

occur. For these reasons, the combined administration of ciclosporin and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin. Tacrolimus has been shown to increase the blood level of phenytoin. As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures. Limited knowledge of interactions between tacrolimus and statins is available. Available data suggests that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus. Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and phenazone.

Other interactions which have led to clinically detrimental effects

Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole+trimethoprim, NSAIDs, ganciclovir or aciclovir). Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus. As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone) should be avoided. Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

Protein binding considerations

Tacrolimus is extensively bound to plasma proteins. Possible interactions with other medicinal products known to have high affinity for plasma proteins should be considered (e.g., NSAIDs, oral anticoagulants, or oral antidiabetics).

PREGNANCY AND LACTATION

Pregnancy

Human data show that tacrolimus is able to cross the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. To date, no other relevant epidemiological data are available.

Due to the need of treatment, tacrolimus can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus. In case of in utero exposure, monitoring of the newborn for the potential adverse effects of tacrolimus is recommended (in particular the effects on the kidneys). There is a risk for premature delivery (<37 week) as well as for hyperkalaemia in the newborn, which, however, normalizes spontaneously.

In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity. Tacrolimus affected male fertility in rats.

Lactation

Human data demonstrate that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving tacrolimus

SIDE EFFECTS

The adverse drug reaction profile associated with immunosuppressive agents is often difficult to establish owing to the underlying disease and the concurrent use of multiple medications. Many of the adverse drug reactions stated below are reversible and/or respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse drug reactions compared with intravenous use. Adverse drug reactions are listed below in descending order by frequency of occurrence: very common; common; uncommon; rare; very rare; not known

Infections and infestations

As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.

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 Tacrolimus.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Blood and lymphatic system disorders

common	anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal
uncommon	coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia
rare	thrombotic thrombocytopenic purpura, hypoprothrombinaemia
not known	pure red cell aplasia, agranulocytosis, haemolytic anaemia

Immune system disorders

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus. Endocrine disorders

rare	hirsutism
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Metabolism and nutrition disorders

very common	hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common	hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities
uncommon	dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Psychiatric disorders

very common	Insomnia
common	anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders
Uncommon	psychotic disorder

Nervous system disorders

very common	tremor, headache
common	seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders
uncommon	coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia
rare	Hypertonia
Very rare	myasthenia

Eye disorders

common	vision blurred, photophobia, eye disorders
rare	uncommon
	cataract
	blindness

Ear and labyrinth disorders

common	tinnitus
Uncommon	hypacusis
rare	deafness
very rare	neurosensory hearing impaired

Cardiac disorders

common	ischaemic coronary artery disorders, tachycardia
uncommon	ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, abnormal ECG investigations, abnormal heart rate and pulse investigations
rare	pericardial effusion
very rare	Abnormal echocardiogram, prolonged ECG QT, Torsades de Pointes

Vascular disorders

very common	hypertension
common	haemorrhage, thrombotic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
uncommon	infarction, venous thrombosis
	deep limb, shock

Respiratory, thoracic and mediastinal disorders

common	dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations
uncommon	respiratory failures, respiratory tract disorders, asthma
	respiratory distress syndrome

Gastrointestinal disorders

very common	diarrhoea, nausea
common	gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms
uncommon	ileus paralytic, acute and chronic pancreatitis, gastrooesophageal reflux disease, impaired gastric emptying
rare	subileus, pancreatic pseudocyst

Hepatobiliary disorders

Common	cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
Rare	hepatic artery thrombosis, venoocclusive liver disease
Very rare	hepatic failure, bile duct stenosis

Skin and subcutaneous tissue disorders

common	pruritus, rash, alopecia, acne, sweating
rare	increased uncom
	mondermatitis, photosensitivity
	toxic epidermal necrolysis (Lyell's syndrome)
	very rare
	Stevens Johnson syndrome

Musculoskeletal and connective tissue disorders

common	arthralgia, muscle spasms, pain in limb, back pain
	uncommon
	joint disorders

Renal and urinary disorders

very common	renal impairment
common	renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms
uncommon	anuria, haemolytic uraemic syndrome
	very rare
	nephropathy, cystitis
	haemorrhagic

Reproductive system and breast disorders

uncommon	dysmenorrhoea and uterine bleeding
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General disorders and administration site conditions

common	asthenic conditions, febrile disorders, oedema, pain and discomfort, body temperature perception disturbed
	uncommon
	multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal
rare	thirst, fall, chest tightness, ulcer
	very rare
	fat tissue increased

Investigations

common	hepatic enzymes and function abnormalities, blood alkaline phosphatase increased, weight increased
uncommon	amylase increased, ECG investigations abnormal, heart rate and pulse investigations abnormal, weight decreased, blood lactate dehydrogenase increased
very rare	echocardiogram abnormal, electrocardiogram QT prolonged

Injury, poisoning and procedural complications

common	primary graft dysfunction
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Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. A number of associated cases of transplant rejection have been reported (frequency cannot be estimated from available data).

SYMPTOMS AND TREATMENT OF OVERDOSE

Experience with overdose is limited. Several cases of accidental overdosage have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy, increased blood urea nitrogen and elevated serum creatinine concentrations, and increase in alanine aminotransferase levels. No specific antidote to Tacrolimus therapy is available. If overdose occurs, general supportive measures and symptomatic treatment should be conducted.

Based on its high molecular weight, poor aqueous solubility, and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus will not be dialysable. In isolated patients with very high plasma levels, haemofiltration or -diafiltration have been effective in reducing toxic concentrations. In cases of oral intoxication, gastric lavage and/or the use of adsorbents (such as activated charcoal) may be helpful, if used shortly after intake.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if tacrolimus is administered in association with alcohol

SHELF LIFE

24 months from date of manufacture

STORAGE CONDITION

Store below 30° C in dry place. Protect from light.

PRESENTATION

Each blister contains 10 capsules. Such 5 blisters are packed in trilaminated pouch with Silica Gel Packet. One or Two Trilaminated pouch is packed in outer carton along with pack insert. Available pack size: 5 x 10's pouch pack
2 x 5 x 10's pouch pack



ALKEM

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