1. NAME OF THE MEDICINAL PRODUCT

Prednisolon EQL Pharma 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains prednisolone 5 mg.
Excipient(s) with known effect: lactose monohydrate 80 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, round, flat tablet with diameter of 7 mm.
The tablet has a score line on one side and can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-specific therapy in conditions where the anti-inflammatory and immunosuppressive effect of prednisolone is desired. Examples include rheumatoid arthritis, SLE, certain vasculitis as arteritis temporalis and periarteritis nodosa, sarcoidosis, bronchial asthma, ulcerative colitis, hemolytic anemia and granulocytopenia and severe allergic conditions.
In tumor therapy, in some cases of acute leukemia, lymphomas, cancer mammae and cancer prostatae.

4.2 Posology and method of administration

Individual. In general, 10-30 mg daily. In very severe emergency cases, up to 50-60 mg or more can be given over a few days. Once satisfactory response is obtained the daily dose should be reduced with 2,5-5 mg every other to every fifth day (faster at the highest doses) to the minimum maintenance dose. It is desirable that this does not exceed 10 mg / day.
If the full maintenance dose is given in the morning (8 AM) prednisolone is working as adrenal cortex natural circadian and causes minimal suppression of the adrenal cortex.
This dosing regimen can generally be considered in the first place. However, in some cases, e.g. for rheumatics with severe morning stiffness and for asthmatics who need corticosteroid protection during the night, a late evening dose or split dosing may be preferred.
In some cases of asthma, allergic conditions, dermatoses, etc. may advantageously provide dual daily dose as a unitary dose every other day in the morning.
The dose should be gradually reduced to the lowest dose, especially in high-dos treatment.
Treatment cessation should be successively due to the patient own ACTH secretion may be impaired after prolonged treatment.
Increased dosage may be administered before, during and after stress situations.
Increased dose at fever and stress.
The insulin dose should be increased for diabetic patients upon cortisone treatment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Systemic fungal infection.

Administration of live vaccines is contraindicated in patients who receive corticosteroids in immunosuppressive dosages.

In general, none of the contraindications applies in conditions where treatment with prednisolon can save life.

4.4 Special warnings and precautions for use

As the complications from glucocorticoid treatment are dependent of dose and treatment duration, a risk/benefit evaluation needs to be done in each individual case in terms of dose and duration of treatment, and if daily or intermittent treatment is to be used.

The lowest possible corticosteroid dosage needed to control the disease under treatment, should be used. Where dose reduction is possible it should be done gradually.

Immunosuppressive effects/increased infection susceptibility

Glucocorticoids, including prednisolone, can result in increased susceptibility to infection, mask symptom of infection and new infections can occur during treatment. Infections, caused by virus, bacteria, fungus, protozoa or helminths, can be related to usage of solely corticosteroids or corticosteroids in combination with other immunosuppressive agents which affect cellular immunity, humoral immunity or function of neutrophils. The infections can be mild, but also severe and in some cases fatal. The risk of infection complications increases with increased dose.

Glucocorticoids should not be used in infections without concomitant causal therapy.

The immunosuppressive effects of glucocorticosteroids may lead to activation of latent infection or exacerbation of adjacent infections.

Monitor for development of infection and consider discontinuation of corticosteroids or dose reduction as needed.

Varicella and measles can have a more severe or even fatal progress among non-immunized children and adults who are treated with corticosteroids. Children, or adults who have not had these diseases, and who takes immunosuppressive dosages of corticosteroids, should be informed of avoidance of exposure to varicella and measles, and to seek care in case of exposure.

Use of prednisolone in active tuberculosis should be restricted to fulminant or disseminated tuberculosis where the corticosteroid is used for treatment of the disease, in combination with appropriate tuberculosis treatment. If corticosteroids are indicated to patients with latent tuberculosis or tuberculin reactivity careful monitoring is necessary since the disease may be reactivated. These patients should be administered tuberculosis prophylaxis in case of long-term corticosteroid treatment.

Corticosteroids in high doses can interfere with active immunization. Vaccination with live vaccine should be given under strict supervision and not to patients who are on long term treatment with corticosteroids in immunosuppressive dosages.

Immune system

As rare cases of skin reactions and anaphylactic/anaphylactoid reactions have occurred among patients treated with corticosteroids, appropriate precautionary measures should be in place before the administration, especially if the patient previously has experienced an allergic reaction to any drug.

The endocrine system

Long term treatment with pharmacological dosages of corticosteroid can lead to secondary adrenal cortex insufficiency. The risk can be reduced by administration of treatment every other day (se section 4.2).

Patients that receive maintenance treatment with corticosteroids and are exposed to exceptional stress (as infection, surgical procedure or trauma) need higher doses of corticosteroids before, during and after the stressful situation.

Abrupt withdrawal of treatment can lead to acute adrenocortical insufficiency which may be fatal. The risk of secondary adrenocortical insufficiency can be decreased by gradual dose reduction. This type of relative insufficiency may remain for months after withdrawal of treatment, wherefore hormonal treatment should be reintroduced in stressful situations arising during this time period. Salts and/or mineralocorticoids should be administered concurrently since the excretion of mineralocorticoids can be reduced.

A “steroid withdrawal syndrome”, apparently without connection to adrenocortical insufficiency, may also occur after abrupt withdrawal of glucocorticoids. This syndrome gives symptoms such as anorexia, nausea, vomiting, lethargy, headache, fever, arthralgia, desquamation, myalgia, weight loss and/or hypotension. These effects are assumed to be caused by the sudden change of the glucocorticosteroid concentration rather than by low corticosteroid levels.

Patients with hypothyroidism or hepatic cirrhosis receive an enhanced effect from corticosteroids.

Pheochromocytoma related crisis, that may be fatal, have been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after consideration of individual benefit / risk.

Metabolism and nutrition

Corticosteroids, including prednisolone, may increase blood glucose levels, deteriorate existing diabetes and increase the risk of developing diabetes in patients on long-term treatment with corticosteroids.

Psychiatric disturbances

Potentially severe psychiatric disturbances may occur with corticosteroid therapy, including prednisolone. It could be a wide range of disturbances from euphoria, sleep disturbances,

mood alteration, personality changes and severe depression to psychotic manifestations. Pre-existing emotional instability and psychotic tendencies may also worsen from corticosteroids (se section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Most reactions reverse after either dose reduction or discontinuation, although specific treatment may be necessary.

Psychological effects have been reported at withdrawal of corticosteroids; the frequency is not known. Patients/carers should be encouraged to seek medical advice if psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.

Central and peripheral nervous system

Corticosteroids should be used with caution in patients with cramp disorders.

Cardiac effects

Adverse reactions of glucocorticoids on the cardiovascular system, i.e. dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors for additional cardiovascular reactions, at high doses and prolonged therapy. Corticosteroids should therefore be introduced to these patients first after careful consideration; risk modifying measures and additional cardiac monitoring should be considered when needed. Low dose and treatment every other day may reduce the complications during therapy with corticosteroids.

Vascular effects

Because cortisone has been reported to increase blood coagulability in rare cases and therefore may accelerate the development of intravascular thrombosis, thromboembolism and thrombophlebitis, corticosteroids should be used with caution in patients with thromboembolic disorders.

Gastrointestinal effects

High doses of prednisolone may cause acute pancreatitis.

There is no clear data demonstrating that corticosteroids cause gastric ulcer. Glucocorticoid treatment may mask peritonitis and other signs and symptoms associated with gastrointestinal conditions as perforation, obstruction or pancreatitis. The risk of gastrointestinal ulcers is increased in combination with NSAIDs.

Corticosteroids should therefore be used with caution for non-specific ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis, newly laid anastomoses, or active or latent peptic ulcer.

Hepatobiliary effects

Rare cases of hepatobiliary diseases have been reported and in the majority of these cases resolution of the adverse events has been observed after treatment was discontinued. Therefore, appropriate monitoring is required.

Musculoskeletal effects

Acute myopathy has been reported with high doses of corticosteroids, usually among patients with disturbances in neuromuscular transmission (e.g. myasthenia gravis), or among patients concurrently treated with anticholinergics, e.g. neuromuscular blocking drugs (as pancuronium) (see section 4.5). The acute myopathy is generalized, may involve eye- and respiratory muscles, and may lead to tetraparesis. Elevated creatine kinase levels may occur. Clinical improvement or recovery after treatment with corticosteroids has been discontinued may take weeks or years.

Corticosteroids should be used with caution in patients with osteoporosis.

Renal and Urinary disorders

Particular care is required when considering the use of corticosteroids in patients with renal insufficiency.

Acute renal crisis (renal crisis at scleroderma)
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 prednisolone or more. Blood pressure and renal function (S-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

Effect on electrolytes and fluid balance

Systemic corticosteroids should be used with caution in patients with congestive heart failure or hypertension. Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with synthetic derivatives, except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary.

All corticosteroids increase calcium excretion.

Ocular effects

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. These may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Tumor lysis syndrome (TLS)

Tumor lysis syndrome (TLS) has been reported in post-marketing experience 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 of TLS, for example patients with tumours that have a high cell division rate, high tumour burden and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precautions taken.

Oral anticoagulants and bleeding risk

Concomitant use of oral anticoagulants and prednisolone may primarily increase the risk of bleeding. There have also been reports of reduced efficacy of oral anticoagulants. In patients treated with vitamin K antagonists, closer monitoring of prothrombin time (INR) is recommended, particularly after initiation of treatment or dose adjustments of prednisolone (see section 4.5).

Pediatric population

Corticosteroids cause growth retardation in infants, children and adolescents and therefore long-term treatment with pharmacological doses should be avoided. If long-term treatment is necessary, the growth and development of the infant/child has to be closely monitored (se section 4.2).

Infants and children in longterm treatment with corticosteroids are at greater risk of developing increased intracranular pressure.

Excipients

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

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4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with prednisolone may require dose adjustment:

Phenobarbital, phenytoin, carbamazepine: Phenobarbital (which is also a metabolite of primidone), phenytoin and carbamazepine singly and in combination to induce the metabolism of hydrocortisone, prednisolone and methylprednisolone (shown in children with asthma) with increased dose requirement as a result.
Interaction probably applies to the entire group of glucocorticoids.

Non-steroid anti-inflammatory drugs:
1) The incidence of gastrointestinal bleeding and ulceration may increase if corticosteroids are given with NSAIDs.
2) Corticosteroids may increase the clearance of high-dose acetylsalicylic acid, which may result in decreased salicylate serum levels. The salicylate serum levels may increase at withdrawal of corticosteroid therapy, which could lead to an increased risk of salicylate toxicity.

Antidiabetics: Glucocorticoids increase blood glucose levels. Patients with diabetes mellitus receiving concurrent insulin and/or oral hypoglycemic agents may require dosage adjustments of such therapy.

Oestrogens (also oral contraceptives containing oestrogen): Oestrogens increase the concentration of transcortin. The effects of glucocorticoids bound to transcortin can be reinforced and dosage adjustments may be required if oestrogens are added to or withdrawn from a stable dosage regimen.

Potassium depleting agents: Potassium depleting diuretics (e.g. thiazides, furosemide, etacrynic acid) and other drugs which reduces potassium levels such as amphotericin B, xanthenes and beta2-agonists, may reinforce the potassium lowering effect of glucocorticoids. Serum-potassium should be carefully monitored in patients administered glucocorticoids and potassium depleting agents.

Rifampicin: Rifampicin induces the microsomal oxidation of glucocorticoids (hydrocortisone, prednisolone, methylprednisolone). This results in an increased need for steroids during rifampicin treatment and reduces the need for steroids after such treatment.

Isoniazid: In addition, there is a potential effect of prednisolone on the acetylation rate and clearance of isoniazid.

Oral anticoagulants: There are reports of altered response of anticoagulants given concomitantly with prednisolone. Prothrombin time (INR) should be monitored during treatment.

CYP3A inhibitors, including cobicistat-containing products: These are 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 effects.

Anticholinergics, neuromuscular blockers: Corticosteroids may influence the effect of anticholinergics.
1) Acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs (see section 4.4).
2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking glucocorticosteroids. This interaction may be expected with all competitive neuromuscular blockers.

Anticholinesterases: Interaction between glucocorticoids and anticholinesterases such as ambenonium, neostigmine and pyridostigmine may lead to pronounced debility for patients with myasthenia gravis. The therapy with anticholinesterases should be withdrawn at least 24 hours before glucocorticoid treatment is introduced, if possible.

4.6 Fertility, pregnancy and lactation

Fertility.
Studies in animal have shown that corticosteroids impair the fertility (see section 5.3).

Pregnancy
Corticosteroids have been shown to cause different kind of malformations (cleft palate, skeletal malformations, see section 5.3) in animal tests. The relevance to human is unknown. After long-term treatment in humans and animals, reduced placental and birth weight has been found. Additionally, there is risk of adrenal suppression in the newborn during long term treatment. Therefore, corticosteroids should be given after special consideration during pregnancy.

Breast-feeding
Prednisolone passes into breast milk, but the risk of affecting the child appears unlikely with therapeutic doses.

4.7 Effects on ability to drive and use machines

The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as dizziness, visual disturbances, and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Aside replacement therapy corticosteroids treatment always involves an overdose compared to the physiological state. Adverse reactions occur mainly at long-term treatment but also depends on the size of dose and individual susceptibility.

The following adverse reactions have been observed and reported during therapy with Prednisolon EQL Pharma, with the following frequencies:
Very common (≥1/10), common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100);
rare (≥ 1/10 000, <1/1000), very rare (<1 /10 000) no known frequency (cannot be estimated from available data).

System Organ Class	**Very common** (≥1/10)	**Common (≥ 1/100, <1/10);**	**Uncommon (≥ 1/1,000, <1/100)**	**Rare (≥ 1/10 000, <1/1000)**	**Very rare (<1/ 10 000)**	**Not known (cannot be estimated from available data).**
Infections and infestations		Opportunistic infection, activation of infection (e.g. tuberculosis).				
Blood and lymphatic system disorders						Leukocytosis (due to a redistribution of intravascular granulocytes)
Immune system disorders						Drug hypersensitivity , anaphylactic reaction, anaphylactoid reaction
Endocrine disorders		Inhibition of the hypothalamic-pituitary-adrenal (HPA) axis , Cushing-like symptoms, growth retardation (in children).				Steroid withdrawal symptom (see section 4.4) pheochromocytoma-related crisis (see section 4.4)

Metabolism and nutrition disorders		Hypokalemia, sodium retention, increased gluconeogenesis, catabolic side effects, osteoporosis.				Metabolic acidosis, fluid retention, hypokalaemic alkalosis. dyslipidemia, decreased glucose tolerance (diabetes mellitus may aggravate and latent diabetes may be manifest), lipomatosis, increased appetite (which may lead to weight increase)
Psychiatric disorders			Activation of previous psychiatric disorders (high dose).	Depression, mania in patients without a history of mental illness.		Affective disorders (including euphoria, affective lability, drug dependence, suicidal thoughts), psychotic disorders (including, delusions, hallucinations, and schizophrenia), mental disorder, personality alterations, confusional state, anxiety, mood alterations, behavioral disturbances, insomnia, irritability
Nervous system disorders				Benign intracranial hypertension		Epidural lipomatosis, attacks of cramp, amnesia, cognitive disturbance, dizziness, headache

Eye disorders			Glaucoma, cataract.			Central serous Chorioretinopathies (see section 4.4), exophthalmos, blurred vision (see section 4.4),
Cardiac disorders						Heart failure (among sensitive patients), bradycardia*
Vascular disorders		Edema, hypertension				Thromboembolic events
Respiratory, thoracic and mediastinal disorders						Hiccup
Gastrointestinal disorders						Peptic ulcer (possibly with perforation and bleeding), intestinal perforation, pancreatitis, ulcerous oesophagitis, distended abdomen, abdominal pain, diarrhoea, dyspepsia, nausea
Skin and subcutaneous tissue disorders		Skin atrophy, impaired wound healing				Angioedema, hirsutism, petechia, ecchymosis, erythema, hyperhidrosis, striae, itching, urticaria, acne
Musculoskeletal and connective tissue disorders		Muscle atrophy		Aseptic bone necrosis, tendon rupture		Muscle weakness, myalgia, myopathy, pathological fracture, neuropathic arthropathy, arthralgia

Renal and urinary disorders						Acute renal crisis (renal crisis at scleroderma) **
Reproductive system and breast disorders						Irregular menstruation
General disorders and administration site conditions						Fatigue, malaise
Investigations						Increased amounts of calcium in urine, elevated alanine aminotransferase, elevated aspartate aminotransferase, elevated alkaline phosphatase in blood, elevated blood urea, suppression of reactions on skin tests[1]

[1] Not MedDRA-term
*Following high doses
** Acute renal crisis (scleroderma renal crisis)
Amongst the different subpopulations the occurrence of acute 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%)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 the national reporting system listed in Appendix V.*

4.9 Overdose

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. Possibly, acute overdose may aggravate pre-existing medical conditions such as ulcers, electrolyte imbalance, infection and oedema.

Treatment: Usually not required. If justified, gastric emptying, charcoal. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: glucocorticoid,
ATC code:H02AB06

Synthetic glucocorticosteroid with anti-inflammatory, immune-suppressive and anti-allergic activity. Prednisolone has per weight 4-5 times higher anti-inflammatory activity than cortisone but affects the electrolyte metabolism less. The mechanism is not yet fully understood.

5.2 Pharmacokinetic properties

Absorption
Prednisolone is rapidly absorbed from the GI tract after oral administration.
Maximum plasma concentration is reached after 1 to 2 hours after oral administration. The half-life in plasma is normally 2 to 4 hours. Its initial absorption, but not its overall bioavailability, is affected by food.

Distribution
Prednisolone is extensively bound to plasma proteins and has high affinity to transcortin. Distribution volume and clearance are reported to increase at transition from low to medium high doses.

Metabolism
Prednisolone is metabolized primarily in the liver to a biological inactive compound. Prednisolone may be reversibly transformed to prednisone by 11β-hydroxisteroiddehydrogenase.

The absolute bioavailability of prednisolone is on average 82% compared to intravenously administered prednisolone after a single dose of 10 mg. For normal dosage the duration of the effect was calculated to 12-36 hours.

Elimination
Prednisolone is excreted in the urine as free and conjugated metabolites, together with small amounts of unchanged prednisolone. More than 90% of the given amount is excreted in urine. 7-15% is excreted unchanged.

5.3 Preclinical safety data

In animal studies, corticosteroids have been shown to cause different malformations (cleft palate, skeletal malformations). Reduced placental and birth weight has been observed in animals after long-term treatment.

Corticosteroids have shown to reduce the fertility when administered to rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Blister: Store below 25°C.
Bottle: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC/aluminium blister package: 25 tablets

White HDPE-bottle with white PP screw cap with tamper evidence: 105 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2018-04-06

10. DATE OF REVISION OF THE TEXT

2026-01-15