Proprietary name:	Deprol 180 and Deprol 360
Dosage form:	Tablets
Active Ingredient:	Mycophenolic acid (as mycophenolate sodium)
Strength per dosage unit:	180 mg and 360 mg per tablet

1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Deprol 180 tablets

Deprol 360 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Deprol 180: Each tablet contains 180 mg of mycophenolic acid (as mycophenolate sodium).

Deprol 360: Each tablet contains 360 mg of mycophenolic acid (as mycophenolate sodium).

Contains Sugar.

Excipient(s) with known effect:

Each **Deprol 180** tablet contains 23,10 mg of lactose anhydrous

Each **Deprol 360** tablet contains 46,20 mg of lactose anhydrous

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Deprol 180: Lime green coloured, round shaped, biconvex, film-coated tablets plain on both sides.

Deprol 360: Pale orange-red coloured, oval shaped, biconvex, film-coated tablets plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Deprol is indicated in combination with ciclosporin for microemulsion and corticosteroids for the prevention of acute organ transplant rejection in adult patients receiving allogenic renal transplants.

4.2 Posology and method of administration

Treatment with **Deprol** should be initiated and maintained by appropriately qualified transplant specialists.

Deprol should be initiated in d*e novo* patients within 48 hours following transplantation.

Posology:

The recommended dose is 720 mg (four 180 mg or two 360 mg **Deprol** tablets) administered twice daily (1440 mg daily dose).

Treatment during rejection episodes:

Renal transplant rejection does not lead to changes in mycophenolic acid (MPA) pharmacokinetics, dosage reduction or interruption of **Deprol** is not required.

Special Populations:

Elderly:

No dose adjustment is required in this population.

*Renal impairment**:***

No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively. Patients with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73 m^2) should be carefully followed up.

Paediatric population:

Safety and efficacy in paediatrics have not been established.

Method of administration:

Deprol can be taken with or without food and should be swallowed whole with a glass of water. Tablets should not be crushed in order to retain the integrity of the enteric coating.

4.3 Contraindications

Deprol is contra-indicated in:

- Patients with hypersensitivity to mycophenolic acid, mycophenolate sodium, mycophenolate mofetil or any other component of **Deprol**.
- Pregnancy and lactation.

Proprietary name:	Deprol 180 and Deprol 360
Dosage form:	Tablets
Active Ingredient:	Mycophenolic acid (as mycophenolate sodium)
Strength per dosage unit:	180 mg and 360 mg per tablet

4.4 Special warnings and precautions for use

WARNING 1: CARCINOGENICITY

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, especially of the skin, may result from immune-suppression. Only medical practitioners experienced in immune-suppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe **Deprol**. Patients receiving the medicines 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 2: TERATOGENICITY

Mycophenolic acid is powerfully teratogenic and mutagenic. Congenital malformation and spontaneous abortions have been reported with use of mycophenolic acid in pregnancy. Woman of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/ ml; the second test should be performed 8-10 days after the first one and immediately before starting treatment with **Deprol**. Repeat pregnancy tests should be performed during routine follow- up visits.

Woman of childbearing potential should use two reliable forms of contraception simultaneously, including at least one highly effective method, before beginning **Deprol** 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 risk associated with the transfer of seminal fluid also 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 **Deprol.**

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with **Deprol** in combination with other immunosuppressive medicines. The mechanism for **Deprol** derivative induced PRCA is unknown; the relative contribution in an immunosuppressive regimen are also unknown. PRCA was found to be reversible with dose reduction or cessation of treatment. In transplant patients, however, reduced immunosuppression may place the graft at risk. Changes to **Deprol** therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see Section 4.8).

Deprol should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles.

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 following discontinuation of mycophenolate.

Patients on **Deprol** therapy should limit their 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 **Deprol** as part of an immunosuppressive regimen, which appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific medicine.

Serious Infections:

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 **Deprol** should be advised to immediately report any evidence of infection, unexpected bruising or bleeding to their medical practitioner.

New and Reactivated Viral Infections:

There is also an increased risk of activation of latent viral infections. These include polymavirus associated nephropathy (PVAN), JC virus-associated progressive multifocal leukoencephalopathy (PML), sometimes fatal, cytomegalovirus (CMV) infections, reactivation of hepatitis B (HBV) or hepatitis C (HCV), and BK virus-associated nephropathy which can lead to renal graft loss.

Monitoring infected patients for signs of active HBV or HCV is recommended.

Neutropenia:

Patients receiving **Deprol** 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 in these patients, as it may be related to **Deprol** itself, concomitant medicines, viral infections, or some combination of these causes.

Treatment with **Deprol** may need to be stopped if severe neutropenia develops.

Vaccinations:

During treatment with **Deprol**, vaccinations may be less effective and the use of live attenuated vaccines should be avoided due to the increased risk of infection. Intra-uterine devices should be used with caution in patients who are on **Deprol** treatment for the same reason.

Hereditary Deficiency:

Deprol is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, therefore, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Effect on digestive system:

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, **Deprol** should be administered with caution in patients with active serious digestive system disease.

Elderly:

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

Excipients:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **Deprol**.

4.5 Interaction with other medicines and other forms of interaction

Antiviral medicines (Acyclovir or valacyclovir, or ganciclovir or valganciclovir): Increases in MPAG and acyclovir plasma concentrations were observed when **Deprol** was administered concomitantly with these medicines, compared to their plasma concentrations when administrated alone. MPAG plasma concentrations as well as the plasma concentrations of these antivirals are increased in the presence of renal impairment when administered alone,

therefore, the potential exists for these medicines to compete for tubular secretion, thus resulting in further increases in concentration when administered concomitantly.

Cholestyramine:

Cholestyramine and concomitant use of **Deprol** 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 **Deprol** efficacy.

Antacids:

Antacids with magnesium and aluminium hydroxides may decrease the absorption of **Deprol**.

Azathioprine:

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

Ciclosporin:

When studied in stable renal transplant patients, ciclosporin pharmacokinetics were unaffected by steady state dosing of **Deprol**.

Tacrolimus:

In a calcineurin cross-over study in stable renal transplant patients, steady-state **Deprol** pharmacokinetics were measured during both ciclosporin 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 ciclosporin treatment.

Probenecid:

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

Live vaccines:

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

Rifampicin:

Rifampicin decreases exposure to mycophenolate (in patients not also taking ciclosporin); MPA concentrations should be monitored when rifampicin and **Deprol** are used together.

Oral contraceptives:

Oral contraceptives undergo oxidative metabolism while **Deprol** is metabolised by glucuronidation. Efficacy of the oral contraceptive may be adversely affected by the **Deprol**.

Antibacterial medicines:

In liver transplant patients the bioavailability of MPA was reduced by concomitant administration of tobramycin and cefuroxime, apparently through inhibition of enterohepatic recycling of MPA by the antibacterial medicines. Norfloxacin, metronidazole or a combination of the two, reduced exposure to MPA and MPAG when given to healthy subjects receiving **Deprol**. A similar reduction in concentration was noted with ciprofloxacin or amoxicillin and clavulanic acid.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential:

Women of childbearing potential should have a negative pregnancy test within 1 week of starting **Deprol** treatment. Women on **Deprol** treatment should use effective contraception from at least 4 weeks prior to starting therapy, until 6 weeks after stopping treatment of **Deprol**.

Pregnancy:

Deprol is contra-indicated in pregnancy.

The use of **Deprol** in pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations (see section 4.3 and section 4.4).

Breastfeeding:

Deprol is contra-indicated during breast feeding.

4.7 Effects on ability to drive and use machines

Patients should avoid operating hazardous machines or driving motor vehicles, as **Deprol** may cause somnolence and drowsiness.

4.8 Undesirable effects

A. Summary of the safety profile

Malignancies:

Patients receiving immunosuppressive regimens involving combinations of medicines, including MPA, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.4).

Opportunistic infections:

All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load (see section 4.4). The most frequent opportunistic infections in new renal transplant patients receiving **Deprol** with other immunosuppressants were cytomegalovirus (CMV), candidiasis and herpes simplex. CMV infection (serology, viraemia or disease) was reported frequently in new and less frequent in maintenance renal transplant patients.

Elderly:

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

B. Tabulated list of the adverse reactions

Adverse reactions reported are shown below. Frequencies were defined using the following convention: *frequent, less frequent, frequency unknown*:

Class/ Frequency	***Adverse reactions***
Infestation and Infections	
Frequent	Viral, bacterial and fungal infections, upper respiratory tract infection, pneumonia
Less frequent	Wound infection, sepsis, osteomyelitis
Frequency unknown	Meningitis, infectious endocarditis, infection, polymavirus associated nephropathy (PVAN), especially due to BK virus.
Blood and the lymphatic system disorders	
Frequent:	Anaemia (including hypochromic anaemia), leucopoenia and thrombocytopenia.
Less frequent	lymphocele, lymphopenia, neutropenia and lymphacenopathy.

Frequency unknown	Aplastic anaemia, bone marrow depression (sometimes fatal), and pure red cell aplasia
Endocrine disorders	
Less Frequent	Diabetes mellitus, parathyroid disorder and Cushing's syndrome
Metabolism and nutrition disorders	
Less frequent	Anorexia, diabetes mellitus, hypercholesterolemia, hypophosphataemia and hyperlipidaemia
Psychiatric disorders	
Less frequent	Abnormal dreams, delusional perception
Nervous system disorders	
Frequent:	Headache
Less frequent	Tremor and insomnia. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal.
Eye disorders	
Less frequent	Conjunctivitis and blurred vision
Class/ Frequency	***Adverse reactions***
Ear and labyrinth disorders	
Less frequent	Deafness
Cardiovascular disorders	
Less frequent	Ventricular extrasystoles and tachycardia.
Respiratory disorders	
Frequent	Cough.
Less frequent	Pulmonary congestion, pulmonary oedema, wheezing.
Frequency unknown	Tuberculosis and atypical mycobacterial infection.
Hepato-biliary disorders	
Frequent	hepatic function tests abnormal

Gastrointestinal disorders	
Frequent	Diarrhoea, abdominal distension, abdominal pain, flatulence, gastritis, loose stools, nausea, vomiting, constipation and dyspepsia.
Less frequent	Abdominal tenderness, eructation, halitosis, ileus, peptic ulcer, subileus, tongue discolouration, gastrointestinal haemorrhage, dry mouth, lip ulceration, parotid duct obstruction, gastro-oesophageal reflux disease, gum hyperplasia, oesophagitis, peritonitis and pancreatitis.
Frequency unknown	Colitis and intestinal perforation, cytomegalovirus (CMV) gastritis and duodenal ulcer.
Skin and subcutaneous tissue disorders	
Less Frequent	Alopecia and confusion
Musculoskeletal disorders	
Less frequent	Arthritis back pain and muscle cramps
Reproductive system disorders	
Less frequent	Impotence
Class/ Frequency	***Adverse reactions***
Renal and urinary disorders	
Frequent	Increased blood creatinine
Less Frequent	Haematuria, renal tubular necrosis, urethral stricture
General disorders	
Frequent	Fatigue and fever
Less frequent	Flu-like syndrome, oedema lower limb, pain, thirst, weakness.
Neoplasms benign and malignant	
Less frequent	Skin papilloma, basal cell carcinoma, Kaposi's sarcoma, squamous cell carcinoma, lymphoproliferative disorder.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 Alternatively all adverse events can be reported to Alkem Laboratories vial the e-mail: pharmacist.rsa@Alkem.com.

4.9 Overdose

There has been no reported experience of overdosage with **Deprol.**

Although dialysis may be used to remove inactive metabolites 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.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.32.2 Other (Immunosuppressants)

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants.

ATC code: L04AA27

Mycophenolic acid (MPA), the active derivative of mycophenolate sodium, is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase and therefore

(IMPDH) and thereby inhibits the pathway of guanosine nucleotide synthesis without incorporation into DNA. Mycophenolic acid is a 5-fold more potent inhibitor of the type II isoform of IMPDH found in activated B- and T-lymphocytes and thus functions as a specific inhibitor of T- and B-lymphocyte activation and proliferation.

Clinical efficacy and safety

The bioequivalence study indicated that **Deprol** is bioequivalent to the reference product with respect to the rate and extent of absorption and was well tolerated by all subjects.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration, mycophenolate sodium is extensively absorbed. The time to maximal concentration (T_{max}) of MPA was approximately 1.5-2 hours which is consistent with enteric coated design. *In vitro* studies demonstrated that the enteric coated formulation of **Deprol** prevents the release of MPA under acidic conditions (such as in the stomach).

In stable renal transplant patients on ciclosporin based immunosuppression, the gastrointestinal absorption of MPA was 93 % and the absolute bioavailability was 72 %. **Deprol** pharmacokinetics is dose proportional and linear over the studied dose range of 180 to 2160 mg.

Compared to the fasting state, administration of a single dose of 720 mg of **[PDODUCT NAME]** with a high fat meal (55 g fat, 1000 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}).

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 medicines with high protein binding). This may put patients at increased risk of MPA-related adverse effects.

Metabolism:

The mean half-life of MPA is 11.7 hours and the clearance is 8.6 L/hr. MPA is metabolised principally by glucuronyl transferase to form phenolic glucuronide of MPA, mycophenolic acid of glucuronide (MPAG). MPAG is the predominant metabolite of MPA and does not manifest biologic activity.

In stable renal transplant patients on ciclosporin-based immunosuppression, approximately 28 % of the oral **Deprol** dose is converted to MPAG by pre-systemic metabolism. The half-life of MPAG is longer than that of MPA, approximately 16 hours, and its clearance is 0.45 L/h.

Elimination:

Although small amounts of MPA are present in the urine (< 3.0 %), 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 **Deprol** dosing a second peak of MPA concentration can be measured, consistent with reabsorption of the deconjugated MPA.

Special populations:

Renal insufficiency:

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 insufficiency:

There are no studies in hepatic insufficiency.

Paediatric patients:

Limited data are available on the use of **Deprol** in children.

Gender:

There are no clinically significant gender differences in pharmacokinetics.

Elderly:

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

6. Pharmaceutical particulars

6.1 List of excipients

Other ingredients are colloidal silicone dioxide, crospovidone, anhydrous lactose, magnesium stearate, maize starch and povidone.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Deprol tablets: 2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep blister in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Deprol 180 is packed into plain aluminium/ aluminium blister strips containing 10 tablets in an outer carton.

Deprol 360 is packed into plain aluminium/ aluminium blister strips containing 10 tablets in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Alkem Laboratories (Pty) Ltd.

R21 Corporate Park

121 Sovereign Drive

Block A, Irene Ext.30,

Centurion, 0157

8 MARKETING AUTHORISATION NUMBER(S)

To be allocated by authority.

9 DATE OF REVISION OF THE TEXT

To be allocated by authority