Summary of Product Characteristics

MYCEPT - S 180/ 360

Mycophenolic Acid Delayed-Release Tablets USP 180mg/ 360 mg

1. Trade Name of the Medicinal Product

MYCEPT-S 180 (Mycophenolic Acid Delayed-Release tablets USP 180 mg).

MYCEPT-S 360 (Mycophenolic Acid Delayed-Release tablets USP 360 mg).

2. Qualitative and Quantitative Composition

Each delayed release tablet contains:

Mycophenolate Sodium USP

Eq. to Mycophenolic Acid ….180mg

Colours: Ferric oxide (Red) and Titanium dioxide

Each delayed release tablet contains:

Mycophenolate Sodium USP

Eq. to Mycophenolic Acid ….360mg

Colours: Ferric oxide (Red) and Titanium dioxide

3. Pharmaceutical Form

- **Pharmaceutical form:** Delayed-Release tablets.
- **Product Description (Mycept-S 180):** Reddish brown coloured, round shaped, coatedtablets & plain on both side.
- **Product Description (Mycept-S 360):** Reddish brown coloured, oblong shaped, coatedtablets, plain on both side.

4. Clinical Particulars

4.1 Therapeutic indications

Mycophenolic Acid is indicated in combination with ciclosporin and corticosteroids for theprophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants.

4.2 Posology and Method of Administration:

Treatment with Mycophenolic Acid should be initiated and maintained by appropriately qualified transplant specialists.

Posology

The recommended dose is 720 mg administered twice daily (1,440 mg daily dose). This dose of mycophenolate sodium corresponds to 1 g mycophenolate mofetil administered twice daily (2 g daily dose) in terms of mycophenolic acid (MPA) content.

For additional information about the corresponding therapeutic doses of mycophenolate sodium and mycophenolate mofetil.

In *de novo* patients, Mycophenolic Acid should be initiated within 72 hours following transplantation.

Special population

Paediatric population

Insufficient data are available to support the efficacy and safety of Mycophenolic Acid in children and adolescents. Limited pharmacokinetic data are available for paediatric renal transplant patients.

Older people

The recommended dose in elderly patients is 720 mg twice daily.

Patients with renal impairment

In patients experiencing delayed renal graft function post-operatively, no dose adjustments areneeded.

Patients with severe renal impairment (glomerular filtration rate <25 ml·min-1·1.73 m-2) shouldbe carefully monitored and the daily dose of Mycophenolic Acid should not exceed 1,440 mg.

Patients with hepatic impairment

No dose adjustments are needed for renal transplant patients with severe hepatic impairment.

Treatment during rejection episodes

Renal transplant rejection does not lead to changes in mycophenolic acid (MPA) pharmacokinetics; dosage modification or interruption of Mycophenolic Acid is not required.

Method of administration

Mycophenolic Acid can be taken with or without food. Patients may select either option but mustadhere to their selected option.

Mycophenolic Acid tablets should not be crushed. Where crushing of Mycophenolic Acid tablets is necessary, avoid inhalation of the powder or direct contact of the powder with skin or mucous membrane. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. This is due to the teratogenic effects of mycophenolate.

4.3 Contraindications

Mycept should not be used in patients with hypersensitivity to mycophenolate sodium, mycophenolic acid or mycophenolate mofetil or to any of the excipients.

Mycept should not be used in women of child bearing potential (WOCBP) who are not usinghighly effective contraception methods.

Mycept should not be initiated in women of child bearing potential without providing a pregnancy test result to rule out unintended use in pregnancy.

Mycept should not be used in pregnancy unless there is no suitable alternative treatment toprevent transplant rejection.

Mycept should not be given to women who are breastfeeding.

4.4. Special Warnings and special Precautions for use

Patients receiving immunosuppressive regimens involving combinations of drugs, including Mycophenolic Acid are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimise the 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.

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

Patients treated with immunosuppressants, including Mycept, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis. Among the opportunistic infections are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving Mycophenolic Acid in combination with other immunosuppressants. In some of these cases, switching MPA derivatives to an alternative immunosuppressant, resulted in serum IgG levels returning to normal. Patients on Mycophenolic acid who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been reports of bronchiectasis in patients who received Mycophenolic acid in combination with other immunosuppressants. In some of these cases, switching MPA derivatives to another immunosuppressant, resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have been also isolated reports of interstitial lung disease. It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated for any evidence of underlying interstitial lung disease.

Reactivation of hepatitis B (HBV) or hepatitis C (HCV) have been reported in patients treated with immunosuppressants, including the mycophenolic acid (MPA) derivatives Mycophenolic acid and mycophenolate mofetil (MMF). Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA

derivatives (which include mycophenolate mofetil and mycophenolate sodium) in combination with other immunosuppressants. The mechanism for MPA derivatives induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of therapy. Changes to Mycept therapy should only be undertaken under appropriate supervision in transplant recipients in orderto minimise the risk of graft rejection.

Patients receiving Mycept should be monitored for blood disorders (e.g. neutropenia or anemia –, which may be related to MPA itself, concomitant medications, viral infections, or some combination of these causes. Patients taking Mycept should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If blood disorders occur (e.g. neutropenia with absolute neutrophil count
<1.5 x 103/µl or anemia) it may be appropriate to interrupt or discontinue Mycophenolic Acid. Patients should be advised that during treatment with MPA vaccinations may be less effectiveand the use of live attenuated vaccines should be avoided.
Influenza vaccination may be of value. Prescribers should refer to national guidelines forinfluenza vaccination.
Because MPA derivatives have been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration and haemorrhage and perforation, Mycept should be administered with caution in patients with active serious digestive system disease.
It is recommended that Mycept not be administered concomitantly with azathioprine because concomitant administration of these drugs has not been evaluated.
Mycophenolic acid (as sodium salt) and mycophenolate mofetil should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles.
Mycept has been administered in combination with corticosteroids and ciclosporin.
There is limited experience with its concomitant use with induction therapies such as anti-T- lymphocyte globulin or basiliximab. The efficacy and safety of the use of Mycept with other immunosuppressive agents (for example, tacrolimus) have not been studied.
Mycept contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The concomitant administration of Mycophenolic Acid and drugs which interfere with enterohepatic circulation, for example cholestyramine or activated charcoal, may result in sub- therapeutic systemic MPA exposure and reduced efficacy.

Mycophenolic Acid is an IMPDH (inosine monophosphate dehydrogenase) 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.

Mycept therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Mycept therapy, during therapy and for six weeks following therapy discontinuation.

Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45-49%) and congenital malformations (estimated rate of 23-27%) have been reported following mycophenolate mofetil exposure during pregnancy. Therefore Mycept is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female and male patients of reproductive potential should be made aware of the risks and follow the recommendations. (e.g. contraceptive methods, pregnancy testing) prior to, during, and after therapy with Mycept. Physicians should ensure that women and men taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

Contraception

Because of the genotoxic and teratogenic potential of Mycept, women with childbearing potential should use two reliable forms of contraception simultaneously before starting Mycept therapy, during therapy, and for six weeks after stopping the 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 for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients treated with Mycept are recommended to use highly effective

contraception during treatment and for a total of 90 days after the last dose of Mycept.

Educational materials

In order to assist patients in avoiding foetal exposure to mycophenolate and to provide additional important safety information, the Marketing Authorisation holder will provide educational materials to healthcare professionals. The educational materials will reinforce the warnings about the teratogenicity of mycophenolate, provide advice on contraception before therapy is started and guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the pregnancy prevention measures should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

Additional precautions

Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate. Men should not donate semen during therapy or for at least 90 days followingdiscontinuation of mycophenolate.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions have been reported between MPA and other medicinal products:

Aciclovir and ganciclovir

The potential for myelosuppression in patients receiving both Mycophenolic Acid and aciclovir or ganciclovir has not been studied. Increased levels of mycophenolic acid glucuronide (MPAG) and aciclovir/ganciclovir may be expected when aciclovir/ganciclovir and Mycophenolic Acid are administered concomitantly, possibly as a result of competition for the tubular secretion pathway.

The changes in MPAG pharmacokinetics are unlikely to be of clinical significance in patients with adequate renal function. In the presence of renal impairment, the potential exists for increases in plasma MPAG and aciclovir/ganciclovir concentrations; dose recommendations for aciclovir/ganciclovir should be followed and patients carefully observed.

Gastroprotective agents:

Magnesium and aluminium containing antacids:

MPA AUC and Cmax have been shown to decrease by approximately 37% and 25%, respectively, when a single dose of magnesium-aluminium containing antacids is given concomitantly with Mycophenolic Acid. Magnesium aluminium-containing antacids may be used intermittently for the treatment of occasional dyspepsia. However the chronic, daily use of magnesium-aluminium containing antacids with Mycophenolic Acid is not recommended due to the potential for decreased mycophenolic acid exposure and reduced efficacy.

Proton pump inhibitors:

In healthy volunteers, no changes in the pharmacokinetics of MPA were observed following concomitant administration of Mycophenolic Acid and pantoprazole given at 40 mg twice daily during the four previous days. No data are available with other proton pump inhibitors given at high doses.

Oral contraceptives

Interaction studies between MMF and oral contraceptives indicate no interaction. Given the metabolic profile of MPA, no interactions would be expected for Mycophenolic Acid and oral contraceptives.

Cholestyramine and drugs that bind bile acids

Caution should be used when co-administering drugs or therapies that may bind bile acids, for example bile acid sequestrates or oral activated charcoal, because of the potential to decrease MPA exposure and thus reduce the efficacy of Mycophenolic Acid.

Ciclosporin

When studied in stable renal transplant patients, ciclosporin pharmacokinetics were unaffected by steady state dosing of Mycophenolic Acid. When co-administered with mycophenolate mofetil, ciclosporin is known to decrease the exposure of MPA. When co-administered with Mycophenolic Acid, ciclosporin may decrease the concentration of MPA as well (by approximately 20%, extrapolated from mycophenolate mofetil data), but the exact extent of this decrease is unknown because such an interaction has not been studied. However, as efficacy studies were conducted in combination with ciclosporin, this interaction does not modify the recommended posology of Mycophenolic Acid. In case of interruption or discontinuation of ciclosporin, Mycophenolic Acid dosage should be re-evaluated depending on the immunosuppressive regimen.

Tacrolimus

In a calcineurin cross-over study in stable renal transplant patients, steady-state Mycophenolic Acid pharmacokinetics were measured during both Neoral and tacrolimus treatment. Mean MPA AUC was 19% higher (90% CI: -3, +47), whereas mean MPAG AUC was about 30% lower (90% CI: 16, 42) on tacrolimus compared to Neoral treatment. In addition, MPA AUC intra- subject variability was doubled when switching from Neoral to tacrolimus. Clinicians should note this increase both in MPA AUC and variability, and adjustments to Mycophenolic Acid dosing should be dictated by the clinical situation. Close clinical monitoring should be performed when a switch from one calcineurin inhibitor to another is planned.

Live attenuated vaccines

Live vaccines should not be given to patients with an impaired immune response. The antibodyresponse to other vaccines may be diminished.

4.6 Pregnancy and lactation

Women of child-bearing potential

Mycept therapy should not be initiated until a negative pregnancy test has been obtained.

Contraception in males and females

Mycept is contraindicated in women of childbearing potential who are not using highly effective contraception.

Because of the genotoxic and teratogenic potential of Mycophenolic Acid, women of childbearing potential should use two reliable forms of contraception simultaneously before beginning Mycophenolic Acid therapy, during Mycophenolic Acid therapy and for six weeks after their last dose of Mycophenolic Acid, 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 for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy.

In addition, female partners of these male patients treated with Mycophenolic Acid are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of Mycophenolic Acid.

Pregnancy

Mycophenolic Acid is contraindicated during pregnancy unless there is no suitable alternativetreatment available to prevent transplant rejection.

Treatment should not be initiated without providing a negative pregnancy test result to rule outunintended use in pregnancy.

Female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations at the beginning of the treatment and must be counseled regarding pregnancy prevention and planning.

Before starting Mycophenolic Acid treatment, women of child bearing potential should have a pregnancy test in order to exclude unintended exposure of the embryo to mycophenolate. Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended; the second test (when appropriate) should be performed 8 – 10 days after the first one and immediately before starting Mycophenolic Acid. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy:

• Spontaneous abortions have been reported in 45 to 49% of pregnant women exposed tomycophenolate mofetil, compared to a reported rate of between 12 and 33% in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.

• Based on literature reports, malformations occurred in 23 to 27% of live births in women exposed to mycophenolate mofetil during pregnancy (compared to 2 to 3 % of live births in the overall population and approximately 4 to 5% of live births in solid organ transplant recipients treated with immunosuppressants other than mycophenolate mofetil).

Congenital malformations, including reports of multiple malformations, have been observed post-marketing in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants during pregnancy. The following

malformations were most frequentlyreported:

• Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear), externalauditory canal atresia;

• Congenital heart disease such as atrial and ventricular septal defects;

• Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of theorbits;

• Abnormalities of the eye (e.g. coloboma);

• Malformations of the fingers (e.g. polydactyly, syndactyly);

• Tracheo-Oesophageal malformations (e.g. oesophageal atresia);

• Nervous system malformations such as spina bifida;

• Renal abnormalities.

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

• Microphthalmia;

• congenital choroid plexus cyst;

• septum pellucidum agenesis;

• olfactory nerve agenesis.

Studies in animals have shown reproductive toxicity.

Breastfeeding

MPA is excreted in milk in lactating rats. It is unknown whether Mycophenolic Acid is excreted in human breast milk. Because of the potential for serious adverse reactions to MPA in breast-fed infants, Mycophenolic Acid is contra-indicated in women who are breast-feeding.

Fertility

No specific studies with Mycophenolic Acid in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen up to a dose of 40 mg/kg and 20 mg/kg respectively

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4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The mechanism of action and pharmacodynamic profile and the reported adverse reactions indicate that an effect is unlikely.

4.8 Undesirable effects

The following undesirable effects cover adverse drug reactions from clinical trials:
Malignancies

Patients receiving immunosuppressive regimens involving combinations of drugs, including MPA, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. Lymphoproliferative disease or lymphoma developed in 2 *de novo* (0.9%) patients and in 2 maintenance patients (1.3%) receiving Mycophenolic Acid for up to 1 year. Non-melanoma skin carcinomas occurred in 0.9% of *de novo* and 1.8% of maintenance patients receiving Mycophenolic Acid for up to 1 year; other types of malignancy occurred in 0.5% of *de novo* and 0.6% of maintenance patients.

Opportunistic infections

All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load. The most common opportunistic infections in de novo renal transplant patients receiving Mycophenolic Acid with other immunosuppressants in controlled clinical trials of renal transplant patients followed for 1 year were cytomegalovirus (CMV), candidiasis and herpes simplex. CMV infection (serology, viraemia or disease) was reported in 21.6% of de novo and in 1.9% of maintenance renal transplant patients.

Older people

Elderly patients may generally be at increased risk of adverse drug reactions due to immunosuppression.

Other adverse drug reactions

Table below contains adverse drug reactions possibly or probably related to Mycophenolic Acid reported in the controlled clinical trials in renal transplant patients, in which Mycophenolic Acid was administered together with ciclosporin microemulsion and corticosteroids at a dose of 1,440 mg/day for 12 months. It is compiled according to MedDRA system organ class.

Adverse reactions are listed according to the following categories:

Very common
Common
Uncommon
Rare
Very rare

Table

(≥1/10)
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to <1/10) (≥1/1,000 to <1/100) (≥1/10,000 to <1/1,000)(<1/10,000)

Infections and infestations	
Very common:	Viral, bacterial and fungal infections
Common:	Upper respiratory tract infections, pneumonia
Uncommon:	Wound infection, sepsis*, osteomyelitis*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	

Uncommon	Skin papilloma*, basal cell carcinoma*, Kaposi´s sarcoma*, lymphoproliferativedisorder, squamous cell carcinoma*
Blood and lymphatic system disorders	
Very common:	Leukopenia
Common:	Anaemia, thrombocytopenia
Uncommon:	Lymphopenia*, neutropenia*, lymphadenopathy*
Metabolism and nutrition disorders	
Very common:	Hypocalcemia, hypokalemia, hyperuricemia
Common:	Hyperkalemia, hypomagnesemia
Uncommon:	Anorexia, hyperlipidaemia, diabetes mellitus*, hypercholesterolaemia*,hypophosphataemia
Psychiatric disorders	
Uncommon:	Abnormal dreams*, delusional perception*, insomnia*
Nervous system disorders	
Common:	Dizziness, headache
Uncommon:	Tremor
Eye disorders	
Uncommon:	Conjunctivitis*, vision blurred*
Cardiac disorders	
Uncommon:	Tachycardia, ventricular extrasystoles
Vascular disorders	
Very common:	Hypertension
Common:	Hypotension
Uncommon:	Lymphocele*
Respiratory, thoracic and mediastinal disorders	
Common:	Cough, dyspnoea
Uncommon:	Interstitial lung disease, pulmonary congestion*, wheezing*, pulmonary oedema*
Gastrointestinal disorders	

Very common	Diarrhoea
Common:	Abdominal distension, abdominal pain, constipation, dyspepsia, flatulence,gastritis, nausea, vomiting
Uncommon:	Abdominal tenderness, gastrointestinal haemorrhage, eructation, halitosis*, ileus*, lip ulceration*, oesophagitis*, subileus*, tongue discolouration*, dry mouth*, gastro-oesophageal reflux disease*, gingival hyperplasia*, pancreatitis, parotid duct obstruction*, peptic ulcer*, peritonitis*

Hepato-biliary disorders	
Common:	Liver function tests abnormal
Skin and subcutaneous tissue disorders	
Common:	Acne, pruritus
Uncommon:	Alopecia
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia
Common:	Myalgia
Uncommon:	Arthritis*, back pain*, muscle cramps
Renal and urinary disorders	
Common:	Blood creatinine increased
Uncommon:	Haematuria*, renal tubular necrosis*, urethral stricture
Reproductive system and breast disorders	
Uncommon:	Impotence*
General disorders and administration site conditions	
Common:	Asthenia, Fatigue, oedema peripheral, pyrexia
Uncommon:	Influenza like illness, oedema lower limb*, pain, rigors*, thirst*, weakness*
Injury, poisoning and procedural complications	
Uncommon:	Contusion*

* Event reported in a single patient (out of 372) only.

Note: renal transplant patients were treated with 1,440 mg Mycophenolic Acid daily up to one year. A similar profile was seen in the de novo and maintenance transplant population although the incidence tended to be lower in the maintenance patients.

Rash and agranulocytosis have been identified as adverse drug reactions from post marketing experience.

The following additional adverse reactions are attributed to MPA derivatives as a class effect:

Infections and infestations:

Serious, life-threatening infections, including meningitis, infectious endocarditis, tuberculosis, and atypical mycobacterial infection. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal

leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Mycophenolic Acid.

Blood and lymphatic system disorders:

Neutropenia, pancytopenia.
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives.

Immune system disorders:
Hypogammaglobulinaemia has been reported in patients receiving Mycophenolic Acid in combination with other immunosuppressants.

Respiratory, thoracic and mediastinal disorders:
There have been isolated reports of interstitial lung disease in patients treated with Mycophenolic Acid in combination with other immunosuppressants. There have also been reports of bronchiectasis in combination with other immunosuppressants.
Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with MPA derivatives. These changes are not associated with impaired neutrophil function. These changes may suggest a 'left shift' in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive Mycophenolic Acid.

Gastrointestinal disorders:
Colitis, CMV gastritis, intestinal perforation, gastric ulcers, duodenal ulcers.

4.9 Overdose
There have been reports of intentional or accidental overdoses with Mycophenolic Acid whereas not all patients experienced related adverse events.
In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the class (mainly blood dyscrasias, sepsis…). Although dialysis may be used to remove the inactive metabolite MPAG, it would not be expected to remove clinically significant amounts of the active moiety MPA. This is in large part

due to the very high plasma protein binding of MPA, 97%. By interfering with enterohepatic circulation of MPA, bile acid sequestrants, such as cholestyramine, may reduce the systemic MPA exposure.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressant, ATC code: L04AA06

MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. 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, MPA has more potent cytostatic effects on lymphocytes than on other cells.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, mycophenolate sodium is extensively absorbed. Approximately 10% of all morning pharmacokinetic profiles showed a delayed Tmax, sometimes up to several hours, without any expected impact on 24 hour/daily MPA exposure.

In stable renal transplant patients on ciclosporin based immunosuppression, the gastrointestinal absorption of MPA was 93% and the absolute bioavailability was 72%. Mycophenolic Acid pharmacokinetics is dose proportional and linear over the studied dose range of 180 to 2,160 mg. Compared to the fasting state, administration of a single dose of Mycophenolic Acid 720 mgwith a high fat meal (55 g fat, 1,000 calories) had no effect on the systemic exposure of MPA (AUC), which is the most relevant pharmacokinetic parameter linked to efficacy. However there was a 33% decrease in the maximal concentration of MPA (C_{max}). Moreover, T_{lag} and T_{max} were on average 3-5 hours delayed, with several patients having a T_{max} of >15 hours. The effect of food on Mycophenolic Acid may lead to an absorption overlap from one dose interval to another.However, this effect was not shown to be clinically significant.

Distribution

The volume of distribution at steady state for MPA is 50 litres. Both mycophenolic acid and mycophenolic acid glucuronide are highly protein bound (97% and 82%, respectively). The free MPA concentration may increase under conditions of decreased protein binding sites (uraemia, hepatic failure, hypoalbuminaemia, concomitant use of drugs with high protein binding). This may put patients at increased risk of MPA-related adverse effects.

Biotransformation

MPA is metabolised principally by glucuronyl transferase to form the phenolic glucuronide of MPA, mycophenolic acid glucuronide (MPAG). MPAG is the predominant metabolite of MPA and does not manifest biological activity. In stable renal transplant patients on ciclosporin-based immunosuppression, approximately 28% of the oral Mycophenolic Acid dose is converted to MPAG by presystemic metabolism. The half-life of MPAG is longer than that of MPA, approximately 16 hours and its clearance is 0.45 l/h.

Elimination

The half-life of MPA is approximately 12 hours and the clearance is 8.6l/h. Although negligible amounts of MPA are present in the urine (<1.0%), the majority of MPA is eliminated in the urine as MPAG. MPAG secreted in the bile is available for deconjugation by gut flora. The MPA resulting from this deconjugation may then be reabsorbed. Approximately 6-8 hours after Mycophenolic Acid dosing a second peak of MPA concentration can be measured, consistent with reabsorption of the deconjugated MPA. There is large variability in the MPA trough levels inherent to MPA preparations, and high morning trough levels (C0 > 10 µg/ml) have been observed in approximately 2% of patients treated with Mycophenolic Acid. However, across studies, the AUC at steady state (0-12h) which is indicative of the overall exposure showed a lower variability than the one corresponding to C_{trough}.

Pharmacokinetics in renal transplant patients on ciclosporin based immunosuppression

Shown in Table are mean pharmacokinetic parameters for MPA following the administration of Mycophenolic Acid. In the early post-transplant period, mean MPA AUC and mean MPA C_{max} were approximately one-half of the values measured six months post-transplant.

Table Mean (SD) pharmacokinetic parameters for MPA following oral administration of

Mycophenolic Acid to renal transplant patients on ciclosporin-based immunosuppression

Adult chronic, multiple dosing 720 mg BID(Study ERLB 301) n=48	Dose	Tmax*(h)	Cmax (µg/ml)	AUC 0-12 (µg x h/ml)
14 days post-transplant	720 mg	2	13.9 (8.6)	29.1 (10.4)
3 months post -transplant	720 mg	2	24.6 (13.2)	50.7 (17.3)
6 months post-transplant	720 mg	2	23.0 (10.1)	55.7 (14.6)
Adult chronic, multiple dosing 720 mg BID18 months post-transplant (Study ERLB 302)	Dose	Tmax*(h)	Cmax (µg/ml)	AUC 0-12 (µg x h/ml)
	720 mg	1.5	18.9 (7.9)	57.4 (15.0)

n=18				
Paediatric 450 mg/m2 single dose(Study ERL 0106) n=16	Dose	Tmax*(h)	Cmax (µg/ml)	AUC o-∞ (µg x h/ml)
	450 mg/m2	2.5	31.9 (18.2)	74.5 (28.3)

* median values

Renal impairment

MPA pharmacokinetics appeared to be unchanged over the range of normal to absent renal function. In contrast, MPAG exposure increased with decreased renal function; MPAG exposure being approximately 8 fold higher in the setting of anuria. Clearance of either MPA or MPAG was unaffected by haemodialysis. Free MPA may also significantly increase in the setting of renal failure. This may be due to decreased plasma protein binding of MPA in the presence of high blood urea concentration.

Hepatic impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on this process probably depend on the particular disease. However, hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Paediatric population and adolescents

Limited data are available on the use of Mycophenolic Acid in children and adolescents. In Table above the mean (SD) MPA pharmacokinetics are shown for stable paediatric renal transplant patients (aged 5-16 years) on ciclosporin-based immunosuppression. Mean MPA AUC at a dose of 450 mg/m2 was similar to that measured in adults receiving 720 mg Mycophenolic Acid. The mean apparent clearance of MPA was approximately 6.7 l/h/m2.

Gender

There are no clinically significant gender differences in Mycophenolic Acid pharmacokinetics.

Older people

Pharmacokinetics in the elderly has not formally been studied. MPA exposure does not appear tovary to a clinically significant degree by age.

5.3 Preclinical safety data

The haematopoetic and lymphoid system were the primary organs affected in repeated-dose toxicity studies conducted with mycophenolate sodium in rats and mice. Aplastic, regenerative anemia was identified as being the dose-limiting toxicity in rodents exposed to MPA. Evaluation of myelograms showed a marked decrease in erythroid cells (polychromatic erythroblasts and normoblasts) and a dose-dependent enlargement of the spleen and increase in extramedullary hematopoiesis. These effects occurred at systemic exposure levels which are equivalent to or lessthan the clinical exposure at the recommended dose of 1.44 g/day of Mycophenolic Acid in renaltransplant patients.

Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or lessthan the clinical exposure at the recommended doses.

The non-clinical toxicity profile of mycophenolic acid (as sodium salt) appears to be consistent with adverse events observed in human clinical trials which now provide safety data of more relevance to the patient population.

Three genotoxicity assays (in vitro mouse lymphoma assay, micronucleus test in V79 Chinese hamster cells and in vivo mouse bone marrow micronucleus test) showed a potential of mycophenolic acid to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other in vitro tests for detection of gene mutation did not demonstrate genotoxic activity.

Mycophenolic acid (as sodium salt) was not tumourigenic in rats and mice. The highest dose tested in the animal carcinogenicity studies resulted in approximately 0.6-5 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 1.44 g/day.

Mycophenolic acid (as sodium salt) had no effect on fertility of male or female rats up to dose levels at which general toxicity and embryotoxicity were observed.

In a teratology study performed with mycophenolic acid (as sodium salt) in rats, at a dose as low as 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly and umbilical hernia. The systemic exposure at this dose

represents 0.05 times the clinical exposure at the dose of 1.44 g/day of Mycophenolic Acid.

In a pre- and postnatal development study in rat, mycophenolic acid (as sodium salt) caused developmental delays (abnormal pupillary reflex in females and preputial separation in males) at the highest dose of 3 mg/kg that also induced malformations.

Mycophenolic acid (as sodium salt) showed a phototoxic potential in an in vitro 3T3 NRU phototoxicity assay.

6. Pharmaceutical Particulars

6.1 List of excipients:

Anhydrous Lactose, Corn Starch, Colloidal Silicon Dioxide, Crospovidone (Type A) (Polyplasdone XL), Povidone (K-30), Isopropyl alcohol, Magnesium Stearate, Opadry II 21K580006 (white), Purified water, Hypromellose Phthalate (55mPa.s) (HP-50), Titanium Dioxide, Ferric oxide (Red), Talc, Triethyl Citrate, Dehydrated Alcohol.

6.2 Incompatibilities

None

6.3 Shelf - Life

24 months

6.4 Storage instructions

Do not store above 30°C, protect from light and moisture.

6.5 Nature and contents of container

3 x 10's tablets: Each Blister strip contains 10 tablets. 3 such blister strips are packed in a cartonalong with a package insert.

6 x 10's tablets: Each Blister strip contains 10 tablets. 6 such blister strips are packed in a cartonalong with a package insert.

12 x 10's tablets: Each Blister strip contains 10 tablets. 12 such blister strips are packed in acarton along with a package insert.

HDPE Bottle pack: 120 numbers of tablets packed in a HDPE bottle. The bottle is closed by 33mm child resistant polypropylene closure cap with induction sealing liner.

6.6 Instructions for user handling

None

7. Marketing Authorization Holder

Panacea Biotec Pharma Ltd.

8. Marketing Authorization Number

TAN 21 HM 0386

9. Date of renewal of Authorization

Not applicable.

10. Date of Preparation of the Text

April, 2022