Proposed Clean Package Insert

WARNING: CARCENOGENICITY

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, especially of the skin, may result from immuno-suppression.
Only medical practitioners experienced in immuno-suppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe MYCOCEPT 500. Patients receiving the medicine should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources.
The medical practitioner responsible for maintenance therapy should have complete information requisite for the follow up of the patient.

WARNING: TERATOGENICITY

Mycophenolate is powerfully teratogenic and mutagenic. Congenital malformations and spontaneous abortions have been reported with use of mycophenolate in pregnancy. Women of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mℓU/mℓ; the second test should be performed 8-10 days after the first one and immediately before starting treatment with MYCOCEPT 500. Repeat pregnancy tests should be performed during routine follow-up visits.
Women of childbearing potential should use two reliable forms of contraception simultaneously, including at least one highly effective method, before beginning MYCOCEPT 500 therapy, during therapy, and for six weeks following discontinuation of therapy; unless abstinence is the chosen method of contraception.
Sexually active men are recommended to use condoms during treatment and for at

least 90 days after cessation of treatment. Condom use applies both for reproductively competent and vasectomised men; because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy.
Female partners of male patients are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of MYCOCEPT 500.

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

MYCOCEPT 500 (film-coated tablets)

COMPOSITION:

Each Mycocept 500 film-coated tablet contains 500 mg mycophenolate mofetil.

Inactive ingredients:

Microcrystalline cellulose, croscarmellose sodium, povidone (K-90F), magnesium stearate, talc and opadry purple.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 32.2 Other (Immuno-suppressants)

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Mycophenolate mofetil (MMF), a prodrug, is the 2-morpholinoethyl ester of mycophenolic acid (MPA) and is rapidly hydrolysed to the active substance, MPA. MPA, the active metabolite is a selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. 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 use salvage pathways.

MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells, and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. Mycophenolate mofetil does not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but blocks the coupling of these events to DNA synthesis and proliferation.

Pharmacokinetic properties:

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.

Absorption:

The mean bioavailability of oral mycophenolate mofetil, based on the plasma-concentration time curve (AUC) for MPA, was 94 % relative to IV mycophenolate mofetil. The AUC for MPA appears to increase in a dose-proportional fashion in renal transplant patients receiving multiple doses of mycophenolate mofetil up to a daily dose of 3 g.

Distribution:

MPA, at clinically relevant concentrations, is 97 % bound to plasma albumin. Mycophenolic acid glucuronide (MPAG) is 82 % bound to plasma albumin at MPAG concentration ranges that are normally seen in stable renal transplant patients; however, at higher MPAG concentrations, the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding. Mean blood to plasma ratio of radio-activity concentrations was approximately 0,6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood. *In vitro* studies to evaluate the effect of other agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 25 mg/dℓ with HSA) and MPAG (at ≥ 460 µg/mℓ with plasma proteins) increased the free fraction of MPA. At concentrations that exceeded what is encountered clinically, ciclosporin, digoxin, naproxen, prednisone, propanolol, tacrolimus, theophylline, tolbutamide and warfarin did not increase the free fraction of MPA. MPA at concentrations as high as 100 µg/mℓ had little effect on the binding of warfarin, digoxin or propanolol, but decreased the binding of theophylline from 53 % to 45 % and phenytoin from 90 % to 87 %.

Metabolism:

Mycophenolate mofetil undergoes complete presystemic metabolism to MPA, the active metabolite. MPA is metabolised principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active.
As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6 to 12 hours post-dose. A reduction in the AUC of MPA of approximately 40 % is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.

Increased plasma concentrations of mycophenolate mofetil metabolites (MPA 50 % increase and MPAG about 3 to 6 fold increase) are observed in patients with renal insufficiency.

Excretion:

Negligible amount of mycophenolate mofetil is excreted as MPA (< 1 % of dose) in the urine. Orally administered radiolabelled mycophenolate mofetil resulted in complete recovery of the administered dose; with 93 % of the administered dose recovered in the urine and 6 % recovered in faeces. Most (about 87 %) of the administered dose is excreted in the urine as MPAG. MPA and MPAG are usually not removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 µg/mℓ), small amounts of MPAG are removed.

Mean (± SD) apparent half-life and plasma clearance of MPA are 17,9 (± 6,5) hours and 193 (± 48) mℓ/min following oral administration and 16,6 (± 5,8) hours and 177 (± 31) mℓ/min following IV administration, respectively.

INDICATIONS:

MYCOCEPT 500 is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, hepatic or cardiac transplants.

MYCOCEPT 500 should be used concomitantly with ciclosporin and corticosteroids.

CONTRAINDICATIONS:

Hypersensitivity to mycophenolate mofetil or mycophenolic acid or any other component of MYCOCEPT 500.

Pregnancy and breastfeeding. (see “PREGNANCY AND LACTATION”).

WARNINGS AND SPECIAL PRECAUTIONS:

Patients on MYCOCEPT 500 therapy should limit the exposure to sunlight and UV light by wearing protective clothing and using sunscreen with high protection factor. There is an increased risk of developing lymphomas and other malignancies, particularly of the skin in patients receiving MYCOCEPT 500 as part of an immuno-suppressive regimen, which appears to be related to the intensity and duration of immuno-suppression rather than to the use of any specific agent.

There can also be an increased susceptibility to infection, including opportunistic infections, fatal infections and sepsis during over suppression of the immune system.

Patients receiving MYCOCEPT 500 should have complete blood counts (CBC), weekly during the first month, twice monthly for the second and third months of treatment, then once a month through the remainder of the first year.

Neutropenia should be monitored for in these patients, as it may be related to MYCOCEPT 500 itself, concomitant medications, viral infections or some combination of these causes.

If neutropenia develops (absolute neutrophil count < 1,3 x $10^3/\mu\ell$) it may be appropriate to interrupt or discontinue treatment with MYCOCEPT 500.

Patients receiving MYCOCEPT 500 should be instructed to immediately report any evidence of infection, unexpected bruising or bleeding or any other manifestation of bone marrow depression to their doctor.

The use of live attenuated vaccines should be avoided during treatment with MYCOCEPT 500, as vaccinations may be less effective.

Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

The risk-benefit should be considered when active digestive system disease is present, because mycophenolate mofetil has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration,

haemorrhage and perforation. MYCOCEPT 500 should be administered with caution in these patients.

MYCOCEPT 500 treatment should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmillar syndrome because MPA is an IMPDH (inosine monophosphate dehydrogenase) inhibitor.

Administration of doses should not be greater than 1 g twice a day to renal transplant patients with severe chronic renal impairment and patients should be carefully observed. No dose adjustment is required for patients with delayed renal graft function post-transplant, however, they should be carefully observed.

Elderly patients may be at an increased risk of adverse events compared to younger individuals.

Concomitant use with azathioprine and cholestyramine is not recommended (see “INTERACTIONS”).

It is recommended that MYCOCEPT 500 therapy should not be initiated until a negative pregnancy test has been obtained (see "PREGNANCY AND LACTATION").

Effects on the ability to drive and use machinery:

Patients should take special care when operating hazardous machinery or driving motor vehicles until they know how MYCOCEPT 500 will affect them.

INTERACTIONS:

Aciclovir, valaciclovir, ganciclovir, valganciclovir: Increases in MPAG and acyclovir plasma concentrations were observed when mycophenolate mofetil was administered concomitantly with these medicines, compared to their plasma concentrations when administrated alone. MPAG plasma concentration as well as the plasma concentrations of

these antivirals are increased in the presence of renal impairment when administered alone and therefore the potential exists for these medicines to compete for tubular secretion, and thus resulting in a further increase in concentrations of these medicines when administered concomitantly. Patients with renal impairment in whom MMF and these medicines are co-administered, should be carefully monitored.

Cholestyramine and concomitant use of MYCOCEPT 500 may decrease the plasma concentration of MPA as a result of interruption of enterohepatic recirculation of MPAG possibly caused by intestinal binding with cholestyramine resulting in reduced MYCOCEPT 500 efficacy.

Antacids with magnesium and aluminium hydroxides may decrease the absorption of MYCOCEPT 500.

Concomitant administration of azathioprine and MYCOCEPT 500 is not recommended due to both having the potential to cause bone marrow suppression.

Ciclosporin pharmacokinetics is unaffected when used simultaneously with MYCOCEPT 500.

Oral contraceptives: The AUC of levonorgestrol was significantly decreased with concomitant use with mycophenolate mofetil and additional birth control methods should be considered (see “PREGNANCY AND LACTATION”).

Medicines such as probenecid that undergo renal secretion may increase the plasma concentrations of the metabolites of MYCOCEPT 500.

Live vaccines: Live vaccines should not be given to patients with impaired immune response. The antibody response to other vaccines may be diminished (see “WARNINGS AND SPECIAL PRECAUTIONS”).

Tacrolimus: In stable renal transplant patients (using mycophenolate mofetil 1 g twice per day) where ciclosporin is replaced with tacrolimus there is about a 30 % increase in MPA plasma AUC and about 20 % decrease in MPAG plasma AUC. The dose of MYCOCEPT 500 should not exceed 1 g twice a day for patients on tacrolimus. Patients should be carefully observed and managed appropriately. Very limited pharmacokinetic data are available for hepatic transplant patients treated with mycophenolate mofetil in combination with tacrolimus.

PREGNANCY AND LACTATION:

MYCOCEPT 500 is contraindicated in pregnancy and during breastfeeding. (see “CONTRAINDICATIONS”)

MYCOCEPT 500 therapy should not be initiated until a negative pregnancy test has been obtained. Patients should be instructed to consult their doctor immediately should pregnancy occur (see “WARNINGS AND SPECIAL PRECAUTIONS”).

Effective contraception must be used before beginning MYCOCEPT 500 therapy, during therapy and for six weeks following discontinuation of therapy (see "INTERACTIONS").

The following malformations were frequently reported:

- Facial malformations such as cleft lip, cleft palate, micognathia and hypertelorism of the orbits
- Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos)
- Malformations of the fingers e.g. polydactyly, syndactyly, brachydactyly)

- Cardiac abnormalities such as atrial and ventricular septal defects
- oesophageal malformations (e.g. oesophageal atresia)
- nervous system malformations (such as spina bifida)

DOSAGE AND DIRECTIONS FOR USE:

Dosage for prophylaxis of renal rejection:

Adults: The initial dose should be given within 72 hours of transplantation. The recommended dose is 1 g orally twice daily.

Standard dosage for prophylaxis of cardiac rejection:

Adults: 1,5 g orally twice daily is recommended. The initial dose should be given within 5 days after a cardiac transplantation.

Children: Safety and efficacy have not been established.

Standard dosage for prophylaxis of hepatic rejection:

Adults: 1,5 g orally twice a day. The dose should be initiated as soon as possible after a transplant.

Children: Safety and efficacy have not been established

Special Dosage Instructions:

Treatment with MYCOCEPT 500 should be initiated and maintained by appropriately qualified transplant specialists.

MYCOCEPT 500 can be taken with or without food.

MYCOCEPT 500 tablets should not be crushed in order to retain the integrity of the enteric coating. In addition Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits.

Renal impairment:

These patients should also be carefully observed. In patients with severe chronic renal impairment (glomerular filtration rate < 25 mℓ/min/1,73 m²), outside of the immediate post-transplant period, doses greater than 1 g, administered twice a day, should be avoided.
No data is available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function post-transplant:

No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively.

Hepatic impairment:

No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data is available for cardiac transplant patients with severe hepatic parenchymal disease.

Elderly:

The recommended dose of 1 g administered twice a day for renal transplant and 1,5 g twice a day for cardiac transplant patients, is appropriate for elderly patients (see “WARNINGS AND SPECIAL PRECAUTIONS”**).**

Neutropenia:

Dosing with MYCOCEPT 500 should be interrupted or the dose reduced (absolute neutrophil count < 1,3 x 10^3/µℓ).

SIDE EFFECTS:

Infections and Infestations:

Frequent: Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster, pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection, bronchitis, pharyngitis, sinusitis, fungal skin infection, skin candida, vaginal candidiasis, rhinitis.

Frequency unknown: Meningitis, endocarditis, tuberculosis, atypical mycobacterial infection.

Neoplasms benign and malignant (including cysts and polyps):

Frequent: Skin cancer, benign neoplasm of skin.

Less frequent: Cysts (including lymphocele and hydrocele).

Blood and lymphatic system disorders:

Frequent: Anaemia (including hypochromic anaemia), leukocytosis, leukopenia, thrombocytopenia, pancytopenia.

Less Frequent: Ecchymosis, polycythaemia, agranulocytosis.

Frequency unknown: Neutropenia, aplastic anaemia, bone marrow depression, red cell aplasia, abnormal neutrophil morphology (including acquired Pelger-Huet anomaly).

Immune system disorders:

***Frequency unknown*:** Hypersensitivity reactions, including angioedema and anaphylactic reaction.

Endocrine disorders:

***Less Frequent*:** Diabetes mellitus, Cushing's syndrome, parathyroid disorder.

Metabolism and nutrition disorders:

Frequent: Disturbances of electrolytes and blood lipids including hypercholesterolemia, hyperglycaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia, hypocalcaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia.

***Less Frequent*:** Acidosis (metabolic or respiratory), increased alkaline phosphatase, dehydration, elevated enzyme levels (SGOTand SGPT), weight gain.

Psychiatric disorders:

Frequent: Agitation, confusional state, depression, anxiety, abnormal thinking, insomnia.

Nervous system disorders:

Frequent: Dizziness, tremor, convulsion, myasthenic syndrome, headache, dysgeusia.

Less Frequent: Hypertonia, paraesthesia, somnolence.

Eye disorders:

Less frequent: Amblyopia, abnormal vision, conjunctivitis.

Ear and labyrinth disorders:

Less frequent: Deafness, tinnitus.

Cardiac disorders:

Frequent: Tachycardia

Less Frequent: Angina pectoris, dysrhythmias, atrial fibrillation, cardiac arrest, congestive heart failure, ventricular extrasystoles.

Vascular disorders:

Frequent: Hypertension, hypotension.

Less Frequent: Postural hypotension, vasodilation, syncope.

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea, pneumonia, increased cough, sinusitis, pleural effusion.

***Less Frequent*:** Asthma, pulmonary oedema, rhinitis.

***Frequency unknown*:** Interstitial lung disease, pulmonary fibrosis.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, constipation, dyspepsia, abdominal pain, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, flatulence, eructation, pancreatitis.

Less Frequent: Gastrointestinal haemorrhage, oral moniliasis, gingivitis, gum hyperplasia, oesophagitis, stomatitis.

***Frequency unknown*:** Intestinal villous atrophy.

Hepato-biliary disorders:

Frequent: Jaundice, hyperbilirubinaemia.

Less frequent: Hepatitis.

Skin and subcutaneous tissue disorders:

Less Frequent: Acne, alopecia, benign neoplasm of skin, fungal dermatitis, hirsutism, skin carcinoma, skin hypertrophy (including actinic keratosis), skin ulcer, rash.

Musculoskeletal disorders:

***Less Frequent*:** Leg cramps, myalgia, myasthenia, arthralgia.

Renal and urinary disorders:

Frequent: Haematuria, renal tubular necrosis, renal impairment.

Less Frequent: Dysuria, urinary frequency, urinary incontinence, urinary retention.

General disorders and administrative site conditions:

Frequent: Asthenia, fever, headache, infection, pain (includes abdominal, back and chest), peripheral oedema, chills.

Less Frequent: Enlarged abdomen, facial oedema, flu syndrome, haemorrhage, malaise, pelvic pain.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There has been no reported experience of overdosage of mycophenolate mofetil in humans.

MYCOCEPT 500 cannot be removed by haemodialysis.

MYCOCEPT 500 can be removed by bile acid sequestrants, such as cholestyramine, by increasing excretion of the substance.

IDENTIFICATION:

Mycocept 500: Lavender coloured, film-coated, biconvex tablet, plain on both the sides.

PRESENTATION:

Mycocept 500 film-coated tablets are packed into 5 x white opaque PVC/PE/PVDC Aluminium foil blister strips of 10 tablets each inside an outer cardboard box.

STORAGE INSTRUCTIONS:

Store at or below 25 °C in the original package.

Keep the blisters in the outer carton until required for use.

Protect from light and moisture.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

43/32.2/0241

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Sandoz SA (Pty) Ltd[1]

72 Steel Road, Spartan

Kempton Park, 1619

DATE OF PUBLICATION OF THE PACKAGE INSERT:

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Date of most recent approval of professional information: 07 December 2012

[1]Company Reg. No.: 1990/001979/07