plasma concentrations tend to increase over time compared to what is observed immediately after transplantation (see non-stationarity in sections 3.2.1 and 3.2.2).

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

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

3.2.5 Pharmacokinetics in Special Populations

Renal impairment

In a single-dose study (6 subjects per group), mean plasma MPA AUCs observed after oral dosing in subjects with severe chronic renal impairment (glomerular filtration rate <25 mL/min/1.73 m^2) were 28-75% higher than those observed in normal healthy subjects or subjects with lesser degrees of renal impairment. The mean single-dose MPAG AUC was 3 to 6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment and normal healthy subjects, consistent with the known renal elimination of MPAG.

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

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

Patients with delayed renal graft function post-transplant

In patients with delayed renal graft function post-transplant, mean MPA AUC_{0-12} was comparable to that seen in post-transplant patients without delayed renal graft function. There may be a transient increase in the free-fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of CellCept does not appear to be necessary (see section *2.2.1 Special Dosage Instructions*). Mean plasma MPAG AUC_{0-12} was 2- to 3-fold higher than in post-transplant patients without delayed renal graft function.

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

Hepatic impairment

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

Pediatric Population (aged ≤18 years):
Pharmacokinetic parameters were evaluated in 55 paediatric renal transplant patients (ranging from 1 year to 18 years of age) given 600 mg/m^2 mycophenolate mofetil 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 posttransplant period. MPA AUC values across age groups were similar in the early and late posttransplant period.

Pharmacokinetics have not been formally evaluated in pediatric lupus nephritis patients. However, in patients with systemic lupus erythematosus (some with renal involvement), similar typical MPA AUC0-12 values following MMF administration were observed in children, adolescent, and adult patients.

Geriatric Population (≥65 years)
The pharmacokinetics of mycophenolate mofetil and its metabolites have not been found to be altered in geriatric transplant patients when compared to younger transplant patients.

3.3 Nonclinical Safety

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

3.3.1 Carcinogenicity

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2-3 times the systemic exposure (AUC or Cmax) 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.

3.3.2 Genotoxicity

Two genotoxicity assays (the mouse lymphoma/thymidine kinase assay and the mouse micronucleus aberration assay) indicated a potential of mycophenolate mofetil to cause chromosomal instability at severely cytotoxic dose levels. Other genotoxicity tests (the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay) did not demonstrate mutagenic activity.

3.3.3 Impairment of Fertility

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 to 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 - 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

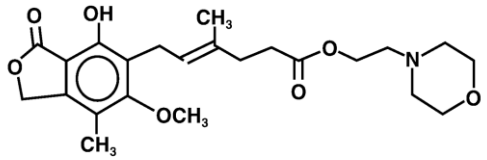
3.3.4 Reproductive Toxicity

In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels is approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. Refer to section 2.5.2 *Pregnancy*.

4 DESCRIPTION

CellCept (mycophenolate mofetil) is an antimetabolite immunosuppressant. It is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor.

The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$, a molecular weight of 433.50, and the following structural formula:



MMF is a white to off-white crystalline powder. It is slightly soluble in water (43 µg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol. The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238. The pKa values for MMF are 5.6 for the morpholino group and 8.5 for the phenolic group.

MMF hydrochloride has a solubility of 65.8 mg/mL in 5% Dextrose Injection USP (D5W). The pH of the reconstituted solution is 2.4 to 4.1.

CellCept is available for oral administration as capsules containing 250 mg of MMF, tablets containing 500mg of MMF, and as a powder for oral suspension which, when reconstituted, contains 200 mg/mL of MMF.

5 PATIENT COUNSELLING INFORMATION

Embryofetal Toxicity

<u>Pregnancy loss and malformations</u>

- CellCept is contraindicated during pregnancy due to its mutagenic and teratogenic potential

Contraception

- Discuss pregnancy testing, pregnancy prevention and planning with females of reproductive potential
- Females of reproductive potential must use an acceptable form of birth control during the entire CellCept therapy and for 6 weeks after stopping CellCept, unless the patient chooses abstinence. CellCept may reduce effectiveness of oral contraceptives. Use of additional barrier contraceptive methods is recommended.
- For patients who are considering pregnancy, discuss appropriate alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of CellCept should be discussed with the patient.
- Advise sexually active male patients and/or their partners to use effective contraception during the treatment of the male patient and for at least 90 days after cessation of treatment. This recommendation is based on findings of animal studies.

Development of Lymphoma and Other Malignancies

- Inform patients that they are at increased risk of developing lymphomas and other malignancies, particularly of the skin, due to immunosuppression.
- Advise patients to limit exposure to sunlight and ultraviolet (UV) light by wearing protective clothing and use of broad-spectrum sunscreen with high protection factor.

Increased Risk of Serious Infections

Inform patients that they are at increased risk of developing a variety of infections due to immunosuppression. Instruct them to contact their physician if they develop any of the signs and symptoms of infection.

Blood Dyscrasias

Inform patients that they are at increased risk for developing blood adverse effects such as anemia or low white blood cells. Advise patients to immediately contact their healthcare provider if they experience any evidence of infection, unexpected bruising, or bleeding, or any other manifestation of bone marrow suppression.

Gastrointestinal Tract Complications

Inform patients that CellCept can cause gastrointestinal tract complications including bleeding, intestinal perforations, and GI ulcers. Advise the patient to contact their healthcare provider if they have symptoms of gastrointestinal bleeding, or sudden onset or persistent abdominal pain.

Vaccinations

Patients should be advised that during treatment with CellCept vaccinations may be less effective and the use of live attenuated vaccines should be avoided.

Administration Instructions

- Advise patients not to crush CellCept tablets and not to open CellCept capsules.
- Advise patients to avoid inhalation or contact of the skin or mucous membranes with the powder contained in CellCept capsules and with the oral suspension. If such contact occurs, they must wash the area of contact thoroughly with soap and water. In case of ocular contact, rinse eyes with plain water.
- Advise patients to take a missed dose as soon as they remember, except if it is closer than 2 hours to the next scheduled dose; in this case they should continue to take CellCept at the usual times.

Blood Donation

Advise patients not to donate blood during therapy and for at least 6 weeks following discontinuation of CellCept.

Semen Donation

Advise males of childbearing potential not to donate semen during therapy and for 90 days following discontinuation of CellCept.

Potential to Impair Driving and Use of Machinery

Advise patients that CellCept can affect the ability to drive or operate machines. Patients should avoid driving or operating machines if they experience somnolence, confusion, dizziness, tremor or hypotension during treatment with CellCept.

6 PHARMACEUTICAL PARTICULARS

6.3 Storage

CellCept capsules: Do not store above 25 °C, store in the original package.

CellCept tablets: Do not store above 25 °C, store in the original package.

CellCept powder for oral suspension: Do not store above 30 °C.

CellCept reconstituted product: Store at 2 - 8°C.

This medicine should not be used after the expiry date (Expiry Date) shown on the pack.

6.4 Special Instructions for Use, Handling and Disposal

CellCept oral administration

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

CellCept powder for oral suspension

Each bottle of CellCept powder for oral suspension contains 35g mycophenolate Mofetil in a 110g powder for oral suspension yielding 1g/5mL after constitution.

It is recommended that CellCept powder for suspension be reconstituted by the pharmacist prior to dispensing to the patient. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle/cap and the table after reconstitution.

CellCept powder for oral suspension should not be mixed with any other medication.

Preparation of suspension

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

Note: If required, CellCept powder for oral suspension can be administered via nasogastric tube with a minimum size of 8 French (minimum 1.7 mm interior diameter).

Taking the medicine

Be sure that you read, understand and follow these instructions carefully to ensure proper dosing of CellCept Oral Suspension.

Important:

- Always use the oral dispenser provided with CellCept Oral Suspension to make sure you measure the right amount of medicine.
- Call your pharmacist if your oral dispenser is lost or damaged.
- Your pharmacist will write the expiration date on your CellCept Oral Suspension bottle label. Do not use after the expiration date.

- Ask your doctor or pharmacist if you have any questions or are unsure about how to take your dose of medicine.

To take a dose of CellCept Oral Suspension, you will need the bottle of medicine and an oral dispenser provided with the medicine (See Figure 1).

Your pharmacist will insert the bottle adapter in the CellCept Oral Suspension bottle.

You need to use the dispenser and bottle adapter supplied with the medicine to measure the dose.

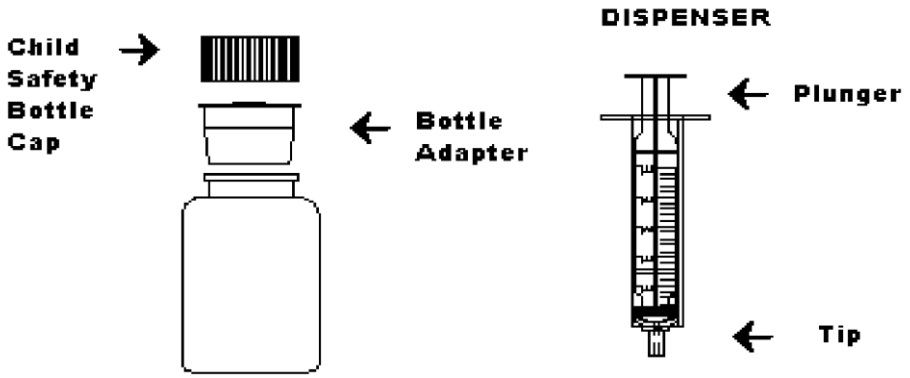


Figure 1

Step 1: With the child-resistant cap on the bottle, shake the closed bottle well for about 5 seconds before each use.

Step 2: Open the bottle by pressing down on the child-resistant bottle cap and turning it counter-clockwise (to the left). Do not throw away the child-resistant bottle cap

Step 3: Before inserting the tip of the oral dispenser into the bottle adapter, tpush the plunger completely down toward the tip of the dispenser. Then put the tip of the dispenser firmly into the opening of the bottle adapter.

Step 4: Carefully turn the whole thing upside down with the oral dispenser in place. Slowly pull the plunger down to withdraw your prescribed dose. Do not pull the plunger out of the oral dispenser (see Figure 2 below).

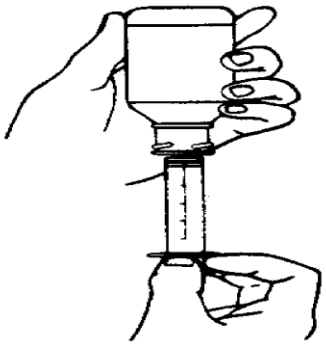


Figure 2

Step 5: Leave the oral dispenser in the bottle and turn the bottle to an upright position. Slowly remove the oral dispenser from the bottle.

Step 6: Place the tip of the oral dispenser in the patient's mouth and slowly push the plunger down until the oral dispenser is empty. The CellCept oral suspension that is in the oral dispenser should not be mixed with any type of liquids before taking the dose.

Step 7: Close the bottle with the child resistant bottle cap after each use.

Step 8: Rinse the oral dispenser under running tap water after each use:

- Remove the plunger from the oral dispenser.
- Rinse the oral dispenser and plunger with water and let them air dry.
- When the oral dispenser and plunger are dry, put the plunger back in the oral dispenser for the next use.

Important:

- Do not let CellCept Oral Suspension come in contact with the skin. If this happens, wash the skin well with soap and water.
- If you spill any oral suspension, wipe it up using paper towels wet with water. Put the child-resistant bottle cap back on the bottle and wipe the outside of the bottle with wet paper towels.

6.5 Packs

Capsules 250 mg	100
Tablets 500 mg	50
Powder for Oral Suspension: Bottle 225ml with 1 bottle adapter and 2 oral dispensers	110 g

6.6 Shelf life

Tablets and Capsules: 36 months when stored at recommended storage conditions.

Powder for Oral Suspension: 24 months when stored at recommended storage conditions. Use the reconstituted suspension within 60 days.

Keep out of reach of children.

6.7 Incompatibilities

No text.

7 DETAILS OF MANUFACTURER

Manufactured by:

F. Hoffmann - La Roche Ltd, Grenzacherstrasse 124, CH-4070 Basel, Switzerland at-
1. Delpharm Milano S.R.L, Via Carnevale 1, 20090 Segrate, Milan, Italy ***(Capsules and Tablets)***
2. Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N7K9, Canada ***(Powder for Oral Suspension).***

Imported and Marketed by:

Roche Products (India) Pvt. Ltd.,
C/O. Parekh Integrated Services Pvt. Ltd, Gala No. B1, Second Floor, Warehouse no. 6, BGR Logistics Park, NH-3, Zone 5, Bhiwandi, Maharashtra (India) – 421302.

8. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Permission no. (122A) Finish) 9195) dated 11 October 2002.

9. DATE OF REVISION

Current at October 2021, Version 15.0