Professional Information for Medicines for Human Use:

TROLIC Tablets

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TROLIC 5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg prednisone.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to off-white, round, flat tablet, scored on one side with a bitter taste.

The break line is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TROLIC 5 mg is indicated for the treatment of diseases responsive to glucocorticosteroid therapy.

These diseases include:

- Rheumatoid arthritis.

  Suppressive and palliative therapy in rheumatoid arthritis which is progressive despite intensive conventional treatment.
- Nephrotic syndrome.

  The nephrotic syndrome attributable to systemic lupus erythematosus or to primary renal disease, except renal amyloidosis, may be benefited by corticosteroid therapy.
- Collagen diseases.

  Manifestations of most of these diseases, except scleroderma are controlled. Morbidity is decreased and the survival times of patients with polyarteritis nodosa and Wegener's granulomatosis is prolonged.
- Fulminating systemic lupus erythematosus.

  This is a life-threatening condition the manifestations of which should be promptly suppressed with large doses.
- Allergic conditions.

  Manifestations of allergic conditions which do not react to anti-histaminic treatment may be suppressed by adequate doses or as a supplement to primary therapy. However, severe reactions such as anaphylaxis require immediate adrenalin subcutaneously.
- Bronchial asthma.

  Acute, or severe chronic asthma, uncontrolled by other measures.
- Acute skin diseases and exacerbations of chronic skin diseases.
- Chronic ulcerative colitis.
- Organ transplantations (for immunosuppression).
- Thrombocytopenia. To decrease the bleeding tendency.

- Acute haemolytic disorders.
- Leukaemia.
- Thrombocytopenic purpura.
- Celiac disease.
- Insulin resistance in diabetes mellitus.
- Liver disorders.

4.2 Posology and method of administration

Posology

General information

1. The dose must be determined individually by the seriousness of the disease and the reaction of the patient.
2. Administration of large doses for short courses cause less side effects than long-term therapy with small doses. Long courses of therapy at high dosage should be reserved for life-threatening diseases.
3. In long-term therapy the dose must be the smallest one to achieve a desired effect. Complete relief is not sought.

Adults

Rheumatoid arthritis

The initial dose should be small, usually about 10 mg and increase slowly until the desired degree of control is attained.

Nephrotic syndrome

60 mg daily in divided doses (2 mg/kg oedema-free body mass in children) for 3 to 4 weeks. If a remission with a diuresis and decreased proteinuria occurs during this period, maintenance treatment is continued for as long as a year. For this the daily dose of prednisone is given only for the first 3 days of each week.

Collagen disease

1 mg/kg daily until remission is induced. The dose is then reduced to the minimal effective level.

Fulminating systemic lupus erythematosus

1 mg/kg daily which may be increased in 20 mg increment daily until a favourable response occurs. After control has been obtained, dosage should be reduced by small steps of 5 mg prednisone per week until further reductions elucidate symptoms.

Bronchial asthma

In status asthmaticus the attack is brought under control by intravenous cortisol whereafter 10 mg prednisone is given for 4 to 5 days. The dose is then reduced in steps to be withdrawn 10 days after initiation of prednisone therapy.

Severe chronic bronchial asthma

To reduce severity without eliminating the manifestations of the disease, 5 to 10 mg daily in divided doses in combination with the usual medication.

Skin diseases

40 mg per day. Up to 120 mg per day may be lifesaving in pemphigus.

Chronic ulcerative colitis

60 to 120 mg per day.

Organ transplantation

50 to 100 mg at the time of surgery. Maintenance doses of 10 to 20 mg per day are continued indefinitely and the dosage increased if rejection is threatened.

Thrombocytopenia

0,5 mg/kg.

Other conditions

The usual dose is up to 60 mg daily in divided doses.

Withdrawal

The dosage should be reduced and therapy discontinued gradually if therapy is continued for more than a few days.

The rate depends on the patient's response, the dose and the duration of therapy. Adrenal function should be monitored throughout withdrawal and symptoms attributable to over-rapid withdrawal should be countered by resuming a higher dose and continuing the reduction at a slower rate.

Abrupt cessation of prolonged, high dosage therapy may produce adrenal insufficiency or sufficient severity to be threatening to life (see section 4.4).

Paediatric population

No data are available.

Method of administration

TROLIC 5 mg is for oral administration.

4.3 Contraindications

- Hypersensitivity to glucocorticosteroids (e.g. prednisone or prednisolone) or any excipients listed in section 6.1.
- Systemic fungal infections.
- Peptic ulcers.
- Osteoporosis(see section 4.4).
- Psychoses and psychoneuroses (see section 4.4).
- Active or doubtfully quiescent tuberculosis - unless treatment is considered lifesaving (see section 4.4).
- Acute bacterial or viral infections including Herpes zoster and Herpes simplex ulceration of the eye (see section 4.4).
- Immunisation using live vaccines (see section 4.4).

4.4 Special warnings and precautions for use

General

Caution and frequent patient monitoring is necessary when oral corticosteroids, such as prednisolone, as in TROLIC 5 mg, are prescribed in patients with the following conditions:

- Congestive heart failure,
- Recent myocardial infarction,
- Hypertension,
- Diabetes mellitus or in those with a family history of diabetes,
- Epilepsy, and/or seizure disorders,
- Glaucoma,
- Infectious diseases,
- Hypothyroidism,
- Chronic renal failure, uraemia, renal insufficiency,
- Hepatic failure,

- Hepatic disease: In patients with acute and active hepatitis, protein binding of the glucocorticoids, such as prednisone, as in TROLIC 5 mg, will be reduced and peak concentrations increased. Elimination will also be impaired. There is an enhanced effect of corticosteroids, such as prednisone, as in TROLIC 5 mg, in patients with cirrhosis (see section 5.2).
- Osteoporosis,
- Menopause, post-menopause: Corticosteroid requirements, such as prednisone, as in TROLIC 5 mg, may be reduced in menopausal and post-menopausal women,
- Patients with a history of severe affective disorders and particularly those with a previous history of steroid-induced psychoses. Existing emotional instability or psychotic tendencies may be aggravated by corticosteroids including prednisolone as in TROLIC 5 mg (see section 4.3),
- Previous steroid myopathy,
- Myasthenia gravis: Glucocorticoids, such as prednisone, as in TROLIC 5 mg, should be used cautiously in patients with myasthenia gravis receiving anticholinesterase therapy,
- Thromboembolic disorders: cortisone, such as prednisone, as in TROLIC 5 mg, has been reported to increase blood coagulability and to precipitate intravascular thrombosis, thromboembolism, and thrombophlebitis; corticosteroids, such as prednisolone, as in TROLIC 5 mg should be used with caution in patients with thromboembolic disorders.

Immunosuppressive effects/increased susceptibility to infection

Glucocorticoids, including prednisone, as in TROLIC 5 mg may cause increases the susceptibility to infections, masking symptoms of infection, and new infections may occur during treatment.

Infections caused by viruses, bacteria, fungi, protozoa or intestinal worms may be associated with the use of corticosteroids alone or corticosteroids in combination with other immunosuppressive medicines that affect cellular immunity, humoral immunity or the function of neutrophils. The infections can be mild, but also difficult and in some cases fatal. The risk of infectious complications increases with increasing dose.

Glucocorticoids, such as TROLIC 5 mg should not be given during infections without concomitant causal treatment.

Chickenpox

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids, such as prednisone, as in TROLIC 5 mg, or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids, such as prednisone, as in TROLIC 5 mg, should not be stopped and the dose may need to be increased.

Measles

Patients taking corticosteroids, such as prednisone, as in TROLIC 5 mg, should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs.

Tuberculosis

The use of TROLIC 5 mg in active tuberculosis must be limited to those cases of fulminant or disseminated tuberculosis where the corticosteroid is used to treat the disease in combination with appropriate tuberculosis therapy. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close monitoring is necessary as the disease can be reactivated. In long-term corticosteroid therapy, these patients should receive tuberculosis prophylaxis.

Live vaccines

Live vaccines should not be given to individuals on high doses of corticosteroids, such as prednisone, as in TROLIC 5 mg, due to impaired immune response. Live vaccines should be postponed until at least 3 months after stopping treatment with TROLIC 5 mg (see also sections 4.3 and 4.5). Killed (inactivated) vaccines or toxoids may be given.

Tumours

Tumourigenicity

Direct tumour-inducing effects of the glucocorticoids, such as prednisone, as in TROLIC 5 mg, are not known, but the particular risk that malignancies in patients undergoing immunosuppression with these or other medicines will spread more rapidly is well-recognised (see section 4.5).

Tumour lysis syndrome (TLS)

Tumour lysis syndrome (TLS) has been reported post-marketing in patients with malignancies, including haematological malignancies and solid tumours, following the use of systemic corticosteroids alone or in combination with other cytotoxic agents. Patients at high risk for TLS, such as patients with tumours that have a high rate of cell division, high tumour burden, and high sensitivity to cytotoxic agents, should be closely monitored and appropriate precautions taken.

Immune system disorders

Since rare cases of skin reactions and anaphylactic / anaphylactoid reactions have occurred in patients treated with corticosteroids (see section 4.8), appropriate precautions should be taken prior to administration, especially if the patient has previously had an allergic reaction to any medicine.

Endocrine system disorders

Adrenocortical insufficiency

Sudden withdrawal or reduction in dosage, or an increase in corticosteroid requirements associated with the stress of infection, or accidental or surgical trauma may cause acute adrenal insufficiency leading to a fatal outcome. Symptoms of adrenal insufficiency include malaise, muscle weakness, mental changes, muscle and joint pain, desquamation of the skin, dyspnoea, anorexia, nausea and vomiting, fever, hypoglycaemia, hypotension and dehydration.
Deaths have followed the abrupt withdrawal of corticosteroids, such as prednisone, as in TROLIC 5 mg.

Pharmacologic doses of TROLIC 5 mg, administered for prolonged periods, may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration, and duration of treatment.

Medicine-induced secondary adrenocortical insufficiency may therefore be minimised by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. During prolonged therapy any intercurrent illness, trauma, or surgical procedure will require a temporary increase in dosage; if TROLIC 5 mg, have been stopped following prolonged therapy they may need to be temporarily reintroduced.

Cushing's disease

Because glucocorticoids, such as prednisone, as in TROLIC 5 mg, can produce or aggravate Cushing's syndrome, glucocorticoids, such as prednisone, should be avoided in patients with Cushing's disease.

Diabetes

Corticosteroids, including prednisone, as in TROLIC 5 mg, can raise blood sugar levels, worsen existing diabetes and increase the risk of developing diabetes in patients on long-term corticosteroid therapy. Insulin requirements in diabetic patients may be increased.

Hypothyroidism

There is an enhanced effect of corticosteroids, such prednisone, as in TROLIC 5 mg, in patients with hypothyroidism.

Pheochromocytoma crisis

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids (see section 4.8). Corticosteroids, such as prednisone, as in TROLIC 5 mg should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

Effects on electrolytes and fluid balance

Electrolyte imbalances may occur, and electrolytes should consequently be monitored at regular intervals.

Systemic corticosteroids, such as TROLIC 5 mg should be used with caution in patients with heart failure or hypertension. Medium and high doses of hydrocortisone or cortisone can lead to increased blood pressure, salt and water retention and increased potassium secretion. These effects are less likely with synthetic derivatives, except when used in high doses. Dietary restrictions with lower salt intake and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Calcium supplementation may be necessary.

Psychiatric adverse reactions

Psychic derangements may appear when corticosteroids, including prednisone, as in TROLIC 5 mg, are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations (see section 4.8). Existing emotional instability and psychotic tendencies can also be exacerbated by corticosteroids (see section 4.8).

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids, such as prednisone, as in TROLIC 5 mg (see section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see section 4.5), although dose levels do not allow prediction of the onset, type, severity, or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected.

Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tampering/withdrawal of systemic steroids, such as TROLIC 5 mg, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids, such TROLIC 5 mg, in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis (see section 4.3).

Nervous system disorders

Seizures

Corticosteroids, such as TROLIC 5 mg, should be used with caution in patients with seizures.

Raised intracranial pressure

Raised intracranial pressure with papilloedema (pseudotumour cerebri) associated with corticosteroid treatment, such prednisone, as in TROLIC 5 mg, has been reported. The onset usually occurs after treatment withdrawal (see section 4.8).

Ocular effects

Prolonged use of corticosteroids, such as prednisone, as in TROLIC 5 mg, may produce posterior subcapsular cataracts and nuclear cataracts, exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids, such as TROLIC 5 mg.

Corticosteroids, such as prednisone, as in TROLIC 5 mg, is contraindicated in patients with ocular herpes simplex because of possible perforation (see section 4.3).

TROLIC 5 mg should also be used with great caution in the presence of glaucoma.

Systemic glucocorticoid treatment, such as TROLIC 5 mg, can cause severe exacerbation of bullous exudative retinal detachment and lasting visual loss in some patients with idiopathic central serous chorioretinopathy (see section 4.8).

Cardiovascular disorders

Cardiac disorders

Side effects of glucocorticoids on the cardiovascular system, for example dyslipidaemia and hypertension, can predispose in treated patients with existing cardiovascular risk factors for additional cardiovascular events at high doses and prolonged treatment times (see section 4.8). Corticosteroids should therefore be introduced to these patients only after careful consideration, and risk modifying

measures as well as extra cardiac monitoring should be considered as needed. Low dose and treatment every other day can reduce the complications of corticosteroid treatment.

Risk of bradycardia

Bradycardia is rare but serious adverse effect of corticosteroids, such as prednisone, as in TROLIC 5mg, that may be both symptomatic and asymptomatic. It is most likely to occur with high doses of corticosteroids; however, bradycardia can occur even with standard doses of oral corticosteroids and is reversible with dose reduction or discontinuation.

Furthermore, patients with pre-existing cardiac or renal problems or electrolyte imbalance are at high risk of experiencing bradycardia (see section 4.8).

The degree of risk may be increased by the concomitant use of other medicines that causes bradycardia as an adverse event.

Vascular disorders

Since cortisone has been reported to increase the blood clotting tendency in rare cases, thereby accelerating the development of intravascular thrombosis, thromboembolism and thrombophlebitis, corticosteroids should be used with caution in patients with thromboembolic disorders.

Gastrointestinal disorders

High doses of corticosteroids, such as TROLIC 5 mg, can cause acute pancreatitis. There are no conclusive data that states that corticosteroids cause ulcers. Glucocorticoid therapy can mask peritonitis and other signs and symptoms associated with gastrointestinal conditions such as perforation, obstruction or pancreatitis. In combination with NSAIDs, the risk of gastrointestinal ulcers is increased.

TROLIC 5 mg should therefore be used with caution in non-specific ulcerative colitis if there is a likelihood of imminent perforation, abscess or other pyogenic infection, diverticulitis, newly created anastomoses, or active or latent peptic ulcer.

Hepatobiliary disorders

Conversion of prednisone to prednisolone has been reported to be impaired in patients suffering with chronic liver disease (see section 5.2).

Diseases of the liver and bile ducts have been reported less frequently and in the majority of these cases the condition was reversible after discontinuation of treatment. Appropriate monitoring measures are required.

Musculoskeletal disorders

Acute myopathy

Acute myopathy has been reported with high corticosteroid doses, most often in patients with neuromuscular transmission disorders (e.g., myasthenia gravis), or in patients concomitantly treated with anticholinergics, e.g. neuromuscular blocking medicines (such as pancuronium) (see section 4.5). This acute myopathy is generalised, may involve eye and respiratory muscles, and may lead to tetraparesis. Elevated creatine kinase may occur. Clinical improvement or recovery after discontinuation of corticosteroid therapy may take weeks or years.

Duchenne muscular dystrophy

Transient rhabdomyolysis and myoglobinuria may occur following strenuous physical activity. It is not known whether this is due to prednisone, as in TROLIC 5 mg, itself, or the increased physical activity. Undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose or whenever possible as a single morning dose on alternate days. Frequent patient review is required to appropriately titrate the dose against disease activity (see section 4.2).

Osteoporosis

Corticosteroids, such as TROLIC5 mg, should be used with caution in patients with osteoporosis. Long-term treatment with TROLIC 5 mg can result in osteoporosis and spontaneous fractures (see section 4.8). Adequate intake of calcium and vitamin D as prophylaxis is recommended.

Renal disorders

Calciphylaxis

Calciphylaxis may occur very rarely during treatment with corticosteroids, such as prednisone, as in TROLIC 5 mg (see section 4.8). Although calciphylaxis is most commonly observed in patients who have end stage kidney failure, it has also been reported in patients taking corticosteroids, such as TROLIC 5 mg, who have minimal or no renal impairment and normal calcium, phosphate and parathyroid hormone levels. Patients/carers should be advised to seek medical advice if symptoms develop.

Scleroderma renal crisis

Caution is required in patients with systemic sclerosis because of an increased incidence of (possibly fatal) scleroderma renal crisis with hypertension and decreased urinary output observed with a daily dose of 15 mg or more prednisone, as in TROLIC 5 mg. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

Use in the elderly

Treatment of elderly patients, particularly if long term, should be planned to bear in mind the more serious consequences of the common side-effects of corticosteroids, such as prednisone, as in TROLIC 5 mg, in old age, especially osteoporosis, diabetes, hypertension, hypokalaemia, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life threatening reactions. TROLIC 5 mg should be used with great caution in elderly patients.

Withdrawal

Adrenal atrophy, as a result of the negative-feedback effects of corticosteroids on the hypothalamic-pituitary-adrenal (HPA) axis, may occur in some cases after therapy for as little as 7 days. This produces secondary acute adrenocortical insufficiency after rapid withdrawal of treatment, which can potentially be life threatening. Symptoms may resemble a clinical relapse of the disease for which the patient has been undergoing treatment.

Other effects include gastrointestinal symptoms (e.g. nausea, vomiting and abdominal pain), dehydration, weakness, lethargy, hypotension, headache, fever and malaise. Management includes intravenous therapy with isotonic sodium chloride solution, with other supplementation where necessary.

A steroid 'withdrawal syndrome' seemingly unrelated to adrenocortical insufficiency may also occur following abrupt discontinuance of glucocorticoids, such as prednisone, as in TROLIC 5 mg (see section 4.8).

Withdrawal of treatment after high doses or long-term therapy should not be abrupt or sudden, but rather gradual and tapered.

Excipients

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Paediatric population

Corticosteroids, such as prednisone, as in TROLIC 5 mg, following even relatively small doses, cause growth retardation in infancy, childhood and adolescence, which may be irreversible. There is also an

increased risk of nuclear cataracts (see section 4.8).

Infants and children who are on long-term corticosteroid therapy are at particular risk of developing elevated intracranial pressure

4.5 Interaction with other medicines and other forms of interaction

CYP3A inhibitors

Co-treatment with CYP3A inhibitors, including cobicistat-containing medicines, is expected to increase the risk of systemic side effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects.

Antacids

The absorption of prednisone, as in TROLIC 5 mg, may be reduced by large doses of some antacids such as magnesium trisilicate or aluminium hydroxide.

Antibacterials

Rifamycins accelerate metabolism of corticosteroids, such as prednisone, as in TROLIC 5 mg, and thus may reduce their effect. This leads to an increased steroid need during rifampicin treatment and reduced steroid need after such treatment.

Erythromycin inhibits metabolism of methylprednisolone and possibly other corticosteroids such as prednisone, as in TROLIC 5 mg.

Prednisone, as in TROLIC 5 mg, can lower plasma levels of isoniazid. Where a reduced response during concurrent use is noted, dosage adjustment of isoniazid may be necessary.

Anticholinesterases

Interaction between glucocorticoids and anticholinesterases such as ambenonium, neostigmine and pyridostigmine may lead to significant potency in myasthenia gravis.

If possible, treatment with anticholinesterase should be discontinued at least 24 hours before administration of glucocorticoid.

Anticoagulants

Response to anticoagulants may be reduced or, less often, enhanced by corticosteroids. Close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Antidiabetic medicines

Glucocorticoids, such as prednisone, as in TROLIC 5 mg, may increase blood glucose levels. Patients with diabetes mellitus receiving concurrent insulin and/or oral hypoglycaemic medicines may require dosage adjustments of such therapy (see section 4.4).

Antiepileptics

Carbamazepine, phenobarbital, phenytoin, and primidone accelerate the metabolism of corticosteroids, and may therefore reduce the effect of prednisone, as in TROLIC 5 mg.

Antifungals

Risk of hypokalaemia may be increased with amphotericin B, therefore concomitant use with corticosteroids, such as prednisone, as in TROLIC 5 mg, should be avoided unless corticosteroids are required to control reactions; ketoconazole inhibits metabolism of methylprednisolone and possibly other corticosteroids such as prednisone.

Antimuscarinics (Anticholinergics) e.g. neuromuscular blockers

Prednisone, as in TROLIC 5 mg, has been shown to have antimuscarinic activity. If used in combination with another antimuscarinic medicine could cause impairment to memory and attention in the elderly.

Acute myopathy has been reported with concomitant use of high doses of corticosteroids and anticholinergics such as neuromuscular blockers (see section 4.4).

Antagonism with the neuromuscular blocking effect of pancuronium and vecuronium has been reported in patients taking glucocorticosteroids. This interaction can be expected with all competitive neuromuscular blockers.

Antithyroids

Prednisone, as in TROLIC 5 mg, clearance is increased by the use of carbimazole and thiamazole.

Antivirals

Plasma concentrations of prednisone, as in TROLIC 5 mg, may be increased with antiviral medicines such as ritonavir and indinavir.

Ritonavir possibly increases plasma concentrations of prednisolone (the active form of prednisone) and other corticosteroids by reduction in clearance of prednisolone through the inhibition of P450 isoenzyme CYP3A4.

Cardiac glycosides

Increased toxicity if hypokalaemia occurs with corticosteroids, such as prednisone, as in TROLIC 5 mg.

Ciclosporin

Concomitant administration of prednisone, as in TROLIC 5 mg, and ciclosporin may result in decreased plasma clearance of prednisolone (i.e. increased plasma concentration of prednisolone). The need for appropriate dosage adjustment should be considered when these medicines are administered concomitantly.

Cytotoxics

Increased risk of haematological toxicity with methotrexate.

Estrogens

Estrogens may potentiate the effects of glucocorticoids, such as prednisone, as in TROLIC 5 mg, and dosage adjustments may be required if estrogens are added to or withdrawn from a stable dosage regimen.

Hepatic microsomal enzyme inducers

Medicines that induce hepatic enzyme cytochrome P-450 (CYP) isoenzyme 3A4 such as phenobarbital, phenytoin, rifampicin, rifabutin, carbamazepine, primidone and aminoglutethimide may reduce the therapeutic efficacy of corticosteroids, such as prednisone, as in TROLIC 5 mg, by increasing the rate of metabolism. Lack of expected response may be observed and the dosage of TROLIC 5 mg may need to be increased.

Hepatic microsomal enzyme inhibitors

Medicines that inhibit hepatic enzyme cytochrome P-450 (CYP) isoenzyme 3A4 (e.g. ketoconazole, troleandomycin) may decrease glucocorticoid, such as prednisone, as in TROLIC 5 mg, clearance. Dosages of glucocorticoids, such as prednisone, given in combination with such medicines may need to be decreased to avoid potential adverse effects.

Hormonal contraceptives

Oral contraceptives increased prednisolone (the active form of prednisone) concentrations by 131 %. May increase AUC and reduce clearance in oral contraceptives containing ethinylestradiol, mestranol, desogestrel, levonorgestrel, norgestrel or norethisterone.

Immunosuppressants

Tumourigenicity: direct tumour-inducing effects of the glucocorticoids, such as prednisone, as in TROLIC 5 mg, are not known, but the particular risk that malignancies in patients undergoing immunosuppression with these or other medicines will spread more rapidly is well-recognised. Mutual inhibition of metabolism may occur between ciclosporin and prednisone, as in TROLIC 5 mg, and may increase the plasma concentration of either medicine.

Liquorice

Glycyrrhizin can delay the clearance of prednisolone (the active molecule of prednisone).

Leukotriene antagonists (e.g. montelukast)

May potentiate sodium and fluid retention caused by TROLIC 5 mg, resulting in an increased risk of developing peripheral oedema.

Mifepristone

Effect of corticosteroids, such as prednisone, as in TROLIC 5 mg, may be reduced for 3 to 4 days after mifepristone.

Non-steroidal anti-inflammatory drugs (NSAIDS)

Concomitant administration of ulcerogenic medicines such as indomethacin during corticosteroid therapy, such as prednisone, as in TROLIC 5 mg, may increase the risk of gastrointestinal (GI) ulceration. Aspirin should be used cautiously in conjunction with glucocorticoids, such as prednisone,

as in TROLIC 5 mg, in patients with hypoprothrombinaemia. Although concomitant therapy with salicylate and corticosteroids does not appear to increase the incidence or severity of GI ulceration, the possibility of this effect should be considered.

Serum salicylate concentrations may decrease when corticosteroids, such as prednisone, as in TROLIC 5 mg, are administered concomitantly. The renal clearance of salicylates is increased by corticosteroids, such as prednisone, and steroid withdrawal may result in salicylate intoxication. Salicylates and TROLIC 5 mg should be used concurrently with caution. Patients receiving both medicines should be observed closely for adverse effects of either medicine.

Other

The desired effects of hypoglycaemic medicines (including insulin), antihypertensives and diuretics are antagonised by corticosteroids, such as prednisone, as in TROLIC 5 mg; and the hypokalaemic effect of acetazolamide, loop diuretics, thiazide diuretics, carbenoxolone and theophylline are enhanced.

Potassium reducing medicines

Potassium-reducing diuretics (e.g., thiazides, furosemide, ethacrynic acid) and other medicines that reduce the amount of potassium such as amphotericin B, xanthines and beta2-agonists (such as the sympathomimetics bambuterol, fenoterol, formoterol, ritodrine, salbutamol, salmeterol and terbutaline), may potentiate the potassium-lowering effect of glucocorticoids, such as prednisone as in TROLIC 5 mg. Therefore, concurrent administration of prednisone and the potassium depleting medicines may cause excessive potassium loss with the increased risk of hypokalaemia.

Serum potassium should be closely monitored in patients receiving TROLIC 5 mg and potassium reducing medicines.

Somatropin

Growth promoting effect may be inhibited.

4.6 Fertility, pregnancy and lactation

The safety in pregnancy and lactation has not been established.

Pregnancy

The ability of corticosteroids, such as prednisolone (the active form of prednisone) to cross the placenta varies between individual medicines, however, 88 % of prednisolone is inactivated as it crosses the placenta. Administration of corticosteroids, such as prednisone, as in TROLIC 5 mg, to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development.

There is no evidence that corticosteroids, such as prednisone, as in TROLIC 5 mg, result in an increased incidence of congenital abnormalities, such as cleft palate/lip. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids, such TROLIC 5 mg, may increase the risk of intra-uterine growth retardation. The use of TROLIC 5 mg, during pregnancy may also result in stillbirth. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important.

Cataracts have been observed in infants born to mothers treated with long-term prednisone, as in TROLIC 5 mg, during pregnancy.

Breastfeeding

Corticosteroids, such as prednisolone (the active form of prednisone), are excreted in small amounts in breast milk (see section 5.2). Corticosteroids, such as prednisolone distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants.
The concentration of the steroid, such as prednisolone, in the milk can be between 5 % and 25 % of those in the serum and the two roughly parallel one another after an oral dose.

There are no reports found regarding neonatal toxicity following exposure to corticosteroids during lactation, however if maternal doses > 40 mg/day of prednisone, as in TROLIC 5 mg, is prescribed, the infant should be monitored for adrenal suppression.

Fertility

No data is available on the safety of LENISOLONE TABLETS with regards to fertility.

4.7 Effects on ability to drive and use machines

TROLIC 5 mg has a minor influence on the ability to drive or operate machinery.
Since adverse reactions such as dizziness and visual disturbances have been reported in patients taking TROLIC 5 mg (see section 4.8)., patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that TROLIC 5 mg does not adversely affect their ability to do so.

4.8 Undesirable effects

a. Summary of the safety profile

A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported.

Reactions are common and may occur. In adults, the frequency of severe reactions has been estimated to be 5 to 6 %. Psychological effects have been reported on withdrawal of corticosteroids, such as prednisone, as in TROLIC 5 mg; the frequency of which, is unknown.

The incidence of predictable undesirable effects, including hypothalamic-pituitary adrenal suppression correlates with the relative potency of the medicine, dosage, timing of administration and the duration of treatment (see section 4.4).

The incidence of side effects rises steeply if dosage increases much above 7,5 mg daily. Short courses at high dosage for emergencies appear to cause less side effects than prolonged courses with lower doses.

b. Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Adverse reactions**
Infections and infestation	Frequency unknown	Sepsis, tuberculosis (see section 4.4), fungal infections, increased susceptibility to, and severity of infections[1], opportunistic infections*, viral infections, masked feeling of well-being*, oesophageal candidiasis.
Blood and the lymphatic system disorders	Frequency unknown	Reduction in the number of circulating lymphocytes, leucocytosis[2].

Immune system disorders	Frequency unknown	Hypersensitivity, anaphylactic reaction, anaphylactoid reaction.
Endocrine disorders	Frequent	Growth suppression in infancy, childhood and adolescence.
	Frequency unknown	Impaired carbohydrate tolerance with the insulin requirements of diabetic patients increased, manifestation of latent diabetes mellitus, hyperactivity of the adrenal cortex[10], Cushingoid facies, suppression of the hypothalamo-pituitary adrenal (HPA) axis[3], steroid withdrawal syndrome (see section 4.4)*, pheochromocytoma - related crisis (see section 4.4).
Metabolism and nutrition disorders	Frequent	Hypokalaemia
	Less frequent	Calciphylaxis (see section 4.4), increased gluconeogenesis.
	Frequency unknown	Sodium and water retention (oedema), electrolyte imbalance (see section 4.4), negative nitrogen and calcium balance, hypokalaemic alkalosis, potassium loss, glucose intolerance[4],

		protein catabolism, increase in high and low density lipoprotein cholesterol concentration in the blood, weight gain, obesity, hyperglycaemia, dyslipidaemia, lipomatosis. increased appetite[5].
Psychiatric disorders	Frequent	Irritability, depressed and labile mood, suicidal thoughts, psychotic reactions, mania, delusions, hallucinations, aggravation of schizophrenia, behavioural disturbances, anxiety, sleep disturbances, cognitive dysfunction including confusion, restlessness, nervousness, amnesia.
	Frequency unknown	Euphoria, psychological dependence, depression,

		psychoses, personality change, insomnia.
Nervous system disorders	Frequency unknown	Dizziness, headache, raised intracranial pressure with papilloedema (pseudotumour cerebri) (see section 4.4)[6], aggravation of epilepsy, epidural lipomatosis, vertebrobasilar stroke[7], mental and neurological disturbances.
Eye disorders	Less frequent	Blurred vision.
	Frequency unknown	Glaucoma, papilloedema, posterior subcapsular cataracts, nuclear cataracts, exophthalmos, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease, severe exacerbation of bullous exudative retinal detachment (lasting visual loss in some patients), with idiopathic central serous chorioretinopathy (see section 4.4).
Ear and labyrinth disorders	Frequency unknown	Vertigo.

Cardiac disorders	Frequency unknown	Congestive heart failure in susceptible patients, hypertension, increased risk of heart failure, increased risk of cardiovascular disease including myocardial infarction (see section 4.4)[8], bradycardia (see section 4.4)[9].
Vascular disorders	Frequent	Oedema hypertension.
	Frequency unknown	Thromboembolism*.
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Hiccup.
Gastrointestinal disorders	Frequent	Dyspepsia, gastric ulceration.
	Frequency unknown	Nausea, peptic ulceration with perforation and haemorrhage, abdominal distension, abdominal pain, diarrhoea, oesophageal ulceration, acute pancreatitis.
Skin and subcutaneous tissue disorders	Frequency unknown	Hyperhidrosis, buffalo hump, skin thinning. hirsutism,

		ecchymosis, flushing, increased bruising*, striae, telangiectasia, acne, pruritus, rash, urticaria, angioedema, petechiae.
Musculoskeletal and connective tissue disorders	Frequency unknown	Proximal myopathy (see section 4.4), osteoporosis (see section 4.4), vertebral and long bone fractures, avascular osteonecrosis, spontaneous fractures, aseptic necrosis of bone, tendon rupture, tendinopathies (particularly of the Achilles and patellar tendons), muscular weakness[9], myalgia, neuropathic arthropathy, arthralgia.
Renal and urinary disorders	Frequency unknown	Scleroderma renal crisis (see section 4.4)*

Pregnancy, puerperium and perinatal conditions	Frequency unknown	During pregnancy: foetal or neonatal adrenal suppression[9].
Reproductive system and breast disorders	Frequency unknown	Menstrual irregularity, amenorrhoea.
General disorders and administrative site conditions	Frequency unknown	Fatigue, malaise, impaired healing.
Investigations	Frequency unknown	Increased intra-ocular pressure (see section 4.4), increased calcium levels in the urine, elevated aspartate aminotransferase, increased blood alkaline phosphatase, elevated blood urea, may suppress reactions to skin tests[10].

*. see section c).

[1.] with suppression of clinical symptoms and signs.

[2.] due to redistribution of intravascular granulocytes.

[3.] particularly in times of stress, as in trauma, surgery or illness.

[4.] diabetes mellitus may deteriorate and latent diabetes become manifest.

[5.] which may result in weight gain.

[6.] usually after treatment withdrawal.

[7.] exacerbation of giant cell arteritis, with clinical signs of evolving stroke has been attributed to prednisone, as in TROLIC 5 mg.

[8.] with high dose therapy.

[9.] following high doses.

[10.] Not MedDRA term.

c) Description of selected adverse reactions

Withdrawal symptoms

Too rapid a reduction of corticosteroid, such as prednisone, as in TROLIC 5 mg, dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see section 4.4). A steroid 'withdrawal syndrome' seemingly unrelated to adrenocortical insufficiency may also occur following abrupt discontinuance of glucocorticoids, such as prednisone, as in TROLIC 5 mg. This syndrome includes symptoms such as anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels. Psychological effects have been reported on withdrawal of corticosteroids, such as prednisone, as in TROLIC 5 mg.

Infections and infestations

Increased susceptibility to all kinds of infection, including sepsis, tuberculosis, fungal infections and viral infections has been reported in patients on prednisone therapy.
Infections may be masked due to marked anti-inflammatory properties with analgesic and antipyretic effects and may produce a feeling of well-being.
The effect on tissue repair is evident by delayed wound healing and increased likelihood of infection.

Scleroderma renal crisis

Amongst the different subpopulations the occurrence of scleroderma renal crisis varies. The highest risk has been reported in patients with diffuse systemic sclerosis. The lowest risk has been reported in patients with limited systemic sclerosis (2 %) and juvenile onset systemic sclerosis (1 %).

Vascular disorders

Increase in blood coagulability may lead to thromboembolic complications.

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 providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
Alternately you can contact Gulf Drug Company (Pty) Ltd at +27 31 538 8700 or per info@gulfdrug.co.za.

4.9 Overdose

Symptoms and signs

See section 4.8.

Reports of acute toxicity and/or death following overdosage of glucocorticoids, such as prednisone, as in TROLIC 5 mg, are rare. High systemic doses of corticosteroids, such as prednisone, as in TROLIC 5 mg, caused by chronic use have been associated with adverse effects such as neuropsychiatric disorders (psychosis, depression, and hallucinations), cardiac dysrhythmias and Cushing's syndrome.

Treatment

Treatment is symptomatic and supportive, and where possible the dosage should be reduced or the medicine slowly withdrawn.

No specific antidote is available. Serum electrolytes should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 21.5.1 Corticosteroids and analogues

Pharmacotherapeutic group: Corticosteroids for systemic use.

ATC code: H02AB06

Mechanism of action

Prednisone is a synthetic glucocorticoid which produces various metabolic effects and in addition modifies the immune reaction of the body to diverse stimuli. It has anti-inflammatory and immunosuppressive properties qualitatively similar to those of cortisone acetate through inhibiting the release of various cytokine, but causes less sodium and fluid retention and is therefore preferred in the treatment of such conditions as asthma, psoriasis, rheumatoid arthritis, thrombocytopenia and ulcerative colitis. Prednisone is not used for adrenal-deficiency states. It is useful in the treatment of the nephrotic syndrome. Prednisone is inactive until converted to prednisolone in the liver.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogues are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoid cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

5.2 Pharmacokinetic properties

Absorption

Prednisone is biologically inactive and is readily absorbed from the gastrointestinal tract after oral administration whereafter it is rapidly converted to the active form prednisolone in the liver: Maximum peak plasma concentrations of prednisolone is achieved 1 - 3 hours after oral administration of prednisone. Plasma half-life is normally about 3 hours. Its initial absorption, but not its overall bioavailability, is affected by food. Prednisolone has a biological half-life lasting several hours, making it suitable for alternate-day administration regimens.

Distribution

Although peak plasma prednisolone levels are somewhat lower after administration of prednisone tablets and absorption is delayed, the total absorption and bioavailability of prednisolone obtained from prednisone is delayed, however the total absorption and bioavailability of prednisolone obtained from prednisone are the same as after plain prednisolone administration.

The absolute bioavailability of prednisolone is on average 82 % compared to intravenously administered prednisolone following a single 10 mg dose. At normal dosing, the effective duration is calculated to be 12 – 36 hours.

Corticosteroids cross the placenta in varying degrees and may be distributed in small amounts into breast milk (see section 4.6).

Prednisolone shows dose dependent pharmacokinetics, with an increase in dose leading to an increase in volume of free, pharmacologically active drug. The volume of distribution and clearance are reported to increase with transition from low to medium doses.
Prednisolone is highly bound to plasma proteins and has high affinity for the transcortin. Reduced doses are necessary in patients with hypoalbuminaemia.

Biotransformation

Prednisone is a biologically inactive prodrug and is rapidly metabolised to the active form prednisolone in the liver. Thereafter prednisolone is metabolised primarily in the liver to a to a biologically inactive compound.
Prednisolone can be reversibly converted to prednisone by 11β-hydroxysteroid dehydrogenase.
Liver disease prolongs the half-life of prednisolone (see section 4.4) and, if the patient has hypoalbuminaemia, also increases the proportion of unbound drug and may thereby increase adverse effects.

Elimination

Prednisolone is excreted via urine as free and conjugated metabolites, along with an appreciable amount of unchanged prednisolone.

More than 90 % of the given amount is excreted in the urine. 7 – 15 % is excreted in unchanged form.

Special populations

Post-menopausal woman

Significant differences in the pharmacokinetics of prednisolone amongst menopausal women have been described. The postmenopausal women had reduced unbound clearance (30 %), reduced total clearance and increased half-life of prednisolone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic calcium phosphate dihydrate

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycollate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

High Density Polyethylene (HDPE) containers: 48 months.

Polypropylene (PP) containers: 24 months.

Low Density Polyethylene (LDPE) Patient ready packs (PRPs): 24 months.

6.4 Special precautions for storage

Store at or below 25 ºC in a cool, dry place.

Protect from light and moisture.

Keep containers tightly closed.

Do not remove tablets from containers/patient ready packs until required for use.

6.5 Nature and contents of container

High Density Polyethylene (HDPE) containers: 500 or 5000 tablets.

Polypropylene (PP) containers: 100 or 1000 tablets.

Low Density Polyethylene (LDPE) Patient ready packs (PRPs): 28, 40, 56 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

G3093 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

22 January 2026