CellCept (mycophenolate mofetil)

با توجه به تنوع تولید داروی مایکوفنولات موفتیل در ایران و لزوم پایش کیفیت و عوارض دارویی و مصرف این دارو در مرکز قلب شهید رجایی به اطلاع پزشکان و پرستاران محترم می رساند که:

۱. مایکو فنولات موفتیل با نام تجارتی معروف Cellcept یک داروی مهار کننده سیستم ایمنی بوده که معمولا بهمراه داروی سیکلوسپورین و کورتیکواستروئیدها برای جلوگیری از رد پیوند کلیه، کبد و قلب استفاده می شود.

۲. **اشکال دارویی:** مایکوفنولات موفتیل در ایران بصورت کپسول و قرص خوراکی ۲۵۰ و ۵۰۰ میلی گرمی از شرکت های دارویی خارجی و داخلی با نام های تجارتی مختلف عرضه می گردد.

نام تجارتی	شرکت دارویی سازنده	شکل دارویی	نام دارو – قدرت دارویی
		CAPSULE	**Mycophenolate Mofetil 250 mg**
		TABLET	**Mycophenolate Mofetil 500 mg**

۳. **عوارض دارویی:**

Common

- Abdominal or stomach cramps or pain, black, tarry stools, bladder pain, bleeding gums, bloating or swelling of the face, arms, hands, lower legs, or feet, blood in the urine or stools, bloody or cloudy urine, blurred vision, burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings, chest pain, confusion, convulsions, cough or hoarseness, decreased urine, difficult or labored breathing, difficult, burning, or painful urination, dizziness, dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position, drowsiness, dry mouth, fainting, fast, slow, pounding, or irregular heartbeat or pulse, fever or chills, flushed, dry skin, frequent urge to urinate, fruit-like breath odor, headache, increased hunger, increased thirst, increased urination, irregular heartbeats, irregular pulse, irritability, lightheadedness, loss of appetite, lower back or side pain, muscle cramps in the hands, arms, feet, legs, or face, muscle pain or cramps, muscle spasms (tetany) or twitching, nausea or vomiting, nervousness, numbness or tingling in the hands, feet, or lips, painful or difficult urination, pale skin, pinpoint red spots on the skin, pounding in the ears, rapid weight gain, rapid, shallow breathing, seizures, sore throat, sores, ulcers, or white spots on the lips or in the mouth, stomach pain and bloating, sweating, swollen glands, tightness in the chest, tingling of the hands or feet, trembling, tremor, troubled breathing with exertion, unexplained weight loss, unusual bleeding or bruising, unusual tiredness or, weakness, unusual weight gain or loss, weakness or heaviness of the legs

Incidence not known

- Back pain, constipation, coughing or spitting up blood, darkened urine, general feeling of illness, indigestion, night sweats, pain, pains in the stomach, side, or abdomen, possibly radiating to the back, severe headache, sudden high fever or low-grade fever for months, tenderness, watery or bloody diarrhea, yellow eyes or skin

Some of the side effects that can occur with mycophenolate mofetil may not need medical attention. As your body adjusts to the medicine during treatment these side effects may go away. Your health care professional may also be able to tell you about ways to reduce or prevent some of these side effects. If any of the following side effects continue, are bothersome or if you have any questions about them, check with your health care professional:

More common

- Acid or sour stomach
- belching
- fear
- heartburn
- lack or loss of strength
- rash
- trouble sleeping
- weight loss

Gastrointestinal

Gastrointestinal side effects appear to have been dose related.

A well designed, placebo-controlled study of mycophenolate (2 or 3 grams daily) combined with cyclosporine and corticosteroids versus cyclosporine and corticosteroids alone for prevention of acute renal allograft rejection reported a similar frequency of adverse events. There was a trend towards more diarrhea (16% vs. 12%), nausea (6% vs. 3%), gastroenteritis (4% vs. 1%), and vomiting (4% vs. 1%) in the mycophenolate group, especially with the higher dose. Gastrointestinal, rectal, and duodenal hemorrhage, hemorrhagic pancreatitis and large intestine perforation occurred rarely and only in the mycophenolate mofetil (the active ingredient contained in CellCept) group. In general, adverse effects occurred with a higher frequency as the dose was increased above 2 grams per day. Mycophenolate mofetil should be used cautiously in patients with active gastrointestinal disease.[Ref]

Gastrointestinal side effects including diarrhea (36%), nausea (20%), and vomiting (13%) have been the most common side effects. A case of mycophenolate mofetil-induced ischemic colitis also has been reported.[Ref]

Hematologic

A well designed, placebo-controlled study noted that hematologic adverse events resolved within one week. Hematologic side effects tend to occur early in the course of treatment and be dose-related. Careful monitoring of hematologic parameters may be warranted early in the course of therapy.

A well designed, placebo-controlled study of mycophenolate mofetil (the active ingredient contained in CellCept) (2 or 3 grams daily) combined with cyclosporine and corticosteroids versus cyclosporine and corticosteroids alone for prevention of acute renal allograft rejection reported a similar frequency of adverse events. A trend towards higher frequencies of leukopenia (11% to 14%) and anemia (4% to 7%) were reported in the active groups. Pancytopenia and agranulocytosis occurred rarely. The proportion of patients with leukopenia between 31 and 180 days after transplantation was 3 times higher in the mycophenolate mofetil group. All observed hematologic effects resolved within one week. Adverse effects occur with a higher frequency as the dose exceeds 2 grams/day.[Ref]

Hematologic side effects have included dose-related leukopenia (11% to 35%), anemia (25%), and thrombocytopenia (9%). Severe neutropenia has occurred in up to 2% of patients. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressive agents. A case in of mycophenolate mofetil causing deep venous thrombosis has also been reported.[Ref]

Immunologic

Immunologic side effects have included immunosuppression. Immunosuppression associated with therapy has resulted in sepsis (primarily cytomegalovirus viremia) in approximately 20% of patients. Other opportunistic infections have included herpes simplex virus (18%), herpes zoster (7%), and invasive candidal infections (1%).

On a positive note, mycophenolate has been found to delay the recurrence of hepatitis C in liver transplant recipients.[Ref]

Immunosuppression appeared to be dose-related.

In three controlled studies for the prevention of rejection, similar rates of fatal infections/sepsis (less than 2%) occurred in patients receiving mycophenolate mofetil or the control drug (usually azathioprine) in addition to other immunosuppressives. A well designed, placebo-controlled study of mycophenolate mofetil (2 or 3 grams daily) combined with cyclosporine and corticosteroids versus cyclosporine and corticosteroids alone for the prevention of acute renal allograft rejection reported a similar frequency of adverse events. Cytomegalovirus tissue-invasive disease (7%), herpes zoster (7%), and herpes simplex (15%) showed a trend towards a higher frequency in the mycophenolate mofetil group. In general, adverse effects occur with a higher frequency as the dose is increased above 2 grams per day.[Ref]

Oncologic

The incidence of new malignancies in patients receiving mycophenolate mofetil (the active ingredient contained in CellCept) followed for greater than 1 year was similar to that reported in the literature for renal allograft recipients.[Ref]

Oncologic side effects including lymphoma and lymphoproliferative disease (1%) and non-melanoma skin carcinoma (2% to 4%) have been associated with therapy.[Ref]

Renal

Epinette, et al reported a long-term follow up (to 13 years) of patients treated with mycophenolate mofetil (the active ingredient contained in CellCept) on a compassionate-use basis for psoriasis. Dosages averaged between 3 and 4 grams daily (range 2 to 7 grams), higher than the currently recommended dose for renal transplant patients. Dysuria, urgency, and frequency occurred in 28% of patients during the first year and decreased to less than 5% thereafter. Subsequent dose reductions after the first year lessened renal adverse effects considerably.[Ref]

Renal side effects have included urinary tract infections (37% to 45%), hematuria (13%), and kidney tubular necrosis (6% to 10%).

BK virus-associated nephropathy has been reported. This infection is associated with serious outcomes, including deteriorating renal function and renal graft loss.[Ref]

Metabolic

Metabolic side effects have included edema (12% to 28%), hyperphosphatemia (13%), hypokalemia (10%), hyperglycemia (10%), and hyperkalemia (9%).[Ref]

Respiratory

Respiratory system side effects have included respiratory infection (23%), dyspnea (16%), and increased cough (16%). A case of primary tuberculosis one year after conversion from azathioprine to mycophenolate mofetil (the active ingredient contained in CellCept) has also been reported.[Ref]

Dermatologic

Dermatologic side effects including acne (10%) and rash (8%) have been reported in clinical trials. A case of dyshidrotic eczema has been reported. A case of papulosquamous psoriatic-like skin eruption has also been reported.[Ref]

Musculoskeletal

Musculoskeletal side effects including a case of mycophenolate mofetil (the active ingredient contained in CellCept) induced myopathy have been reported.[Ref]

Other

Abdominal pain has been reported to be a critical complication of mycophenolate mofetil (the active ingredient contained in CellCept) in renal transplant recipients.

Other side effects have included abdominal pain and postmarketing reports of congenital malformations and an increased incidence of first trimester pregnancy loss.

Hepatic

Hepatic side effects including a case of mycophenolate sodium-induced hepatotoxicity have been reported.[

Table 11 : Adverse Events Reported in 3% to < 20% of Patients Treated With CellCept in Combination With Cyclosporine and Corticosteroids

BODY SYSTEM	
Body as a Whole	abdomen enlarged, abscess, accidental injury, cellulitis, chills occurring with fever, cyst, face edema, flu syndrome, hemorrhage, hernia, lab test abnormal, malaise, neck pain, pelvic pain, peritonitis
Hematologic and Lymphatic	coagulation disorder, ecchymosis, pancytopenia, petechia, polycythemia, prothrombin time increased, thromboplastin time increased
Urogenital	acute kidney failure, albuminuria, dysuria, hydronephrosis, hematuria, impotence, kidney failure, kidney tubular necrosis, nocturia, oliguria, pain, prostatic disorder, pyelonephritis, scrotal edema, urine abnormality, urinary frequency, urinary incontinence, urinary retention, urinary tract disorder
Cardiovascular	angina pectoris, arrhythmia, arterial thrombosis, atrial fibrillation, atrial flutter, bradycardia, cardiovascular disorder, congestive heart failure, extrasystole, heart arrest, heart failure, hypotension, pallor, palpitation, pericardial effusion, peripheral vascular disorder, postural hypotension, pulmonary hypertension, supraventricular tachycardia, supraventricular extrasystoles, syncope, tachycardia, thrombosis, vasodilatation, vasospasm, ventricular extrasystole, ventricular tachycardia, venous pressure increased
Metabolic and	abnormal healing, acidosis, alkaline phosphatase increased, alkalosis,
Nutritional	bilirubinemia, creatinine increased, dehydration, gamma glutamyl transpeptidase increased, generalized edema, gout, hypercalcemia, hypercholesteremia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypochloremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, hypovolemia, hypoxia, lactic dehydrogenase increased, respiratory acidosis, SGOT increased, SGPT increased, thirst, weight gain, weight loss
Digestive	anorexia, cholangitis, cholestatic jaundice, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis,

	gastrointestinal disorder, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, infection, jaundice, liver damage, liver function tests abnormal, melena, mouth ulceration, nausea and vomiting, oral moniliasis, rectal disorder, stomach ulcer, stomatitis
Respiratory	apnea, asthma, atelectasis, bronchitis, epistaxis, hemoptysis, hiccup, hyperventilation, lung edema, lung disorder, neoplasm, pain, pharyngitis, pleural effusion, pneumonia, pneumothorax, respiratory disorder, respiratory moniliasis, rhinitis, sinusitis, sputum increased, voice alteration
Skin and Appendages	acne, alopecia, fungal dermatitis, hemorrhage, hirsutism, pruritus, rash, skin benign neoplasm, skin carcinoma, skin disorder, skin hypertrophy, skin ulcer, sweating, vesiculobullous rash
Nervous	agitation, anxiety, confusion, convulsion, delirium, depression, dry mouth, emotional lability, hallucinations, hypertonia, hypesthesia, nervousness, neuropathy, paresthesia, psychosis, somnolence, thinking abnormal, vertigo
Endocrine	Cushing's syndrome, diabetes mellitus, hypothyroidism, parathyroid disorder
Musculoskeletal	arthralgia, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis
Special Senses	abnormal vision, amblyopia, cataract (not specified), conjunctivitis, deafness, ear disorder, ear pain, eye hemorrhage, tinnitus, lacrimation disorder

Pediatrics

The type and frequency of adverse events in a clinical study in 100 pediatric patients 3 months to 18 years of age dosed with CellCept oral suspension 600 mg/m² bid (up to 1 g bid) were generally similar to those observed in adult patients dosed with CellCept capsules at a dose of 1 g bid with the exception of abdominal pain, fever, infection, pain, sepsis, diarrhea, vomiting, pharyngitis, respiratory tract infection, hypertension, leukopenia, and anemia, which were observed in a higher proportion in pediatric patients.

CellCept Intravenous

The adverse event profile of CellCept Intravenous was determined from a single, double-blind, controlled comparative study of the safety of 2 g/day of intravenous and oral CellCept in renal transplant patients in the immediate posttransplant period (administered for the first 5 days). The potential venous irritation of CellCept Intravenous was evaluated by comparing the adverse events attributable to peripheral venous infusion of CellCept Intravenous with those observed in the intravenous placebo group; patients in this group received active medication by the oral route.

Adverse events attributable to peripheral venous infusion were phlebitis and thrombosis, both observed at 4% in patients treated with CellCept Intravenous.

In the active controlled study in hepatic transplant patients, 2 g/day of CellCept Intravenous were administered in the immediate posttransplant period (up to 14 days). The safety profile of intravenous CellCept was similar to that of intravenous azathioprine.

Postmarketing Experience

Congenital Disorders: Embryofetal Toxicity: Congenital malformations and an increased incidence of first trimester pregnancy loss have been reported following exposure to mycophenolate mofetil during pregnancy (see **PRECAUTIONS**: **Pregnancy**).

Digestive: Colitis (sometimes caused by cytomegalovirus), pancreatitis, isolated cases of intestinal villous atrophy.

Hematologic and Lymphatic: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept in combination with other immunosuppressive agents.

Infections (see **WARNINGS**: **Serious Infections**, **New or Reactivated Viral Infections**):

- Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally.
- There is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection.
- Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with CellCept. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune function.
- Polyomavirus associated neuropathy (PVAN), especially due to BK virus infection, has been observed in patients receiving immunosuppressants, including CellCept. This infection is associated with serious outcomes, including deteriorating renal function and renal graft loss.
- Viral reactivation has been reported in patients infected with HBV or HCV.

Respiratory: Interstitial lung disorders, including fatal pulmonary fibrosis, have been reported rarely and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in posttransplant patients receiving CellCept.

۴. **موارد منع مصرف:** بروز عارضه HIT ، خونریزی و حساسیت شدید به هپارین. استفاده از هپارین حاوی بنزیل الکل برای نوزادان، اطفال، خانم های باردار و شیر ده ممنوع می باشد.

۵. **تداخلات دارویی** : مصرف همزمان با سایر داروهای ضد انعقاد، ضد پلاکت و ترومبولیتیک احتمال خونریزی را افزایش می یابد.

دکتر ناصر هداوند

بخش خدمات و مراقبتهای دارویی – مرکز آموزشی، تحقیقاتی و درمانی قلب و عروق شهید رجایی