SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CORLTO 5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance(s):

Prednisolone ..... 5 mg

Excipient(s) with known effect:

Lactose monohydrate (from cow's milk) ..... 74 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White or almost white, round tablet with scores.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Endocrine disorders

- Primary and secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogues can be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance)
- Congenital adrenal hyperplasia
- Nonsuppurative thyroiditis
- Hypercalcemia associated with cancer

Rheumatic disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
- Ankylosing spondylitis
- Acute and subacute bursitis
- Acute nonspecific tenosynovitis
- Post-traumatic osteoarthritis
- Synovitis of osteoarthritis
- Psoriatic arthritis
- Epicondylitis
- Acute gouty arthritis

Collagen diseases

During an exacerbation or as maintenance therapy in selected cases of:

- Systemic lupus erythematosus
- Systemic dermatomyositis (polymyositis)
- Acute rheumatic carditis

Dermatologic diseases

- Bullous dermatitis herpetiformis
- Severe erythema multiforme (Stevens-Johnson syndrome)
- Severe seborrheic dermatitis
- Exfoliative dermatitis
- Mycosis fungoides
- Pemphigus
- Severe psoriasis

Allergic states

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:

- Seasonal or perennial allergic rhinitis
- Drug hypersensitivity reactions
- Serum sickness
- Contact dermatitis
- Bronchial asthma
- Atopic dermatitis

Ophthalmic diseases

Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as:

- Allergic corneal marginal ulcers
- Herpes zoster ophthalmicus
- Anterior segment inflammation
- Diffuse posterior uveitis and choroiditis
- Sympathetic ophthalmia
- Keratitis
- Optic neuritis
- Allergic conjunctivitis
- Chorioretinitis
- Iritis and iridocyclitis

Respiratory diseases

- Symptomatic sarcoidosis
- Berylliosis
- Loeffler's syndrome not manageable by other means
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
- Aspiration pneumonitis

Hematologic disorders

- Idiopathic thrombocytopenic purpura in adults
- Secondary thrombocytopenia in adults
- Acquired (autoimmune) hemolytic anemia
- Erythroblastopenia (red blood cell anemia)
- Congenital (erythroid) hypoplastic anemia

Neoplastic diseases

For palliative management of:

- Leukemias and lymphomas in adults
- Acute leukemia of childhood

Edematous states

- To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus

Gastrointestinal diseases

To tide the patient over a critical period of the disease in:

- Ulceratif colitis
- Regional enteritis

Miscellaneous

- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
- Trichinosis with neurological or myocardial involvement

4.2. Posology and method of administration

Posology/frequency and duration of administration:

The starting dose of CORLTO varies from 5 to 60 mg per day, depending on the specific disease being treated. Divided daily doses are usually used. Although lower doses are usually sufficient for less severe cases, higher starting doses may be required in selected patients.

The following therapeutic principles should be kept in mind when using corticosteroids:

Corticosteroids provide palliative symptomatic treatment due to their anti-inflammatory effects. They are never curative.

The appropriate individual dose should be determined by trial-and-error and should be re-evaluated regularly according to disease activity.

Incidence of side effects will increase as corticosteroid therapy is prolonged and the dose is increased.

Starting doses are maintained or adjusted until a satisfactory response is obtained. If there is no adequate clinical response after a reasonable period of time, CORLTO should be discontinued and the patient transferred to another appropriate treatment.

IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT.

After a positive response is obtained, the lowest maintenance dose that will maintain an adequate clinical response should be determined by reducing the starting dose gradually at appropriate intervals. It should be remembered that drug dose should be constantly monitored. Situations that may necessitate dose adjustments include changes in clinical status due to improvements and exacerbations in the disease process, the patient's individual response to the drug, and the effects of exposure to stressors not directly related to the disease being treated, in which case it may be necessary to increase the CORLTO dose for a period of time commensurate with the patient's condition. If long-term therapy is necessary, every other day dosing regimen should be considered. If it is necessary to discontinue the drug after long-term treatment, it is recommended to reduce the dose gradually rather than abruptly (see section 4.4 Special warnings and precautions for use).

In patients receiving systemic corticosteroids for more than 3 weeks and in excess of the physiological dose (approximately 7.5 mg prednisolone or equivalent), the drug should not be discontinued abruptly. The method of reducing the dose should be applied largely depending on the disease, and the possibility of relapse in case of reducing the dose of systemic corticosteroids should be taken into account when making this decision. Clinical evaluation of disease activity may be required when the drug is discontinued. If relapse is unlikely with discontinuation of systemic corticosteroid treatment, but there is doubt about hypothalamic-pituitary-adrenal (HPA) suppression, the dose of systemic corticosteroids may be rapidly tapered to physiologic doses. Once a daily dose equivalent to 7.5 mg prednisolone is reached, dose reduction should be slower to allow recovery of the HPA axis.

If there is no risk of relapse, abrupt discontinuation of systemic corticosteroid therapy lasting up to three weeks is appropriate. Abrupt discontinuation of prednisolone or equivalent in doses of up to 40 mg for three weeks is unlikely to cause clinically significant HPA axis suppression in most patients. In the following patient groups, systemic corticosteroid therapy should be gradually reduced, even if treatment lasts 3 weeks or less:

- Patients receiving repeated cycles of systemic corticosteroids (especially if the cycles are longer than 3 weeks)
- Patients who received short-term treatment within one year of stopping long-term treatment (months or years)
- Patients who may develop adrenocortical insufficiency due to reasons other than exogenous corticosteroid therapy
- Patients receiving systemic corticosteroid therapy with more than 40 mg prednisolone (or equivalent) per day
- Patients taking repeated doses in the evening

(See section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects)

During long-term treatment, within the periods of stress or exacerbation of the disease, it may be necessary to temporarily increase the dose (see "Special warnings and precautions for use").

If a satisfactory clinical response is not obtained, the drug should be gradually tapered off and the patient should be transferred to another treatment.

Intermittent dosing regimen: A single dose of CORLTO in the morning, every other day or at longer intervals, may be acceptable for some patients. If this regimen is followed, the degree of pituitary-adrenal suppression, protein catabolism, and other side effects can be minimized.

Special dosing principles: Following advices may be applied to some diseases. Acute or severe disease may require high-dose therapy initially, but the lowest effective maintenance dose should be started as soon as possible. During chronic therapy, dose reductions should not exceed 5-7.5 mg per day.

Allergic and skin diseases: Generally, a starting dose of 5-15 mg per day is sufficient.

Collagenous: A starting dose of 20-30 mg per day is often effective. Those with more severe symptoms may require higher doses.

Rheumatoid arthritis: Starting dose is 10 -15 mg daily. The lowest daily maintenance dose that provides tolerable symptomatic relief is recommended.

Blood diseases and lymphoma: The starting dose is usually 15–60 mg daily and should be reduced after an adequate clinical or hematologic response is achieved. Higher doses may be required to induce remission in acute leukemia.

Method of administration
For oral use.

Additional information on special populations

Renal/Hepatic impairment: No special dose adjustment is necessary in renal or hepatic impairment.

Pediatric patients: As in adults, dose should be adjusted depending on the clinical response, although appropriately reduced adult doses are used (see section 4.4 Special warnings and precautions for use). Corticosteroids cause growth retardation in infancy, childhood, and adolescence. Treatment should be limited to the minimum dose and shortest duration possible. If possible, treatment should be administered every other day and in a single dose to minimize hypothalamic-pituitary-adrenal axis suppression and growth retardation.

Elderly patients: When treating elderly patients, especially when planning long-term treatment, it should be borne in mind that the frequent side effects of corticosteroids may lead to more serious consequences in the elderly (see section 4.4 Special warnings and precautions for use).

4.3. Contraindications

- Hypersensitivity to any of the ingredients in the tablet formulation
- Systemic fungal infection
- Systemic infections if specific anti-infective treatment is not administered
- Ocular herpes simplex due to possible perforation

4.4. Special warnings and precautions for use

Patients and/or their caregivers should be warned about the potential for severe psychiatric adverse reactions to systemic steroids (see section 4.8 Undesirable effects). Symptoms usually appear within a few days or weeks following the start of treatment. Risks may increase with higher doses/systemic exposure (see section 4.5 Interactions with other medicinal products and other forms of interaction - pharmacokinetic interactions which may increase the risk of adverse effects) but it is not possible to predict the onset, type, severity or duration of reactions at dose levels. Most reactions go away after the dose is reduced or stopped. However, specific treatment may be necessary. Patients/caregivers should be encouraged to seek medical attention if they are concerned about the development of psychological symptoms, particularly depressed mood or suicidal thoughts. Patients/caregivers should also be alert for possible psychiatric disorders that may occur during or following dose reduction or discontinuation of systemic steroids. But such reactions are rare.

Special care is required when considering systemic corticosteroids in patients with a history of or current severe affective disorders in themselves or in first-degree relatives. Such patients include those with depressive or manic-depressive illness and those with a history of steroid-induced psychosis.

Caution and frequent monitoring are required in patients with the following conditions who are receiving oral corticosteroids such as CORLTO.

- Tuberculosis: Those who have had tuberculosis before or who have X-ray changes characteristic of tuberculosis. However, the emergence of active tuberculosis can be prevented by the use of prophylactic anti-tuberculosis drugs.
- Hypertension
- Congestive heart failure
- Hepatic impairment
- Renal impairment
- Those with diabetes mellitus or a family history of diabetes
- Osteoporosis: It is of particular importance in postmenopausal women, especially those at risk.
- Patients with a history of severe affective disorders, and particularly those with a previous history of steroid-induced psychosis. Additionally, those experiencing emotional turmoil or those with psychotic tendencies may be aggravated by corticosteroids such as prednisolone.
- Diseases that cause epilepsy and/or seizures
- Stomach ulcer

- Those who have had steroid-induced myopathy before
- Glucocorticoids should be used cautiously in myasthenia gravis patients receiving anticholinesterase therapy.
- Corticosteroids should be used cautiously in patients with thromboembolic disorders since cortisone has been reported to increase blood clotting and precipitate intravascular thrombosis, thromboembolism, and thrombophlebitis in rare cases.
- Duchenne muscular dystrophy: Transient rhabdomyolysis and myoglobinuria may occur after strenuous physical activity. It is not known if this is due to prednisolone or intense physical activity.

Undesirable effects can be minimized by using the lowest effective dose for the shortest duration and by administering the daily dose every other day as a single morning dose. Frequent patient review is necessary to titrate the dose appropriately against disease activity (see section 4.2 Posology and method of administration).

Adrenocortical insufficiency

Long-term pharmacological doses of corticosteroids may lead to HPA suppression (secondary adrenocortical insufficiency). The duration and severity of adrenocortical insufficiency vary from patient to patient, depending on the dose, frequency, timing and duration of glucocorticoid therapy.

In addition, sudden discontinuation of glucocorticoids can cause acute adrenal insufficiency, which can be fatal. Therefore, secondary adrenocortical insufficiency due to the drug can be minimized by gradually reducing the dose. This type of relative insufficiency may persist for months after treatment has been discontinued. Therefore, in case of any stress occurring during this period, hormone therapy should be rearranged. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concomitantly. During long-term therapy, an intervening illness, trauma, or surgical procedure will necessitate a temporary increase in dose; if corticosteroids are discontinued after prolonged therapy, they may need to be temporarily restarted.

Patients should carry their “steroid treatment” cards with them, which include details about the prescriber, the medication, the dose and duration of the medication, so that the necessary precautions can be taken to minimize risks.

Anti-inflammatory/immunosuppressive effects and infection

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. When using corticosteroids such as prednisolone, the clinical picture can often be atypical and serious infections such as septicaemia and tuberculosis may be masked and reach an advanced stage without being diagnosed. The immunosuppressive effects of glucocorticoids may lead to activation of latent infection or exacerbation of intercurrent infections.

Children being treated with immunosuppressive drugs are more susceptible to infections than healthy children. For example, chickenpox and measles may be more severe, even fatal, in children receiving immunosuppressant corticosteroids. Children or adults who have not had these diseases and are taking corticosteroids in doses that would cause immunosuppression should be warned to avoid contact with people who have chickenpox or measles and to seek medical attention if they have had such contact. In case of exposure, use of varicella zoster immunoglobulin (VZIG) or pooled intravenous immunoglobulin (IVIG) may be indicated. If a patient develops chickenpox, treatment with antiviral agents should be considered. Passive immunization with Varicella-zoster immunoglobulin (VZIG) is required in patients who are receiving systemic corticosteroids or who have used these drugs in the last three months if exposed. This should be administered within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the disease requires specialized care and emergency treatment. Corticosteroids should not be discontinued and the dose should be increased if necessary.

The effects of corticosteroids are enhanced in patients with chronic liver disease, hypothyroidism, and hepatic impairment.

CORLTO in active tuberculosis should be limited to cases of fulminant or disseminated tuberculosis where corticosteroids are used in combination with an appropriate antituberculosis treatment regimen.

If corticosteroids are required in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. Chemoprophylaxis should be administered to these patients during long-term corticosteroid therapy.

Measles

Patients should be advised to take special precautions to avoid measles and to seek medical attention if exposed. Prophylaxis with intramuscular normal immunoglobulin may be required.

Vaccination with live vaccine

Live vaccines should not be administered to patients receiving high-dose corticosteroids because the immune response is impaired. Administration of live vaccines should be postponed for at least 3 months after discontinuation of corticosteroid therapy (see section 4.5 Interactions with other medicinal products and other forms of interaction).

Ocular effects

Long-term use of corticosteroids may lead to posterior subcapsular cataracts and nuclear cataracts (especially in children), exophthalmos or increased intraocular pressure and glaucoma with possible damage to the optic nerve. The incidence of secondary fungal or viral infections in the eye may be increased in individuals receiving glucocorticoids.

Corticosteroids should be used cautiously in ocular herpes simplex patients due to possible perforation.

Cushing's disease

Glucocorticoids should be avoided in patients with Cushing's disease because glucocorticoids may cause or aggravate Cushing's syndrome.

The effect of corticosteroids is increased in patients with hypothyroidism and cirrhosis.

When using corticosteroids, including prednisolone, psychic disturbances ranging from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic symptoms may occur. Corticosteroids, including prednisolone, may also increase existing emotional lability or exacerbate existing emotional instability of psychotic tendencies.

Steroids should be used cautiously in non-specific ulcerative colitis (with the possibility of perforation, abscess or other pyogenic infection), diverticulitis, recent intestinal anastomosis, active or latent peptic ulcer, renal impairment, hypertension, seizure disorders, and osteoporosis.

General

The lowest dose of corticosteroid that maintains control of the condition being treated should be used, and if the dose is reduced, it should be gradual.

When patients receiving corticosteroids are exposed to unusual stress (e.g., infection, surgery, trauma), they may require increased dose before, during, and after the stressful situation.

Moderate or high doses of hydrocortisone and cortisone may cause elevation of blood pressure, salt and water retention, and increased potassium excretion. These effects are less likely to occur with synthetic derivatives except at high doses. Dietary salt restriction and additional potassium may be required. All corticosteroids increase calcium excretion.

Fatal crises associated with pheochromocytoma have been reported following systemic administration of corticosteroids. Patients with known or suspected pheochromocytoma should be given systemic corticosteroids only after individual benefit-risk consideration.

Use in children

Corticosteroids may cause growth retardation in infants, children and adolescents. This event may be irreversible, therefore prolonged administration of pharmacological doses should be avoided. If long-term therapy is required, therapy should be restricted to minimize suppression of the HPA axis and growth. The growth and development of babies and children should be closely monitored. If possible, treatment should be administered as a single dose every other day.

The growth and development of infants or children receiving long-term corticosteroid therapy should be carefully observed.

Use in the elderly

When treating elderly patients, especially when planning long-term treatment, it should be kept in mind that common side effects of corticosteroids, such as osteoporosis, diabetes, hypertension, hypokalemia, susceptibility to infection and thinning of the skin, may lead to more serious consequences in the elderly. Close clinical supervision is required to avoid life-threatening reactions.

This medicinal product contains lactose. Patients with rare hereditary galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medication.

4.5. Interactions with other medicinal products and other forms of interaction

Hepatic microsomal enzyme inducers: Drugs that induce cytochrome P-450 (CYP) 3A4, such as phenobarbital, phenytoin, rifampicin, rifabutin, carbamazepine, primidone, and aminoglutethimide, may reduce the therapeutic efficacy of corticosteroids by increasing the rate of metabolism. Therefore, in patients stabilized on glucocorticoid therapy, it may be necessary to adjust the dose of glucocorticoids when these drugs are started or discontinued. The expected response may not be obtained and in this case the dose of CORLTO tablets may need to be increased.

Hepatic microsomal enzyme inhibitors: Drugs that inhibit cytochrome P-450 (CYP) 3A4 (e.g., ketoconazole, troleandomycin) may reduce glucocorticoid clearance. Doses of glucocorticoids given concomitantly with such drugs should be reduced to avoid possible adverse effects.

Antidiabetic agents: Glucocorticoids may increase blood glucose levels. Dose adjustments may be required in patients with diabetes mellitus who are concomitantly receiving insulin and/or oral hypoglycemic agents.

Non-steroidal anti-inflammatory agents: Concomitant administration of ulcerogenic drugs such as indomethacin with corticosteroids may increase the risk of gastrointestinal ulceration. The combination of aspirin and glucocorticoids should be administered with caution in patients with hypoprothrombinemia. Although concomitant use of salicylates and glucocorticoids does not increase the incidence or severity of gastrointestinal ulceration, the possibility of such an effect should be borne in mind. When corticosteroids are used concomitantly, serum salicylate levels may decrease. Similarly, if corticosteroid therapy is discontinued in patients receiving salicylates, serum salicylate concentrations may increase and, rarely, salicylate intoxication may occur. Caution should be taken when using salicylates and corticosteroids concomitantly. Patients taking both drugs should be carefully monitored for adverse effects of either drug.

Antibacterials: Rifamycins may accelerate the metabolism of corticosteroids and thereby reduce their effects. Some macrolide antibiotics (e.g. erythromycin) and some quinolones (e.g. ciprofloxacin), which inhibit the CYP3A4 enzyme, may inhibit the metabolism of methylprednisolone and possibly other corticosteroids.

Anticoagulants: When used concomitantly with corticosteroids, the response to anticoagulants may be decreased or, less frequently, increased. Close monitoring of INR or prothrombin time is necessary to prevent spontaneous bleeding. Rarely, cortisone has been reported to increase blood clotting and may require an increase in the anticoagulant dose in patients treated with oral anticoagulants.

Antifungals: The risk of hypokalemia may be increased with concomitant use of amphotericin, therefore concomitant use should be avoided unless corticosteroids are required for reaction control. Ketoconazole inhibits the metabolism of methylprednisolone and possibly other corticosteroids.

Antivirals: Ritonavir probably increases plasma concentrations of prednisolone and other corticosteroids.

Cardiac glycosides: Toxicity increases in case of hypokalemia when used concomitantly with corticosteroids.

Cyclosporine: Concomitant administration of prednisolone and cyclosporine may reduce the plasma clearance of prednisolone. Appropriate dose adjustment is required when these two drugs are administered concomitantly. Plasma concentrations of cyclosporine may also increase during concomitant administration with methylprednisolone.

Cytotoxics: The risk of hematologic toxicity is increased with methotrexate.

Mifepristone: Effects of corticosteroids may wane over the course of 3-4 days following mifepristone.

Vaccines and toxoids: Corticosteroids may reduce the response to toxoids and live or inactivated vaccines because they will inhibit antibody responses. Additionally, corticosteroids may facilitate the growth of some organisms present in live attenuated vaccines. Supraphysiological doses of drugs may potentiate neurological reactions to some vaccines. Routine administration of vaccines or toxoids should be postponed while corticosteroid therapy is continued. If immunization is necessary in a patient receiving corticosteroids, serological tests may be required to determine whether the antibody response is sufficient and additional doses of vaccine or toxoid may be required.

Estrogens: Estrogens may enhance the effects of hydrocortisone, possibly by increasing transcortin concentration and thereby decreasing the amount of hydrocortisone available for metabolism. The effects of other glucocorticoids that bind to transcortin may similarly be potentiated and dose adjustments may be required if estrogens are added or withdrawn during prednisolone therapy.

Somatropin: Its growth-promoting effect may be inhibited.

Sympathomimetics: High-dose corticosteroids used concomitantly with high-dose bambooterol, fenoteral, formoteral, ritodrine, salbutamol, salmetorol and terbutaline may increase the risk of hypokalemia.

Potassium-depleting agents: Potassium-depleting diuretics (e.g., thiazides, furosemide, ethacrynic acid) and other potassium-depleting drugs such as amphotericin B may potentiate the potassium-depleting effects of glucocorticoids. Serum potassium should be carefully monitored in patients receiving glucocorticoids and potassium-depleting drugs concomitantly.

Anticholinesterase agents: The interaction between glucocorticoids and anticholinesterase agents such as ambenonium, neostigmine, or pyridostigmine (and possibly organophosphate anticholinesterase

pesticides) may cause severe muscle weakness in patients with myasthenia gravis. Anticholinesterase treatment should be discontinued at least 24 hours prior to the start of glucocorticoid therapy.

Other: The desired effects of antihypertensives and diuretics may be antagonized by corticosteroids. The hypokalemic effect of acetazolamide, loop diuretics, thiazide diuretics, carbenoxolone and theophylline may be enhanced.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category "C".

Women of childbearing potential/Birth control (Contraception)

See section 4.5 Interactions with other medicinal products and other forms of interaction.

Pregnancy

There is insufficient data on the use of prednisolone in pregnant women. The passage of corticosteroids across the placenta varies from drug to drug, but 88% of prednisolone is inactivated upon passage across the placenta. Administration of corticosteroids to pregnant animals can produce abnormalities in fetal development such as cleft palate, intrauterine growth retardation, and effects on brain growth and development. There is no evidence that corticosteroids cause an increased incidence of congenital abnormalities such as cleft palate/lip in humans. However, when administered long-term or repeatedly during pregnancy, corticosteroids may increase the risk of intrauterine growth retardation. Theoretically, hypoadrenalism may occur in the newborn after prenatal exposure to corticosteroids. However, this condition resolves spontaneously after birth and is rarely of clinical significance. Cataracts have been observed in infants born to mothers treated with long-term prednisolone during pregnancy. As with all medications, corticosteroids should only be administered if the benefits to mother and baby outweigh the possible risks. When corticosteroids are essential however, patients with normal pregnancy may be treated as though they were in the non-gravid state. Patients with pre-eclampsia or fluid retention should be monitored closely.

Breastfeeding

Glucocorticoids can cross the placenta and pass into breast milk in small amounts. Glucocorticoids excreted in breast milk may suppress growth of the breastfed infant and inhibit endogenous glucocorticoid production. Because adequate reproductive studies have not been conducted in humans with glucocorticoids, these drugs should be administered to the breastfeeding mothers only if the potential benefits outweigh the potential risks to the infant.

Fertility

Studies in animals have shown reproductive toxicity and that corticosteroids may also impair fertility (see section 5.3). The potential risk to humans is unknown.

4.7. Effects on the ability to drive and use machines

The effect of prednisolone on the ability to drive and use machines has not been evaluated. There is no evidence that prednisolone affects these abilities. If patients experience dizziness or fatigue after taking CORLTO, they should be advised not to drive or operate machinery until these effects subside.

4.8. Undesirable effects

The incidence of predictable undesirable effects, including HPA suppression, varies with the potency, dose, frequency and duration of administration of glucocorticoid therapy (see section 4.4 Special warnings and precautions for use).

The cases reported more than once are listed below by frequency of occurrence and system organ class: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1.000, <1/100) and rare (≥1/10.000, <1/1.000), very rare (< 1/ 10000), not known (cannot be estimated from the available data).

Infections and infestations
Common: Inhibition of defense against infections, activation of infections (e.g. tuberculosis)

Blood and lymphatic system disorders
Not known: Leukocytosis (due to redistribution of intravascular granulocytosis)

Immune system disorders
Not known: Hypersensitivity

Endocrine disorders
Common: Inhibition of endogenous ACTH and cortisol secretion, Cushingoid symptoms, inhibition of growth and development in children
Not known: Crisis due to pheochromocytoma, suppression of the pituitary-adrenal axis (especially in stress situations such as trauma, surgery or illness)

Metabolism and nutrition disorders
Common: Hypokalemia, sodium retention, increased gluconeogenesis, catabolic effects, osteoporosis
Not known: Increased appetite (may cause weight gain), water retention, impaired glucose tolerance

Psychiatric disorders
Uncommon: Activation of past psychological disorders (at high dose)
Rare: Depression, mania in patients with no history of mental illness

Nervous system disorders
Rare: Benign intracranial hypertension
Not known: Epidural lipomatosis, convulsions, dizziness, headache

Eye disorders
Uncommon: Glaucoma, posterior cataract
Not known: Central serous chorioretinopathy, exophthalmos

Ear and labyrinth disorders
Not known: Vertigo

Cardiac disorders
Not known: Congestive heart failure (in sensitive individuals)

Vascular diseases
Common: Edema, hypertension
Uncommon: Thrombosis

Respiratory, thoracic and mediastinal disorders
Not known: Pulmonary embolism

Gastrointestinal disorders
Not known: Peptic ulcer (with possible perforation and bleeding), pancreatitis, ulcerative esophagitis, abdominal distension, abdominal pain, diarrhea, dyspepsia, nausea

Skin and subcutaneous tissue disorders
Common: Skin atrophy, impaired wound healing
Not known: Hirsutism, petechiae, ecchymoses, erythema, hyperhidrosis, suppression of reactions to skin tests, pruritus, rash, erythematous rash, urticaria

Musculoskeletal, connective tissue and bone disorders
Common: Muscle atrophy
Rare: Aseptic bone necrosis, tendon disorder

Not known: Myopathy, muscle weakness, myalgia, osteonecrosis (femoral and humeral heads), pathological fracture (long bones), growth retardation

Reproductive system and breast disorders
Not known: Menstrual irregularity

General disorders and administration site conditions
Not known: Fatigue, exhaustion

Laboratory tests
Not known: Increased intraocular pressure, decreased carbohydrate tolerance, increased insulin requirement (or increased oral hypoglycemic agent requirement in diabetics), decreased blood potassium levels, negative nitrogen balance (due to protein catabolism)

Effects on carbohydrate tolerance may exacerbate diabetes and cause manifestation of latent diabetes.

Injury, poisoning and procedural complications
Not known: Spinal compression fracture

Discontinuation of the drug: A too rapid reduction in corticosteroid dose after prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see section 4.4 Special warnings and precautions for use and 4.2 Posology and method of administration). A steroid "withdrawal syndrome" that appears unrelated to adrenocortical insufficiency may occur following abrupt discontinuation of glucocorticoids. This syndrome includes the following symptoms: anorexia, nausea, vomiting, lethargy, headache, fever, arthralgia, desquamation, myalgia, arthralgia, rhinitis, conjunctivitis, painful and pruritic 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.

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 the national reporting system.

4.9. Overdose and treatment
Reports of toxicity and/or death from overdose with glucocorticoids are rare. For overdose, there is no specific antidote; the treatment is supportive and symptomatic. Serum electrolytes can be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group : Glucocorticoids
ATC code : H02AB06

Prednisolone is chemically 11,17,21-trihydroxypregna-1,4-diene-3,20-dione. Its empirical formula is $C_{21}H_{28}O_5$ and its molecular weight is 360.

Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, and are readily absorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as adjunctive therapy in cases of adrenocortical insufficiency. CORLTO, a drug product containing prednisolone, is a potent synthetic glucocorticoid with anti-inflammatory, hormonal and metabolic effects, similar to cortisone and hydrocortisone. Synthetic analogs are used primarily for their potent anti-inflammatory effects in diseases of many organ systems.

Glucocorticoids produce a wide range of metabolic effects. They also alter the body's immune reactions to various stimuli.

5.2. Pharmacokinetic properties

General properties

Absorption: Prednisolone is rapidly and almost completely absorbed after oral administration, reaching peak plasma concentrations after 1-3 hours. However, the high degree of interpersonal differences suggests malabsorption in some individuals. The plasma half-life is around 3 hours in adults and slightly less in children. Its absorption is affected by food, but its total bioavailability is not affected by food. Prednisolone has a biological half-life of several hours, which enables an every-other-day administration regimen.

Distribution: Prednisolone shows dose-dependent pharmacokinetics, with increasing doses producing an increase in volume of distribution and plasma clearance. The degree of plasma protein binding determines the distribution and clearance of the pharmacologically active drug. Lower doses are required in patients with hypoalbuminemia.

Biotransformation: Prednisolone is metabolized primarily in the liver to the inactive compound. Liver disease prolongs the half-life of prednisolone and if the patient has hypoalbuminemia the proportion of unbound drug increases and thus adverse effects may be increased.

Elimination: Prednisolone is excreted in the urine as small amounts of unchanged prednisolone and free and conjugated metabolites.

Linearity/Non-linearity: No data available.

5.3. Preclinical safety data

Animal studies showed corticosteroids cause various deformities (cleft palate, skeletal deformities). After long-term treatment in animals, decreases in placental and natal weights have been observed. Corticosteroids have been demonstrated to cause fertility impairment in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (from cow’s milk)
Microcrystalline cellulose
Hydroxypropyl cellulose
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

No specific data.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C, protected from moisture and light.

6.5 Nature and contents of container

The primary packaging material of the product is transparent PVC/PVDC and aluminum foil blister. Blisters are packed in cardboard boxes. Each box includes a package leaflet and blisters of 20 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2019/482

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 01.10.2019
Date of renewal of authorization :

10. DATE OF REVISION OF THE TEXT