RICHYGOLD INTERNATIONAL LIMITED (pharmaceutical formulations)

Product Name= RGI DEXA 0.5MG TABLET

SPC-Summary of Product Characteristics

Product Information

1. Name of the Medicinal Product

RGI Dexa Tablets (Dexamethasone BP 0.5 mg)

2. Qualitative and Quantitative Composition

Each uncoated tablet contains

Dexamethasone BP	0.5 mg
Excipients	q.s.

3. Pharmaceutical Form

Oral Tablets

4. Clinical Particulars

4.1 Therapeutic Indications

Neurology

Cerebral oedema caused by brain tumours, neurosurgery, bacterial meningitis, brain abscess.

Pulmonary and respiratory diseases

Severe acute asthma attack.

Dermatology

Oral initial treatment of extensive, severe, acute skin diseases that respond to glucocorticoids, such as erythroderma, pemphigus vulgaris, acute eczema.

Autoimmune disorders/rheumatology

Oral initial treatment of autoimmune diseases, such as systemic lupus erythematosus (especially visceral forms).

Severely progressive form of active rheumatoid arthritis, e.g. rapidly destructive forms and/or with extra-articular manifestations.

Infectology

Severe infections with toxic conditions (e.g. tuberculosis, typhoid) only with concomitant anti-infective therapy.

Oncology

Palliative treatment of malignant tumours.

Endocrinology

Congenital adrenogenital syndrome in adulthood.

4.2 Posology and Method of Administration

Posology

Dosage depends on the nature and severity of the disease and the individual response of the patient to treatment. In general, relatively high initial doses are administered, and they should be significantly higher in acute severe forms than in chronic diseases.

Unless otherwise prescribed, the following dosage recommendations apply:

- Cerebral oedema: Depending on the cause and severity, initial dose of 8–10 mg (up to 80 mg) i.v., followed by 16–24 mg (up to 48 mg)/day orally, divided into 3–4 (up to 6) individual doses for 4–8 days. A longer-term, lower-dose administration of Dexamethasone may be required during irradiation and in the conservative treatment of inoperable brain tumours.
- Cerebral oedema due to bacterial meningitis: 0.15 mg/kg body weight every 6 hours for 4 days, children: 0.4 mg/kg body weight every 12 hours for 2 days, starting before the first antibiotics.
- Severe acute asthma attack: Adults: 8–20 mg, then, if necessary, 8 mg every 4 hours. Children: 0.15–0.3 mg/kg body weight.
- Acute skin diseases: Depending on the nature and extent of the disease, daily doses of 8–40 mg. Followed by treatment with decreasing doses.
- Active phases of rheumatic systemic diseases: systemic lupus erythematosus 6–16 mg/day.
- Severely progressive form of active rheumatoid arthritis: in rapidly destructive forms 12–16 mg/day, in extra-articular manifestations 6–12 mg/day
- Severe infectious diseases, toxic states (e.g. tuberculosis, typhoid): 4–20 mg for a few days, only with concomitant anti-infective therapy.

- Palliative treatment of malignant tumours: initially 8–16 mg/day, in prolonged treatment 4–12 mg/day.
- Congenital adrenogenital syndrome in adulthood: 0.25–0.75 mg/day as a single dose. If necessary, addition of a mineralcorticoid (fludrocortisone). In cases of particular physical stress (e.g. trauma, surgery), intercurrent infections, etc., a 2- to 3-fold dose increase may be required and under extreme stress (e.g. birth) a 10-fold increase.

The tablets should not be split to adjust doses. If patients need a dose that cannot be provided by one or more tablets of 0.5mg, other appropriate formulations should be used.

Method of administration

The tablets should be taken during or after a meal. They should be swallowed whole, with a sufficient amount of liquid. The daily dose should be administered as a single dose in the morning, if possible (circadian therapy). In patients who require a high-dose therapy because of their disease, multiple daily dosing is often required to achieve maximum effect.

Depending on the underlying disease, clinical symptoms and response to therapy, the dose can be reduced at a faster or slower rate and the therapy stopped, or the patient is stabilised on a maintenance dose as low as possible and, if necessary, adrenal axis monitored. Basically, the dose and duration of treatment should be kept as high and long as necessary, but as low and short as possible. In principle, the dose should be reduced gradually.

In long-term therapy which is deemed necessary following initial treatment, patients should be switched to prednisone/prednisolone, because this leads to lower adrenal suppression.

In hypothyroidism or liver cirrhosis, low doses may be sufficient or a dose reduction may be necessary.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special Warnings and Precautions for use

Depending on the dose and duration of therapy, adrenocortical insufficiency caused by glucocorticoid therapy can continue for several months and in individual cases more than a year

after cessation of therapy. In cases of particular physical stress situations (trauma, surgery, childbirth, etc.) during treatment with Dexamethasone, a temporary increase in dose may be required. Because of the potential risk in stress situations, patients on extended therapy should be issued a steroid card. Also in prolonged adrenal insufficiency after cessation of treatment, the administration of glucocorticoids may be necessary in physical stress situations. In case of intended withdrawal, treatment-induced acute adrenal insufficiency may be minimized by slow dose reduction.

Through immunosuppression, treatment with Dexamethasone can lead to an increased risk of bacterial, viral, parasitic, opportunistic and fungal infections. It can mask the symptoms of an existing or developing infection, thereby making a diagnosis more difficult. Latent infections, like tuberculosis or hepatitis B, can be reactivated.

Treatment with Dexamethasone should only be implemented in the event of the strongest indications and, if necessary, additional targeted anti-infective treatment administered for the following illnesses:

- Acute viral infections (Herpes zoster, Herpes simplex, Varicella, herpetic keratitis)
- HBsAG-positive chronic active hepatitis
- Approximately 8 weeks prior to 2 weeks after vaccinations with live vaccines
- Systemic mycoses and parasitoses (e.g. nematodes)
- In patients with suspected or confirmed strongyloidiasis (infection with threadworms), glucocorticoids can lead to activation and mass proliferation of these parasites
- Poliomyelitis
- Lymphadenitis after BCG vaccination
- Acute and chronic bacterial infections
- In a history of tuberculosis (reactivation risk), use only under tuberculostatic protection

In addition, treatment with Dexamethasone should only be implemented under strong indications and, if necessary, additional specific treatment must be implemented for:

- Gastrointestinal ulcers
- Osteoporosis
- Severe cardiac insufficiency

- High blood pressure that is difficult to regulate
- Diabetes mellitus that is difficult to regulate
- Psychiatric disorders (also in the past), including suicidality: neurological or psychiatric monitoring is recommended
- Narrow- and wide-angle glaucoma, ophthalmic monitoring and adjunctive therapy are recommended
- Corneal ulcerations and corneal injuries, ophthalmic monitoring and adjunctive therapy are recommended

Because of the risk of an intestinal perforation, Dexamethasone may only be used under urgent indication and under appropriate monitoring for:

- Severe ulcerative colitis with threatened perforation, possibly without peritoneal irritation
- Diverticulitis
- Enteroenterostomy (immediately postoperatively)

Signs of peritoneal irritation after gastrointestinal perforation may be absent in patients receiving high doses of glucocorticoids.

The possibility of a higher need for insulin or oral antidiabetics must be taken into consideration when administering Dexamethasone to diabetics.

Regular blood pressure monitoring is necessary during treatment with Dexamethasone, particularly during administration of higher doses and in patients with high blood pressure that is difficult to regulate.

Because of the risk of deterioration, patients with severe cardiac insufficiency should be carefully monitored.

With high doses of dexamethasone bradycardia may occur.

Severe anaphylactic reactions may occur.

The risk of tendon disorders, tendinitis and tendon rupture is increased when fluoroquinolones and glucocorticoids are administered together.

A concurrent myasthenia gravis may initially worsen during treatment with Dexamethasone.

Vaccinations with inactivated vaccines are generally possible. However, it should be noted that the immune response and thus the vaccine may be compromised at higher doses of corticosteroids.

During long-term therapy with Dexamethasone, regular medical checkups (including ophthalmologic every three months) are indicated.

At high doses, sufficient calcium intake and sodium restriction should be ensured and serum potassium levels should be monitored.

Depending on the dose and duration of treatment, a negative effect on calcium metabolism can be expected; therefore, the prevention of osteoporosis is recommended. This applies especially to patients with concomitant risk factors, such as familial predisposition, advanced age, postmenopausal period, insufficient protein and calcium intake, heavy smoking, excessive alcohol consumption and lack of physical activity. Prevention consists of sufficient calcium and vitamin D intake and physical activity. In already existing osteoporosis, additional drug therapy should be considered.

Upon termination of long-term administration of glucocorticoids, the following risks must be taken into account: exacerbation or relapse of the underlying disease, acute adrenal insufficiency, cortisone withdrawal syndrome.

Certain viral diseases (chickenpox, measles) may be very severe in patients treated with glucocorticoids. Immunocompromised patients without previous chickenpox or measles infection are particularly at risk. If these patients have contact with people infected with measles or chickenpox while undergoing treatment with Dexamethasone, a preventative treatment should be introduced, if necessary.

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Visual disturbance

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

Paediatric population

In the growth phase of children, the benefit-risk balance of treatment with Dexamethasone should be carefully weighed.

Therapy should be of limited duration or in case of long-term therapy, it should be carried out alternatingly.

Preterm neonates: Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours) of premature infants with chronic lung disease at starting doses of 0.25mg/kg twice daily.

Elderly patients

Because elderly patients are at an increased risk of osteoporosis, the benefit-risk balance of treatment with Dexamethasone should be carefully weighed.

4.5 Interactions with other medicinal products and other forms of interactions

Oestrogens (e.g. oral contraceptives): The half-life of glucocorticoids may be prolonged. Therefore, the effect of corticoids may be increased.

Antacids: Concomitant administration of aluminum hydroxide or magnesium hydroxide can lead to a reduction in the absorption of glucocorticoids with reduced efficacy of Dexamethasone. There should be a 2-hour interval between the intake of one and the other drug.

Drugs that induce CYP3A4, such as rifampicin, phenytoin, carbamazepine, barbiturates and primidone: The effect of corticoids may be reduced.

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.

Drugs that inhibit CYP3A4, such as ketoconazole and itraconazole: The effect of corticoids may be increased.

Ephedrine: The metabolism of glucocorticoids may be accelerated and thus their effectiveness reduced.

ACE inhibitors: Increased risk of blood count changes.

Cardiac glycosides: The effect of glycosides may be increased by potassium deficiency.

Saluretics/laxatives: Potassium excretion may be increased.

Antidiabetics: The hypoglycaemic effect may be reduced.

Coumarin derivatives: The anticoagulant effect may be reduced or increased. Dosage adjustment of the anticoagulant may be necessary when co-administered.

Nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates and indomethacin: The risk of gastrointestinal ulcers and bleeding is increased.

Non-depolarizing muscle relaxants: The muscle-relaxing effect may last longer.

Atropine, other anticholinergics: Additional intraocular pressure increases are possible during concomitant use.

Praziquantel: Corticosteroids may cause a fall in praziquantel concentration in the blood.

Chloroquine, hydroxychloroquine, mefloquine: There is an increased risk of myopathies, cardiomyopathies.

Somatropin: The effect of somatropin may be reduced under long-term therapy.

Protirelin: Reduced increase in TSH may be noted during administration of protirelin.

Immunosuppressive agents: Increased susceptibility to infections and possible aggravation or manifestation of latent infections. Additionally, for ciclosporin: The blood levels of cyclosporine are increased: There is an increased risk of seizures.

Fluoroquinolones may increase the risk of tendon disorders.

Effect on investigation methods: Skin reactions in allergy tests can be suppressed.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Dexamethasone crosses the placenta. During pregnancy, especially in the first trimester, the drug should only be administered after careful benefit-risk assessment.

In long-term treatment with glucocorticoids during pregnancy, foetal growth disorders cannot be excluded. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. If glucocorticoids are administered towards the end of pregnancy, there is a risk of atrophy of the foetal adrenal cortex, which may necessitate replacement therapy in the newborn, which has to be slowly reduced.

Breast-feeding

Dexamethasone is excreted in breast milk. There are no known cases of harm to the infant. Nevertheless, the drug should be strongly indicated during lactation. If the disease requires higher doses, breast-feeding should be discontinued.

Fertility

Dexamethasone decreases testosterone biosynthesis and endogenous ACTH secretion which has an effect on the spermatogenesis and the ovarian cycle.

4.7 Effects on ability to drive and use machines

There have been no studies on the effects on the ability to drive and use machines.

4.8 Undesirable Effects

- 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)

Hormone replacement therapy:

Low risk of undesirable effects with the use of recommended doses.

RICHYGOLD INTERNATIONAL LIMITED (pharmaceutical formulations)
Product Name= RGI DEXA 0.5MG TABLET

Pharmacotherapy:

The following undesirable effects may occur; they are highly dependent on the dose and duration of treatment, so their frequency cannot be specified:

Infections and infestations	Masking of infections, manifestation and exacerbation of viral infections, fungal infections, bacterial, parasitic and opportunistic infections, activation of strongyloidiasis.
Blood and lymphatic system disorders	Moderate leukocytosis, lymphocytopenia, eosinopenia, polycythemia.
Immune system disorders	Hypersensitivity reactions (e.g. drug eruption), severe anaphylactic reactions, such as arrhythmias, bronchospasm, hypo- or hypertension, circulatory collapse, cardiac arrest, weakening of the immune system.
Endocrine disorders	Adrenal suppression and induction of Cushing's syndrome (typical symptoms: moon face, central obesity and plethora).
Metabolism and nutrition disorders	Sodium retention with oedema, increased potassium excretion (risk of arrhythmias), weight gain, reduced glucose tolerance, diabetes mellitus, hypercholesterolemia and hypertriglyceridemia, increased appetite.
Psychiatric disorders	Depression, irritability, euphoria, increased drive, psychoses, mania, hallucinations, emotional lability, anxiety, sleep disorders, suicidality.
Nervous system disorders	Pseudotumor cerebri, manifestation of latent epilepsy, increase in seizure susceptibility in manifest epilepsy.
Eye disorders	Cataract, especially with posterior subcapsular opacity, glaucoma, deterioration of symptoms associated with corneal ulcer, increased occurrence of viral, fungal and bacterial inflammation of the eye,

	deterioration of bacterial inflammation of the cornea, ptosis, mydriasis, chemosis, iatrogenic scleral perforation, chorioretinopathy, vision, blurred.
Vascular disorders	Hypertension, increased risk of atherosclerosis and thrombosis, vasculitis (also as withdrawal syndrome after long-term therapy), increased capillary fragility.
Gastrointestinal disorders	Gastrointestinal ulcers, gastrointestinal bleeding, pancreatitis, stomach discomfort.
Skin and subcutaneous tissue disorders	Striae rubra, atrophy, telangiectasias, petechiae, ecchymosis, hypertrichosis, steroid acne, rosacea-like (perioral) dermatitis, changes in skin pigmentation.
Musculoskeletal and connective tissue disorders	Myopathy, muscle atrophy and weakness, osteoporosis (dose-dependent, possible also in short-term administration), aseptic bone necrosis, tendon disorders, tendinitis, tendon rupture, epidural lipomatosis, growth inhibition in children. Note: Too rapid dose reduction after long-term treatment may cause symptoms such as muscle and joint pain.
Reproductive system and breast disorders	Disorders of sexual hormone secretion (consequently: irregular menstruation up to amenorrhea, hirsutism, impotence).
General disorders and administration site conditions	Delayed wound healing.

4.9 Overdose

Symptoms

Acute intoxications with dexamethasone are not known. In case of chronic overdosing, an increase in undesirable effects, especially endocrine, metabolic and electrolyte-related effects, can be expected.

Management

There is no known antidote to dexamethasone.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: corticosteroids for systemic use, glucocorticoids, ATC code: H02AB02.

Mechanism of action

Dexamethasone is a mono-fluorinated glucocorticoid with pronounced anti-allergic, anti-inflammatory and membrane-stabilizing properties and effects on carbohydrate, protein and fat metabolism.

Dexamethasone has an approximately 7.5 times greater glucocorticoid effect than prednisolone, and compared to hydrocortisone it is 30 times more effective, lacking mineralocorticoid effects.

Glucocorticoids, such as dexamethasone, exert their biological effects by activating the transcription of corticosteroid-sensitive genes. The anti-inflammatory, immunosuppressive and anti-proliferative effects are caused by decreased formation, release and activity of inflammatory mediators, by the inhibition of specific functions and the migration of inflammatory cells. In addition, the effect of sensitized T lymphocytes and macrophages on target cells may be prevented by corticosteroids.

When long-term corticoid treatment is required, the possibility of induction of transient adrenal insufficiency must be considered. The suppression of the hypothalamic-pituitary-adrenal axis also depends on individual factors.

5.2 Pharmacokinetics

Absorption and distribution

After oral administration, dexamethasone is rapidly and almost completely absorbed in the stomach and small intestine. Its bioavailability is 80–90%. Maximum blood levels are reached

between 60 and 120 minutes. The binding of dexamethasone to plasma albumins is dose-dependent. At very high doses, the largest portion circulates freely in the blood. In hypoalbuminaemia the proportion of the unbound (active) corticoid rises.

Biotransformation

The average (serum) elimination half-life of dexamethasone in adults is 250 minutes (+ 80 minutes). Due to its long biological half-life of more than 36 hours, daily continuous administration of dexamethasone can lead to accumulation and overdosing.

Elimination

The elimination is largely renal in the form of free dexamethasone alcohol. Dexamethasone is partly metabolised, the metabolites are excreted as glucuronates or sulfates, also mainly by the kidneys.

Renal and hepatic impairment

Renal function impairment has no relevant effect on the clearance of dexamethasone. However, the elimination half-life is prolonged in severe liver disease.

5.3 Pre-Clincal Safety Data

Acute toxicity:

In mice and rats, the LD_{50} for dexamethasone after a single oral dose is 16 g/kg body and over 3 g/kg body weight, respectively, within the first 7 days. Following a single subcutaneous dose, the LD_{50} in mice is more than 700 mg/kg body weight and in rats about 120 mg/kg body weight, within the first 7 days.

Over a period of 21 days, these values become lower, which is interpreted as a consequence of serious infectious diseases caused by the hormone-induced immunosuppression.

Chronic toxicity:

There are no data on chronic toxicity in humans and animals. Corticoid-induced intoxications are not known. In longer-term treatment with doses above 1.5 mg/day, pronounced undesirable effects can be expected.

Mutagenic and tumorigenic potential:

The available study findings for glucocorticoids show no evidence of clinically relevant genotoxic properties.

Reproductive toxicity:

In animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates; not in horses and sheep. In some cases these divergences were combined with defects of the central nervous system and of the heart. In primates, effects in the brain were seen after exposure. Moreover, intrauterine growth can be delayed. All these effects were seen at high dosages.

6. Pharmaceutical Particulars

6.1 List of Excipients

Maize Starch BP

Dibasic Calcium Phosphate BP

Gelatin BP

Purified Talc BP

Magnesium Stearate BP

Sodium Methylparaben BP

Sodium Propylparaben BP

Sodium Starch Glycolate BP

Purified Water BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 months from the Date of Manufacture

6.4 Special precautions for Storage

RICHYGOLD INTERNATIONAL LIMITED (pharmaceutical formulations)
Product Name= RGI DEXA 0.5MG TABLET

Store in a cool dry place not above 30°C

6.4 Nature and contents of Container

Alu PVC Blister of 10 Tablets and Such 10 blisters are packed in an outer carton along with Pack Insert

6.5 Special precautions for disposal

7. Manufactured by

Richygold International Ltd.(Pharmaceutical Formulations)
103c Amuwo-Odofin Industrial Scheme Oshodi Apapa Express Way, Lagos Nigeria

8. Marketing Authorisation Numbers Not applicable

9. Date of First Authorisation/Renewal of Authorisation

Not applicable