SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prednisolon "Nycomed“ 5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg prednisolone.

Excipients with known effect:
Each 5 mg tablet contains 62 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
White round, bilaterally flat tablets with rounded edges. With score line on one side embossed with “PD” above and with “5.0” below the score line. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prednisolon "Nycomed" 5 mg Tablets are indicated at indication- and substance-dependent dosage for the treatment of any disorders responding to systemic glucocorticoid therapy.

Pharmacodynamic therapy:
- Rheumatic disorders including collagenoses.
- Allergic disorders (e.g. hay fever, bronchial asthma, urticaria, drug allergies).
- Respiratory diseases: chronic bronchitis (with antibacterial coverage).
- Pulmonary fibroses, sarcoidosis.
- Inflammatory bowel diseases such as ulcerative ileitis/colitis.
- Certain renal disorders such as minimally proliferative glomerulonephritis (lipoid nephrosis), nephrotic syndrome
- Acute severe dermatoses such as pemphigus vulgaris, erythrodermia, Lyell syndrome.
- Blood disorders such as thrombocytopenic purpura, chronic lymphadenosis with autoimmune phenomena (haemolytic anemia, thrombopenia).
- Tumors, in combination with chemotherapy.

Substitution therapy:
- Primary adrenal insufficiency (Addison’s disease) und hypopituitarism (Sheehan syndrome). Prednisolone is not to be considered as treatment of first choice in adrenocortical insufficiency. Hydrocortisone and cortisone are the agents of first choice.
- Inhibitory therapy for androgenital syndrome.

4.2 Posology and method of administration

General treatment guidelines:
When therapy with glucocorticoids is started, the following guidelines must be observed and followed: Initial dosage must be appropriate for achieving the desired therapeutic success and will depend on clinical evaluation. Dosage must be evaluated at regular intervals, as the course of the underlying disease will change or complications of therapy may develop. Dosage must be reduced at regular increments to

the lowest dose ensuring and maintaining a satisfactory clinical response. Dosage may need to be increased during long-term therapy or in the event of an exacerbation of the underlying disease.

If a prolonged therapy with prednisolone (normally longer than 3 weeks) has to be discontinued, discontinuation must be gradual and in increments for avoiding a withdrawal syndrome. Abrupt discontinuation of therapy may be lethal (see section 4.8). Dosage must be gradually reduced over weeks or even months depending on dose level, treatment duration, the patient's underlying disease and individual response. If prednisolone is given for shorter periods than 3 weeks, it is unlikely for most patients that abrupt discontinuation will result in a clinically relevant suppression of the hypothalamic-pituitary-adrenal axis. However, it should be considered that the responses and the withdrawal tolerance with a glucocorticoid therapy will show high interindividual variations. Therefore, gradual tapering should also be considered when discontinuing treatment after short treatment periods or with administration of higher doses and in patients with other risk factors for adrenocortical insufficiency.

The dosing schedule for gradual tapering of dosage should be selected on an individual basis. Most patients will tolerate a reduction of the prednisolone dose at increments of 2.5 mg every 3-7 days until a dose of 5-10 mg/day has been reached. Higher doses must be gradually tapered over a period of 9-12 months.
With a slow dose reduction the evening dose should initially be omitted, followed by omission of the dose that may have been given at noon, in the afternoon or in the evening so that only the morning dose will finally be given after a period of about 10 days. With long-term therapy alternating glucocorticoid therapy (1 dose every other day in the morning) has been shown to be effective because of the lacking adrenocortical suppression.

Method of administration:
For oral use together with some fluid, after meals.

Dosage based on indication:
Adults:
Inflammatory diseases: The usual dose ranges between 5 to 60 mg/day depending on the condition to be treated.
Generally, the complete daily dose should be taken early in the morning between 6 and 8 o'clock. (Circadian therapy).

Physiological substitution therapy: The recommended starting dose is 5 mg given in two divided doses in the morning and in the evening.

Dosage in special patient populations:
Dosage in patients with hypothyroidism:
In patients with hypothyroidism dose reduction may be required.

Dosage with impairment of hepatic function:
As patients with impaired hepatic function show reduced protein binding due to hypoalbuminemia the likelihood of severe adverse effects is increased. Dose adjustment may be required.

Dosage with impairment of renal function:
For patients with impaired renal function no dose adjustment is required.

Dosage in children and adolescents:
No data are available. As regards growth retardation, children are considered to be especially at risk (see sections 4.4 and 4.8); therefore, indication for use requires especially strict evaluation in children.
In children at growth age, treatment should principally be alternating or intermittent. Gradual reduction of dosage to a dose providing for satisfactory clinical response and causing a minimum of adverse effects is essential.

Inflammatory or immunosuppressive effects:

The usual dosage of prednisolone is 0.1 to 2 mg/kg/day. Dosage may be divided to 1 to 4 daily doses. The lowest effective dose will generally be determined by clinical response.
Acute asthma: The usual dose of prednisolone is 1 to 2 mg/kg/day. This dosage may be divided into 1-2 daily doses and given for 3 to 5 days.
Physiological substitution therapy: The usual dose is 4-5 mg/m²/day.
Nephrotic syndrome: The usual dose is 2 mg/kg/day (maximum dose: 60-80 mg/day, given in 2-4 daily doses).

Dosage in geriatric patients:
Elderly patients:
Prolonged use of corticosteroids in elderly patients may induce exacerbation of diabetes, hypertension, congestive heart diseases and osteoporosis or cause depression (see section 4.8). It is essential to reduce dosage to the minimum dose providing for a clinically satisfactory response and associated with a minimum of adverse effects.

4.3 Contraindications

Prednisolone is contraindicated in the presence of the following conditions/disorders:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Systemic mycoses
- Vaccinations with bacterial or viral live vaccines are contraindicated in patients undergoing immunosuppressive corticosteroid therapy (as the inadequate immune response to live vaccines may allow development of infections).

With prolonged treatment:
- Duodenal ulcer
- Peptic ulcer
- Severe osteoporosis
- Severe myopathies (with the exception of myasthenia gravis)
- History with psychiatric disorders
- Acute viral infections (herpes zoster, herpes simplex, varicella)
- HBsAg-positive chronic active hepatitis
- Glaucoma
- Poliomyelitis
- Lymphadenitis following BCG vaccination
- Approximately 8 weeks before to 2 weeks after vaccinations

4.4 Special warnings and precautions for use

- Patients with particular physical problems, such as febrile conditions, injuries or surgery, during treatment may require a temporary adjustment of the daily corticoid dose.
- The risk of tendon disorders, tendinitis or tendon ruptures will increase with the concomitant use of fluoroquinolones and corticosteroids.
- Long-term use should be accompanied by ophthalmologic controls at intervals of three months.
- Moreover, long-term use may be associated with an accelerated progression of Kaposi‘s sarcoma.
- With the exception of use for substitution therapy, corticosteroids will not be curative, but will show palliative effects as a result of their anti-inflammatory and immunosuppressive activity. Depending on dosage and duration of treatment, prolonged use will be associated with an increased likelihood of adverse effect. Patients undergoing prolonged treatment with systemic corticosteroids should be monitored for suppression of the hypothalamic-pituitary-adrenal axis (HPA, adrenocortical insufficiency), Cushing syndrome, hyperglycemia and glycosuria (see section 4.8).
- Following prolonged administration of corticosteroids treatment must be gradually tapered off for avoiding a withdrawal syndrome (see section 4.2). Adrenocortical insufficiency may persist for months after discontinuation of a corticosteroid and may require substitution therapy in the case of stress situations (surgery, disease). The risk of adrenal insufficiency may be reduced by alternating administration on every other day instead of daily administration (see section 4.2).

- As a result of their anti-inflammatory and immunosuppressive action the use of corticosteroids at doses being higher than those required for substitution therapy is associated with an increased risk of infection, potential exacerbation of an existing infection and possible activation of a latent infection. The anti-inflammatory action may mask symptoms of infection until the infection has reached a more advanced stage. If new infections develop during treatment the fact that it may be impossible to localize such infection must specifically be considered (see section 4.8).
- Corticosteroid therapy may increase the risk of tuberculosis (TB) in patients with dormant TB. These patients must be closely monitored for reactivation of TB. If long-term therapy is required in such patients anti-tuberculosis chemotherapy may be indicated. The use of corticosteroids in patients with active TB must be restricted to cases with exacerbation or with disseminated disease, if the use of corticosteroids is intended for the management of the disease together with a suitable anti-tuberculosis therapy.
- Systemic corticoid therapy may increase the risk of severe or lethal infections in individuals exposed to viral diseases such as chickenpox or measles in their environment (patients must be warned to avoid any such a risk and immediately seek medical consultation in the presence of such a risk). Corticosteroids may predispose for bacterial infections and fungal infections (Candida infections). Corticoids may activate dormant amebic infections; therefore, it is essential to exclude potential dormant amebic infections before starting corticoid therapy.
- Prednisolone enhances gluconeogenesis. Approximately one fifth of patients treated with high-dosed steroids develop benign steroid diabetes with low sensitivity for insulin and a low renal threshold for glucose. This benign steroid diabetes is reversible upon discontinuation of therapy. In patients with known diabetes corticoid therapy will produce deregulation that may be compensated by adjustment of the insulin dosage (see section 4.8).
- Long-term treatment with prednisolone will affect calcium and phosphate metabolism and increase the risk of osteoporosis (see section 4.8). Prednisolone enhances calcium and phosphate deficiency and may thus affect the vitamin D levels and consequently cause a dose-related reduction of serum osteocalcin (a bone structure protein correlating with bone formation).
- In children prednisolone therapy for a few weeks will increase the risk of growth retardation associated with a reduced secretion of growth hormone and a reduced peripheral sensitivity for this hormone (see sections 4.2 and 4.8).
- Corticoids may induce mental disorders including euphoria, insomnia, fluctuations of mood, personality changes, depression and psychotic tendency (see section 4.8).
- 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
- Prolonged administration of systemic glucocorticoids may cause development of posterior subcapsular cataract and glaucoma (due to increased intraocular pressure) and may involve an increased risk of ocular infection (see section 4.8). In the case of glaucoma, corneal ulcers and corneal injuries close ophthalmologic supervision and treatment is indicated. Patients with herpes infection show an increased risk of corneal damage as prednisolone may mask the infection.

Special precautions:

Corticosteroids must be used with caution under the following circumstances:

- gastrointestinal conditions such as unspecific ulcerative colitis, diverticulitis potentially associated with threatening colon perforation, colon abscess or any other pyogenic infections, colon obstruction or marked fistulas and sinus tracts, fresh intestinal anastomoses, dormant peptic ulcers. The anti-inflammatory properties of glucocorticoids may mask the signs of gastrointestinal perforations and thus lead to delayed diagnosis and consequently to a potentially fatal outcome.
- hypertension and/or congestive heart disease (due to the mineralocorticoid effect of prednisolone which may lead to fluid and salt retention, see section 4.8),
- osteoporosis (because corticosteroids may potentiate the symptoms of osteoporosis)
- known and suspected infections
- known lymph tumors, because acute tumor lysis syndrome following administration of glucocorticoids has been reported

- heart failure or renal insufficiency: concomitant effective therapy of underlying disease and ongoing continual monitoring
- hepatic disease (see section 4.2)
- hypothyroidism (see section 4.8)
- myasthenia gravis because myopathy may be potentiated
- cerebral malaria (coma may be prolonged, incidence of pneumonia and of gastrointestinal bleeding may be increased)
- latent epilepsy
- hyperparathyroidism (because prednisolone may cause manifestation of the condition),
- treatment of patients with acetylsalicylic acid or nonsteroidal anti-inflammatory drugs (because of the increased ulcer risk)
- 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.
- potassium-reducing diuretics (see section 4.5).
- 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 prednisolone. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

Diet should be potassium-, protein- and vitamin-rich, but also low-fat, low-carbohydrate and low-salt.

Elderly patients:
Elderly patients should be monitored for adverse effects like osteoporosis and tendon disorders, especially during long-term therapy.

Children:
For children at growth age, circadian or alternating therapy is recommended, if possible.

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

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 inducers like rifampicin, phenytoin, primidone, barbiturates, carbamazepine, aminoglutethimide: Corticoid effect reduced.

CYP3A4 blocking substances (ketoconazole, Ritonavir), erythromycin, troleandromycin: corticoid effect increased.

Gastrointestinal organs and metabolism
Hypoglycemic agents:
Prednisolone counteracts the effects of hypoglycemic agents by increasing blood glucose levels (see section 4.8).
Risk of reduced effectiveness of hypoglycemic agents with a consequent risk of hyperglycemia.

Cardiovasular
Potasssium-reducing diuretics (thiazides, furosemide):
Additive renal potassium loss.
Increased risk of hyperglycemia and associated cardiac arrhythmias.

Cardiac glycosides: Enhanced glycoside effect due to potassium deficiency.
ACE inhibitors: The risk of changes in blood counts may be increased.

Antihypertensives: Reduced blood pressure lowering.

Hormones for systemic use
Oral contraceptives:
The serum levels of prednisolone may increase due to a reduced metabolism of prednisolone.
Increased risk of adverse effects of corticosteroids.

Excessive use of glucocorticoids may inhibit the growth stimulating effect of somatropine.

Antiinfectives
Rifampicin:
Enhanced metabolism of prednisolone.
Reduced effect of prednisolone.

Amphotericin B:
Additional potassium loss and fluid retention.
Risk of hypokalemia and cardiac arrhythmias.

Fluoroquinolones:
Increased risk of tendon ruptures.

Ketoconazole may potentiate the effects of prednisolone.

Muscles, joints and bone
Acetylsalicylic acid:
a) Acetylsalicylic acid is known as gastroirritant and prednisolone may mask such adverse effects. The mechanism is unknown.
b) Increase of acetylsalicylic acid clearance by prednisolone has been reported.
There is an increased risk of gastrointestinal bleeding and ulceration (a) and a risk of reduced effectiveness of acetylsalicylic acid (b) (see 4.4). Thus, the risk of adverse effects of salicylates will be increased when discontinuing prednisolone.

NSAIDs (nonsteroidal anti-inflammatory drugs):
NSAIDs are gastroirritant and prednisolone may mask these adverse effects.
There is a risk of gastrointestinal bleeding and ulcerations.

Non-depolarizing muscle relaxants: prolonged muscle relaxation.

Central nervous system
Barbiturates:
Barbiturates are agents inducing hepatic enzymes and increasing the metabolism of prednisolone.
Reduced effect of prednisolone.

Phenytoin and fosphenytoin:
Enhanced hepatic metabolism of prednisolone.
Reduced effectiveness of prednisolone.

Quetiapine:
Induction of the P450-mediated metabolism of quetiapine by corticosteroids.
Adverse effect: Reduced quetiapine serum levels.
Increased doses of quetiapine may be required for ensuring maintained control of schizophrenia symptoms.

Bupropione: Concomitant use together with systemic glucocorticoids may increase the risk of seizures.

Immunosuppressants
Methotrexate: Mechanism unknown. Increased effect of prednisolone.
Prednisolone may increase the plasma levels of ciclosporin.

Influence on laboratory tests and investigations
- Skin reactions to allergy tests may be suppressed.
- Protireline: TSH increase reduced.

Other agents:
Bacterial or viral live vaccines:
Reduced immune response will allow for the emergence of infections caused by live vaccines and may also result in a reduced effectiveness of vaccination.
There is an increased risk of generalized, potentially life-threatening infections with vaccinations with live vaccines.

Ephedrine: The metabolism of glucocorticoids may be accelerated and consequently their effectiveness may be reduced.
Laxatives and beta-sympathomimetics: Potassium loss increased
Chloroquine, hydroxychloroquine, mefloquine: Increased risk of occurrence of myopathies, cardiomyopathies.
Coumarin derivatives: Their effect is reduced by prednisolone.
Theophylline: Possible trend towards increased clearance during treatment with prednisolone.
Cyclophosphamide: Single doses of prednisolone may inhibit the activation of cyclophosphamide, but activation rate increases after long-term administration.
Thalidomide may enhance the effect of prednisolone.
Praziquantel: Possible decrease of praziquantel blood concentrations caused by corticosteroids.
Atropine: Possible additive increase of intraocular pressure upon concomitant use with prednisolone.
Liquorice: Inhibition of corticosteroid metabolism by liquorice. Involves an increased risk of corticosteroid adverse effects.

4.6 Fertility, pregnancy and lactation

Prednisolone crosses the placenta. Animal studies have shown a dose-related increase of adverse effects (cleft palate in the offspring of mice, effects on brain growth and brain development).
In summary, however, the study data available suggest only a low risk for the fetus when prednisolone is used during pregnancy. However, prednisolone therapy during pregnancy should only be given after careful benefit/risk assessment.
If glucocorticoids are given in the final stage of pregnancy, there will be a theoretical risk of adrenal suppression for the fetus which may require tapering off of substitution treatment of the neonate.

The amount of prednisolone excreted into breast milk has been estimated with 0.1% of the maternal dose. The dose absorbed by the breast-fed infant may be minimized, if the mother avoids breast-feeding for 3-4 hours after the administration of prednisolone. Children of mothers taking daily doses of 40 mg or more should be monitored for signs of adrenal suppression.

4.7 Effects on ability to drive and use machines

Prednisolone has no or only negligible influence on the ability to drive and use machines.

4.8 Undesirable effect

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).

In general, the incidence of predictable adverse effects, including suppression of the hypothalamic-pituitary-adrenal axis, is dependent on dosage, timing of administration and duration of treatment (see sections 4.2. and 4.4). Adverse effects may be minimized by using the lowest effective dose for the shortest period possible.

Infections and infestations

Very common: Increased risk of infection, worsening of an existing infection, activation of latent infections, masking of infection symptoms (due to the immunosuppressive and anti-inflammatory effects of prednisolone, see section 4.4).

Blood and lymphatic system disorders
Very common: Reduced eosinophil and lymphocyte counts.
Common: Increased WBC and platelet counts.
Rare: Increased risk of thrombosis due to blood coagulation.

Immune system disorders
Very common: Masking or worsening of existing diseases (see section 4.4).
Uncommon: Allergic reactions.

Endocrine disorders
Very common: Adrenal insufficiency (starting with hypothalamic inhibition and culminating in actual atrophy of the adrenal cortex) with continual use of oral prednisolone (see section 4.4), withdrawal syndrome due to adrenal insufficiency (headache, nausea, drowsiness, anorexia, asthenia, emotional lability, lethargy and inadequate stress management (see section 4.4), "steroid-induced diabetes" with low insulin sensitivity, increased blood glucose in patients with existing diabetes (100%). Growth retardation in children due to reduced secretion of growth hormone and reduced sensitivity for this hormone.
Common: Cushing's syndrome including altered body fat distribution (moon-shaped face, truncal obesity, buffalo hump) with continual administration of supraphysiologic doses (oral) (usually more than 50 mg daily) (see section 4.4), hypokalemia due to sodium retention alternating with potassium, amenorrhea in fertile females, elevated levels of cholesterol, triglycerides and lipoproteins upon high-dosed oral treatment, increased appetite and weight gain.
Uncommon: Diabetes mellitus (<1%) with low-dosed oral treatment, elevated levels of cholesterol, triglycerides and lipoproteins upon low-dosed oral treatment.
Rare: Disturbances of thyroid function.
Very rare: Ketoacidosis and hyperosmolar coma, manifestation of latent hyperparathyroidism (see section 4.3), predisposition for porphyria, tumor lysis syndrome (see section 4.4), disorders of sexual hormone secretion (menstruation disorders, hirsutism, impotence)

Psychiatric disorders
Common: Euphoria, depression, corticosteroid-induced psychosis (5%).
Uncommon: Insomnia, mood fluctuations, personality changes, mania (see section 4.4), hallucinations.

Nervous system disorders
Rare: Coma may be prolonged in cerebral malaria, cognitive impairments (e.g. poor memory), dementia, epidural lipomatosis (fat deposits around the spine)
Very rare: Manifestation of latent epilepsy, pseudotumor cerebri (benign intracranial hypertension with symptoms such as headache, blurred vision and visual disturbances).

Eye disorders
Very common: Increased intraocular pressure (in up to 40% of patients treated with oral prednisolone), cataracts in 30% of patients treated with oral prednisolone for prolonged periods.
Rare: Treatment with prednisolone is associated with an increased corneal destruction in the presence of concurrent ocular herpes infection due to a masking of such an infection (see section 4.4), glaucoma with long-term oral therapy.
Very rare: Exophthalmus (after long-term therapy).
Not known: Blurred vision (see also section 4.4)

Cardiac disorders
Common: Hypertension (as a result of sodium retention leading to water retention), worsening of congestive heart disease (due to sodium retention).
Very rare: Cardiomyopathy with the risk of reduced cardiac performance, arrhythmias due to hypokalemia, circulatory collapse

Vascular disorders
Not known: Increased risk of arteriosclerosis and thrombosis, vasculitis (may also occur as withdrawal symptom after long-term therapy)

Respiratory, thoracic and mediastinal disorders
Very common: Pulmonary abscess (12%).
Common: Increased risk of tuberculosis.
Uncommon: Myopathy of respiratory musculature.

Gastrointestinal disorders
Very common: Oral candidiasis, especially in cancer patients (33 %).
Common: Increased symptoms and risk of gastrointestinal perforation with colitis, ileitis, diverticulitis.
Uncommon: Peptic and duodenal ulcers with concomitant use of acetylsalicylic acid or NSAIDs, gastrointestinal bleeding (0.5%), gastrointestinal perforations.
Very rare: Pancreatitis after prolonged high-dose therapy.
Not known: Esophageal ulcers and esophageal candidiasis.

Skin and subcutaneous tissue disorders
Very common: Fungal infections of mucous membranes (30 %).
Common: Striae, acne-like eruptions, bruising, dermatitis, ecchymosis, facial erythema, atrophy, hirsutism, impaired wound healing, increased sweating, teleangiectasia and thinning of skin, masking or worsening of existing skin disorders.
Very rare: Epidermal necrolysis, Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders
Very common: Osteoporosis associated with symptoms such as back pain, limited mobility, acute pain, vertebral compression fractures and reduction of body height, fractures of long bones (25% with oral long-term treatment, see section 4.4). Myopathy (10%) with high-dosed treatment.
Uncommon: Aseptic necrosis of bone structure.
Very rare: Tendinopathy, especially of the Achilles or patellar tendon (see section 4.5)
Not known: muscular atrophy, tendon disorders, tendinitis, tendon ruptures.

Renal and urinary disorders
Common: Increased frequency of nocturnal urination.
Uncommon: Urolithiasis due to increased calcium and phosphate excretion.
Not known: Scleroderma renal crisis (see below).

General disorders and administration site conditions
Not known: Delayed wound healing, disturbed appetite

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%)

Note:
Upon excessively rapid dose reduction after prolonged treatment, problems like muscle and joint pain, fever, rhinitis, conjunctivitis and weight loss may develop.

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:

Bundesamt für Sicherheit im Gesundheitswesen
Traisengasse 5
1200 Wien

Österreich
Fax: + 43 (0) 50 555 36207
Website: www.basg.gv.at

4.9 Overdose

Symptoms:
Reports of acute toxicity and/or death due to overdose are rare.
No specific antidote is available.

Treatment:
Treatment of overdose is essentially symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code: H02AB06.

Mechanism of action:
Prednisolon "Nycomed" 5 mg Tablets contain a glucocorticoid with a relative glucocorticoid potency of 4 and a relative mineralocorticoid activity of 0.6.
The Cushing threshold dose is 7.5 mg/day. Prednisolone is a corticosteroid with both types of glucocorticoid activity, anti-inflammatory activity and also mineralocorticoid activity, though to a lesser extent. Like other corticosteroids, prednisolone induces multiple mechanisms including 1) inflammatory activity, 2) immunosuppressant properties, and 3) antiproliferative effects. Other mechanisms include effects on carbohydrate metabolism, fat distribution, hematologic parameters, calcium excretion, body height, mood and suppression of the hypothalamic-pituitary-adrenal axis.

1. The anti-inflammatory effect is achieved by a reduced formation and a reduced activity of inflammatory mediators (quinine, histamine, liposomal enzymes, prostaglandins and leukotrienes) reducing the initial manifestations of the inflammation process. Prednisolone inhibits cell migration to the regions affected and reverses dilation and increased vascular permeability in these regions resulting in a reduced migration of cells to these regions. The vasoconstrictor effect reduces serum extravasation, swelling and physical complaints.

2. The immunosuppressive properties reduce the response to delayed hypersensitivity reactions and to those of the immediate type (types III and IV) by inhibiting the toxic effects of antigens and antibody complexes inducing allergic vasculitis in the vascular walls of the skin and by inhibition of lymphokines, target cells and macrophages (inducing allergic contact dermatitis by combined action).

3. The antiproliferative effects reduce the hyperplastic tissue qualities of dermatologic disorders like psoriasis.

5.2 Pharmacokinetic properties

Absorption:
Following oral application prednisolone is rapidly and completely absorbed in the gastrointestinal tract (availability up to 85%, dose-related), bioavailability is lower with higher doses. Peak plasma levels are reached after approximately 1-2 hours. In contrast, however, the maximum biologic effect is achieved significantly later (as a rule not before 4-8 hours).
Food will delay the peak plasma levels, but not the complete bioavailability.

Distribution:
Generally, prednisolone binding is 90-95%, primarily to glucocorticoid-binding globulin (transcortin), but also to plasma albumin, when transcortin binding is saturated.
Only 5-10% of prednisolone is unbound and biologically active.

Biotransformation:
Prednisolone is the primary active metabolite of prednisone. Prednisolone is primarily metabolized in the liver; 25% are eliminated in unchanged form via the kidneys.

Elimination:
Biological half-life is 18-36 hours. Plasma half-life is 2-4 hours and will be shortened by drugs inducing the hepatic enzymes (see section 4.5).

Pharmacokinetic/pharmacodynamic relationships:
In patients with severe liver disease (hepatitis, cirrhosis) clearance is lower and elimination half-life is prolonged. In patients with liver disease associated with hypoalbuminemia the free active fraction may increase substantially. In patients with severely impaired hepatic function bioavailability may be lower.

5.3 Preclinical safety data

Toxicity (subchronic/chronic): Light- and electron-microscopic changes on the islet of Langerhans cells of rats have been seen after daily intraperitoneal administration of 33 mg/kg over 7-14 mg/kg bodyweight.
Experimental liver damage was induced in rabbits by daily administration of 2-3 mg/kg bodyweight for 2-4 weeks. Histotoxic effects (muscle necrosis) have been observed after administration for several weeks of 0.5-5 mg/kg in guinea pigs and 4 mg/kg in dogs.

Mutagenicity and cancerogenicity:
There is an inadequate number of studies of mutagenicity of prednisolone or prednisone. To date, no evidence of mutagenicity has been described. The relevance of these findings is unclear.
No long-term studies of the tumorigenic potential of prednisolone in animals are available.

Reproduction toxicity:
Teratogenic effects of prednisolone shown in animal experiments since 1950 could not be confirmed in humans.
In animal experiments in mice, hamsters and rabbits prednisolone caused cleft palate.
In rats, minor anomalies on skull, jaws and tongue were described with parenteral administration.
To date no intrauterine growth disturbances have been reported.

The 200 cases published to date for humans (140 prednisone and 60 prednisolone) do not provide any evidence of increased teratogenicity. However, the number of cases studied is not sufficient to allow exclusion of any risk. Clinical experience with glucocorticoids during the first trimester of pregnancy to date produced no evidence of teratogenicity in humans.

Reversible disorders of spermatogenesis persisting for several months after discontinuation of the drug were observed when glucocorticoids were given for prolonged periods and at high doses (30 mg/day for at least 4 weeks).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Maize starch
Pregelatinized starch
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light. Do not store above 25°C.

6.5 Nature and contents of container

10, 40 and 100 tablets in PVC/PVDC deep draw foil for blister pack; aluminum foil with PVDC coating.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Acino Pharma AG
Birsweg 2, 4253 Liesberg
Switzerland

8. MARKETING AUTHORISATION HOLDER

11-62-81

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 -September -2018
Date of latest renewal: NA

10. DATE OF REVISION OF THE TEXT

12/2018

GENERAL CLASSIFICATION FOR SUPPLY

Subject to medical prescription, available in pharmacies only, no repeat dispensing.