Prednisolone TD 5 mg tablets
Prednisolone TD 20 mg tablets

1. Name of the medicinal product

Prednisolone TD 5mg tablets
Prednisolone TD 20 mg tablets

2. Qualitative and quantitative composition

Prednisolone TD 5 mg: each tablet contains 5mg prednisolone.
Prednisolone TD 20 mg: each tablet contains 20mg prednisolone.

Excipient with known effect
Each 5mg tablet contains 62,245mg of Lactose Monohydrate Ph.Eur.
Each 20mg tablet contains 243,605mg of Lactose Monohydrate Ph.Eur.

For the full list of excipients see section 6.1.

3. Pharmaceutical form

Tablets
5 mg tablets
20 mg tablets
5 mg tablets: small, white, circular, flat-beveled edge tablets
20 mg tablets: white, round, biconvex tablet with a cross-scoreline on one side.

4. Clinical particulars

4.1 Therapeutic indications

Prednisolone is indicated in the management of all conditions deemed likely to benefit from short or long-term glucocorticoid therapy. These include:

Allergic states: Severe, incapacitating allergies unresponsive to conventional treatment; asthma serum sickness; drug hypersensitivity reactions.

Collagen disorders: e.g. systemic lupus erythematosus, polyomyositis, polymyalgia rheumatic and temporal (giant cell) arteritis, mixed connective tissue disease syndrome, acute rheumatic carditis.

Blood disorders: haemolytic anaemia (auto-immune), leukaemia (acute and chronic lymphatic), lymphoma, multiple myeloma, idiopathic thrombocytopenia purpura.

Gastro-intestinal disease: During acute exacerbation in ulcerative colitis and regional ileitis (Crohn's disease).

Muscular disorders: polymyositis, dermatomyositis.

Respiratory disease: allergic pneumonitis, asthma, occupational asthma, pulmonary aspergillosis, pulmonary fibrosis, pulmonary alveolitis, aspiration of foreign body, aspiration of stomach contents, pulmonary sarcoid, drug induced lung disease, adult respiratory distress syndrome, spasmodic croup, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculosis chemotherapy.

Rheumatic disorders: Usually given as an adjunctive therapy for short term administration during an acute episode or exacerbation of rheumatoid arthritis, psoriatic arthritis.

Skin conditions: Life-threatening or incapacitating skin conditions such as pemphigus and exfoliative dermatitis.

4.2 Posology and method of administration

Posology

Adults and the elderly
The lowest effective dose should be used for the minimum period.

Children
Prednisolone should only be used when specifically indicated, at the lowest dose possible and for the shortest possible time.

The initial dosage of Prednisolone may vary from 5mg to 60mg daily depending on the disorder being treated. Divided daily dosage may be used. Administration as a once daily dose in the morning or on alternate days can reduce the risk of adrenocortical suppression (see Section 4.4 “Special warnings and precautions for use”). In some patients this may not be possible e.g. patients with rheumatoid arthritis with pronounced morning stiffness where an evening dose may need to be given.

The following therapeutic guidelines should be kept in mind for all therapy with corticosteroids:

The lowest dose to produce an acceptable result should be given. Initial dosage should be adjusted until the desired clinical response has been achieved. The dose should be gradually reduced until the lowest dose which will maintain an adequate clinical response is reached. As a guide, the daily dose should be reduced by 2.5 – 5mg every second to fifth day (more rapidly at the higher initial dose levels) until the lowest possible maintenance dose is reached. Preferably this should not exceed 10mg per day. Use of the lowest effective dose will tend to minimize side-effects. The incidence of side-effects increases with dose and duration of treatment (see Section 4.4 “Special warnings and special precautions for the use”).

Particular care should be exercised in patients who have received higher than 7.5mg prednisolone daily or equivalent for more than three weeks, owing to a greater risk

of suppression of the hypothalamtic-pituitary-adrenal (HPA) axis in these patients. The speed with which dose can be reduced is also dependent on risk of elapse of the disease being treated. After prolonged treatment, tapering dose below 7.5mg (regarding as "equivalent" to physiological levels of glucocorticoids) should be conducted particularly cautiously.

More rapid withdrawal of systemic corticosteroid treatment that has been given for less than 3 weeks is appropriate if it is considered that the disease is unlikely to relapse. Withdrawal of doses of up to 40mg daily of prednisolone, or equivalent that have been administered for less than 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be considered even after courses lasting 3 weeks or less:

- patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks.
- when a short course has been prescribed within one year of cessation of long-term-therapy (months or years).
- patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
- patients receiving doses of systemic corticosteroid greater than 40mg daily of prednisolone (or equivalent).
- patients repeatedly taking doses in the evening.

(See Section 4.4 "Special warnings and special precautions for use" and Section 4.8 "Undesirable effects")

During prolonged therapy, dosage may need to be temporarily increased during periods of stress or during exacerbations of the disease (see Section 4.4 "Special warnings and special precautions for use").

If there is a lack of satisfactory clinical response to Prednisolone tablets, the drug should be gradually discontinued and the patient transferred to alternative therapy.

Intermittent dosage regimen A single dose of Prednisolone tablets in the morning on alternate days or at longer intervals is acceptable therapy for some patients. When this regimen is practical, the degree of pituitary-adrenal suppression can be minimized.

Specific dosage guidelines The following recommendations for some corticosteroid-responsive disorders are for guidance only. Acute or severe disease may require initial high dose therapy with reduction to the lowest effective maintenance dose as soon as possible. Dosage reductions should not exceed 5-7.5mg daily during chronic treatment.

Allergic and skin disorders Initial doses of 5-15mg daily are commonly adequate.

Collagenosis Initial doses of 20-30mg daily are frequently effective. Those with more severe symptoms may require higher doses.

Rheumatoid arthritis The usual initial dose is 10-15mg daily. The lowest daily maintenance dose compatible with tolerable symptomatic relief is recommended.

Blood disorders and lymphoma An initial daily dose of 15-60mg is often necessary with reduction after an adequate clinical or haematological response. Higher doses may be necessary to induce remission in acute leukaemia.

Special populations
Use in elderly Treatment of elderly patients, particularly if long-term, should be undertaken with caution bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age (see also "Special warnings and special precautions for use").

Use in children Although appropriate fractions of the adult dose may be used, dosage will usually be determined by clinical response as in adults (see also Section 4.4 "Special warnings and special precautions for use" and Section 4.8 "Undesirable effects"). Alternate day dosage is preferable where possible.

Method of administration
For oral administration.

4.3 Contraindications

Prednisolone is contraindicated in:
- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- Systemic infections unless specific anti-infective therapy is employed.
- Ocular herpes simplex because of possible perforation.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (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 also section 4.5 pharmacokinetic interactions that can increase the risk of side effects), 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 during or immediately after dose tapering/withdrawal of systematic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids 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.

Tumorigenicity: direct tumor-inducing effects of the glucocorticoids are not known, but the particular risk that malignancies in patients undergoing immunosuppression with these or other drugs will spread more rapidly is a well-recognised problem (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Calciphylaxis may occur very rarely during treatment with corticosteroids (see section 4.8 Undesirable effects). Although calciphylaxis is most commonly observed in patients who have end stage kidney failure, it has also been reported in patients taking corticosteroids 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 (possible fatal) scleroderma renal crisis with hypertension and decreased urinary output observed with a daily dose of 15 mg or more prednisolone. Blood pressure and renal function (s-creatine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, 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.

Caution is necessary when oral corticosteroids, including Prednisolone Tablets, are prescribed in patients with the following conditions, and frequent patient monitoring is necessary.

- Tuberculosis: Those with a previous history of, or X-ray changes characteristics of, tuberculosis. The emergence of active tuberculosis can, however, be prevented by the prophylactic use of anti-tuberculosis therapy.
- Inflammatory bowel disease: Symptoms recurred in a patient with Crohn's disease on changing from conventional to enteric-coated tablets of prednisolone. This was not an isolated occurrence in the author's unit, and it was advocated that only non-enteric coated prednisolone tablets should be used in Crohn's disease, and that the enteric coated form should be used with caution in any condition characterized by diarrhea or a rapid transit time.
- Hypertension.
- Congestive heart failure.

- Liver failure.
- Hepatic disease: In patients with acute hepatitis, protein binding of the glucocorticoids will be reduced and peak concentrations of administered glucocorticoids increased. Elimination of prednisolone will also be impaired. There is an enhanced effect of corticosteroids in patients with cirrhosis.
- Renal insufficiency.
- Diabetes mellitus or in those with a family history of diabetes.
- Osteoporosis: This is of special importance in post-menopausal females who are at particular risk.
- Corticosteroid requirements 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.
- Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids including prednisolone.
- Epilepsy, and/or seizure disorders.
- Peptic ulceration.
- Previous steroid myopathy.
- Glucocorticoids should be used cautiously in patients with myasthenia gravis receiving anticholinesterase therapy.
- Because cortisone has been reported rarely to increase blood coagulability and to precipitate intravascular thrombosis, thromboembolism, and thrombophlebitis, corticosteroids should be used with caution in patients with thromboembolic disorders.
- Duchenne's muscular dystrophy: transient rhabdomyolysis and myoglobinuria may occur following strenuous physical activity. It is not known whether this is due to prednisolone itself or the increased physical activity.

Undesirable effects may be minimized by using the lowest effective dose for the minimum period and by administering the daily requirement as a single morning dose on alternate days. Frequent patient review is required to titrate the dose appropriately against disease activity (see section 4.2 "Posology and method of administration").

Adrenocortical insufficiency: Pharmacologic doses of corticosteroids 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 glucocorticoid therapy.

In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Drug-induced secondary adrenocortical insufficiency may therefore be minimized 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 mineralcorticoid secretion may be impaired, salt and/or a mineralcorticoid should be administered concurrently. During prolonged therapy any intercurrent illness, trauma, or surgical procedure will require a temporary

increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

Patients should carry “Steroid treatment” cards which give clear guidance on the precautions to be taken to minimize risk and which provide details of prescriber, drug, dosage and the duration of treatment.

Anti-inflammatory / Immunosuppressive effects and infection Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation may often be atypical and serious infection such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognized when corticosteroids including prednisolone are used. The immunosuppressive effects of glucocorticoids may result in activation of latent infection or exacerbation of intercurrent infections.

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 immunization with varicella-zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids 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 should not be stopped and the dose may need to be increased.

Measles Patients should be advised to take particular care to avoid exposure to measles, and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

Administration of Live Vaccines Live vaccines should not be given to individuals on high doses of corticosteroids, due to impaired immune response. Live vaccines should be postponed until at least 3 months after stopping corticosteroid therapy (See also section 4.5 “Interaction with other medicinal products and other forms of interaction”).

Occular Effects Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), 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.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible perforation.

Systemic glucocorticoid treatment 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 “Undesirable effects”).

Cushing's disease Because glucocorticoids can produce or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease.

There is an enhanced effect of corticosteroids in patients with hypothyroidism.

Psychic derangements may appear when corticosteroids, including prednisolone, are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations (see Section 4.8 "Undesirable effects").

Raised intracranial pressure Raised intracranial pressure with papilloedema (pseudotumor cerebri) associated with corticosteroid treatment has been reported in both children and adults. The onset actually occurs after treatment withdrawal (See section 4.8 "Undesirable effects").

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Use in elderly
Treatment of elderly patients, particularly if long term, should be undertaken with caution bearing in mind the more serious consequences of the common side-effects of corticosteroids 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.

Paediatric population
Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible, and therefore long-term administration of pharmacological doses should be avoided. If prolonged therapy is necessary, treatment should be limited to the minimum suppression of the hypothalamo-pituitary adrenal axis and growth retardation. The growth and development of infants and children should be closely monitored. Treatment should be administered where possible as a single dose on alternate days.

Excipients
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccines	Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.
Antacids	The absorption of prednisolone may be reduced by large doses of some antacids such as magnesium trisilicate or aluminium hydroxide.
Antibacterials	Rifamycins accelerate metabolism of corticosteroids and thus may reduce their effect. Erythromycin inhibits metabolism of methylprednisolone and possibly other corticosteroids. Prednisolone can lower plasma levels of isoniazid. Where a reduced response during concurrent use is noted, dosage adjustment of isoniazid may be necessary.
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 agents	Glucocorticoids may increase blood glucose levels. Patients with diabetes mellitus receiving concurrent insulin and/or oral hypoglycaemic agents (e.g. metformin, sulphonamides) may require dosage adjustments of such therapy.
Antiepileptics	Carbamazepine, phenobarbital, phenytoin, and primidone accelerate metabolism of corticosteroids and may reduce their effect.
Antifungals	Risk of hypokalaemia may be increased with amphotericin, therefore concomitant use with corticosteroids should be avoided unless corticosteroids are required to control reactions; ketoconazole inhibits metabolism of methylprednisolone and possibly other corticosteroids.
Antimuscarinics (Anticholinergics)	Prednisolone has been shown to have antimuscarinic activity. If used in combination with another antimuscarinic drug could cause impairment to memory and attention in the elderly.
Antithyroids	Prednisolone clearance increased by the use of carbimazole and thiamazole.
Ciclosporin	Concomitant administration of prednisolone and ciclospiron 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 drugs are administered concomitantly.
Cytotoxics	Increased risk of haematological toxicity with methotrexate.
Hepatic microsomal enzyme inducers	Drugs that include 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 by increasing the rate of metabolism. Lack of expected response may be observed and dosage of prednisolone tablets may need to be increased.
Hepatic microsomal enzyme inhibitors	Drugs that inhibit hepatic enzyme cytochrome P-450 (CYP) isoenzyme 3A4 (e.g. ketoconazole, troleandomycin) may decrease glucocorticoid clearance. Dosages of glucocorticoids given in combination with such drugs may need to be decreased to avoid potential adverse effects.
Hormonal contraceptives	Oral contraceptives increased prednisolone concentrations by 131 %. May increase AUC and reduce clearance in oral contraceptives containing ethinylestradiol, mestranol, desogestrel, levonergestrel, norgestrel or norethisterone.
Immunosupressants	Tumorigenicity: direct tumor-inducing effects of the glucocorticoids are not known, but the particular risk that malignancies in patients undergoing immunosuppression with these or other drugs will spread more rapidly is a well-known problem.
Liquorice	Glycyrrhizin can delay the clearance of prednisolone.
Mifepristone	Effect of corticosteroids may be reduced for 3-4 days after mifepristone.
Non-steroidal anti-inflamamtory drugs	Concomitant administration of ulcerogenic drugs such as indomethacin during corticosteroid therapy may increase the risk of GI ulceration. Aspirin should be used cautiously in conjunction with glucocorticoids in patients with hypothrombinaemia. 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 are administered concomitantly. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Salicylates and corticosteroids should be used concurrently with caution. Patients receiving both drugs should be observed closely for adverse effects of either drug.
Oestrogens	Oestrogens may potentiate the effects of glucocorticoids and dosage adjustments may be required if oestrogens are added to or withdrawn from a stable dosage regimen.
Protease inhibitors	Ritonavir possibly increases plasma concentrations of prednisolone and other corticosteroids by reduction in clearance of prednisolone through the inhibition of P450 isoenzyme CYP3A4.
Other	The desired effects of hypoglycaemic agents (including insulin), antihypertensives and diuretics are antagonized by corticosteroids; and the hypokalaemic effect of

	acetazolamide, amphothericin B (by IV administration), loop diuretics, thiazide diuretics, carbenoxolone and theophylline are enhanced.
Somatropin	Growth promoting effect may be inhibited.
Sympathomimetics	Increased risk of hypokalaemia if high doses of corticosteroids given with high doses of bambuterol, fenoteral, formoterol, ritodrine, salbutamol, salmeterol and terbutaline.

4.6 Fertility, pregnancy and lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs, however 88% of prednisolone is inactivated as it crosses the placenta. Administration of corticosteroids 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 result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intrauterine growth retardation. Hypoadrenalism may occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. Cataracts have also been rarely reported. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential, however, patients with abnormal pregnancies may be treated as though they were in the non-gravid state.

Patients with pre-eclampsia or fluid retention require close monitoring.

Breast-feeding

Corticosteroids are excreted in small amounts in breast milk where they may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. Since adequate reproductive studies have not been performed in humans with glucocorticoids, these drugs should be administered to nursing mothers only if the benefits of therapy are judged to outweigh the potential risk to the infant.

The concentration of the steroid in the milk can be between 5 and 25 % of those in the serum.

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

Fertility

Corticosteroids may alter the motility and number of spermatozoa in certain patients.

4.7 Effects on ability to drive and use machines

The effect of prednisolone on the ability to drive or use machinery has not been evaluated. There is no evidence to suggest that prednisolone may affect these abilities.

4.8 Undesirable effects

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 both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6 %. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown.

The incidence of predictable undesirable effects, including hypothalamic-pituitary adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see Section 4.4 “Special warnings and special precautions for use”).

Undesirable effects are listed by MedDRA Organ Classes.

Assessment of undesirable effects is based on the following frequency groupings:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000
Not known: cannot be estimated from the available data

System Organ Class	Frequency	Undesirable Effect
Infections and Infestations	Not known	Increases susceptibility to, and severity of infections[1], opportunistic infections, recurrence of dormant tuberculosis[2], oesophageal candidiasis.
Blood and lymphatic system disorders	Not known	Leucocytosis
Immune system disorders	Not known	Hypersensitivity including anaphylaxis
Endocrine disorders	Not known	Suppression of the hypothalamo-pituitary adrenal axis[3], cushingoid facies, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, manifestation of latent diabetes mellitus.

Metabolism and nutrition disorders	Not known	Sodium and water retention, hypokalaemic alkalosis, potassium loss, negative nitrogen and calcium balance, glucose intolerance and protein catabolism. Increase both high and low density lipoprotein cholesterol concentration in the blood. Increased appetite[4]. Weight gain, obesity, hyperglycaemia, dyslipidaemia.
Psychiatric disorders	Common	Irritability, depressed and labile mood, suicidal thoughts, psychotic reactions, mania, delusions, hallucinations, and aggravation of schizophrenia. Behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia.
	Not known	Euphoria, psychological dependence, depression
Nervous system disorders	Not known	Depression, insomnia, dizziness, headache, vertigo. Raised intercranial pressure with papilloedema (pseudotumor verebri)[6]. Aggravation of epilepsy, epidural lipomatosis. Vertebrobasilar stroke[7]
Eye disorders	Not known	Vision blurred (see also section 4.4), glaucoma, papilloedema, posterior subcapsular cataracts, nuclear cataracts (particularly in children), exophthalmos, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease. Severe exacerbation of bullous exudative retinal detachment, central serous chorioretinopathy or lasting visual loss in some patients with idiopathic central serous chorioetinopathy. [8]
Ear and labyrinth disorders	Not known	Vertigo.
Cardiac disorders	Not known	Congestive heart failure in susceptible patients, hypertension, increased risk of heart failure. Increased risk of cardiovascular disease, including myocardial infarction.[9]

Vascular disorders	Not known	Thromboembolism.
Gastrointestinal disorders	Not known	Dyspepsia, nausea, peptic ulceration with perforation and haemorrhage, abdominal distension, abdominal pain, diarrhea, oesophageal ulceration, acute pancreatitis.
Skin and subcutaneous tissue disorders	Not known	Hirsutism, skin atrophy, bruising, striae, telangiectasia, acne, increased sweating, pruritus, rash, urticaria.
Musculoskeletal and connective tissue disorders	Not known	Proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, tendinopathies (particularly of the Achilles and patellar tendons), myalgia, growth suppression in infancy, childhood and adolescence.
Renal and urinary disorders	Not known	Scleroderma renal crisis[10]
Reproductive system and breast disorders	Not known	Menstrual irregularity, amenorrhoea.
General disorders and administration site conditions	Not known	Fatigue, malaise, impaired healing
Investigations	Not known	Increased intra-ocular pressure, may suppress reactions to skin tests.

[1] with suppression of clinical symptoms and signs
[2] see Section 4.4 “Special warnings and precautions for use”
[3] particularly in times of stress, as in trauma, surgery or illness
[4] which may result in weight gain
[5] see Section 4.4 “Special warnings and precautions for use”
[6] usually after treatment withdrawal
[7] exacerbation of giant cell arteritis, with clinical signs of evolving stroke has been attributed to prednisolone
[8] see Section 4.4 “Special warnings and precautions for use”
[9] with high dose therapy
[10] 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 %)

Withdrawal symptoms
Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see Section 4.2 “Posology and method of administration”). A steroid “withdrawal syndrome” seemingly unrelated to adrenocortical insufficiency may also occur following abrupt discontinuance of glucocorticoids. 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmacovigilance, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, website: www.bfarm.de.

4.9 Overdose

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. No specific antidote is available; treatment is supportive and symptomatic. Serum electrolytes should be monitored.

High systemic doses of corticosteroids caused by chronic use have been associated with adverse effects such as neuropsychiatric disorders (psychosis, depression, hallucinations), cardiac dysrhythmias and Cushing's syndrome.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: glucocorticoid steroid, ATC code: H02A B06

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

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

5.2 Pharmacokinetic properties

Prednisolone is rapidly and apparently almost completely absorbed after oral administration; it reaches peak plasma concentrations after 1-3 hours. There is however wide inter-subject variation suggesting impaired absorption in some individuals. Plasma half-life is about 3 hours in adults and somewhat less in children. 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.

Although peak plasma prednisolone levels are somewhat lower after administration of prednisolone and absorption is delayed, total absorption and bioavailability are the same after plain prednisolone. Prednisolone shows dose dependent

pharmacokinetics, with an increase in dose leading to an increase in volume of distribution and plasma clearance. The degree of plasma protein binding determines the distribution and clearance of free, pharmacologically active drug. Reduced doses are necessary in patients with hypoalbuminaemia.

Prednisolone is metabolized primarily in the liver to a biologically inactive compound. Liver disease prolongs the half-life of prednisolone and, if the patient has hypoalbuminaemia, also increases the proportion of unbound drug and may thereby increase adverse effects.

Prednisolone is excreted in the urine as free and conjugated metabolites, together with small amounts of unchanged prednisolone.

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.

5.3 Preclinical safety data

There are no non-clinical data of relevance to the prescriber that are not already covered in other sections of the SmPC.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone
Talc, purified
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.
Keep the blisters in the outer carton to protect from light and moisture.

6.5 Nature and contents of container

Prednisolone TD 5 mg: blisters of ALU/PVC containing packs of 24 tablets.
Prednisolone TD 20 mg: blisters of ALU/PVC containing packs of 2o tablets.

6.6 Special precautions for disposal and other handling

Not available.

7. Pharmaceutical company and Manufacturer

T&D Pharma GmbH
Lemgoer Straße 16
32689 Kalletal / Germany

8. Marketing authorization number(s)

Not applicable.

9. Date of first authorization / renewal of the authorization

Not applicable.

10. Date of revision of the text

01. June 2018