# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Dexsol 2 mg/ 5 ml Oral Solution

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Dexamethasone 2mg/5ml (as dexamethasone sodium phosphate)

Excipients with known effect:
Propylene glycol (E1520) – 450.6mg/5ml
Liquid maltitol (E965) - 1375mg/5ml
Sorbitol, liquid (non-crystallising) (E420) - 700mg/5ml
Benzoic acid (E210) – 5mg/5ml

For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Oral Solution

A colourless to faint yellow solution with odour of mint.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Dexamethasone is a corticosteroid. It is designed for use in certain endocrine and non-endocrine disorders, in certain cases of cerebral oedema and for diagnostic testing of adrenocortical hyperfunction.

Endocrine disorders:
Endocrine exophthalmos.

Non-endocrine disorders:
Dexamethasone may be used in the treatment of non-endocrine corticosteroid responsive conditions including:

Allergy and anaphylaxis*:* Anaphylaxis.

Arteritis collagenosis: Polymyalgia rheumatica, polyarteritis nodosa.

Haematologicaldisorders: Haemolytic anaemia (also auto immune), leukaemia, myeloma, idiopathic thrombocytopenic purpura in adults,reticulolymphoproliferative disorders (see also under oncological disorders)**.**

Gastroenterological disorders: For treatment during the critical stage in: ulcerative colitis (rectal only); regional enteritis (Crohn's disease),certain forms of hepatitis.

Muscular disorders: Polymyositis.

Neurological disorders: Raised intra-cranial pressure secondary to cerebral tumours**,** acute exacerbations of multiple sclerosis.

Ocular disorders: Anterior and posterior uveitis, optic neuritis, chorioretinitis, iridocyclitis, temporal arteritis, orbital pseudotumour.

Renal disorders: Nephrotic syndrome

Pulmonary disorders: Chronic bronchial asthma, aspiration pneumonitis, chronic obstructive pulmonary disease (COPD), sarcoidosis, allergic pulmonary disease such as farmer's and pigeon breeder's lung, Löffler's syndrome, cryptogenic fibrosing alveolitis.

Rheumatic disorders: some cases or specific forms (Felty's syndrome, Sjörgen's syndrome) of rheumatoid arthritis, including juvenile rheumatoid arthritis, acute rheumatism, lupus erythematosus disseminatus, temporal arteritis (polymyalgia rheumatica).

Skin disorders: Pemphigus vulgaris, bullous pemphigoid, erythrodermas, serious forms of erythema multiforme (Stevens-Johnson syndrome), mycosis fungoides, bullous dermatitis herpetiformis.

Oncological Disorders: lymphatic leukaemia, especially acute forms, malignant lymphoma (Hodgkin's disease, non-Hodgkin's lymphoma), metastasized breast cancer, hypercalcaemia as a result of bone metastasis or Kahler's disease, Kahler's disease.

Various: intense allergic reactions; as immunosuppressant in organ transplantation; as an adjuvant in the prevention of nausea and vomiting and in the treatment of cancer with oncolytics that have a serious emetic effect.

Childhood Croup:
Heterogeneous group of illnesses affecting the larynx, trachea and bronchi. Laryngotracheitis, laryngotracheobronchitis, laryngotracheobronchopneumonitis and spasmodic croup are included in the croup syndrome.

Covid-19:
Dexsol is indicated in the treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) who require supplemental oxygen therapy.

**4.2 Posology and method of administration**

**Posology**

**Adults**

General considerations:
The dosage should be titrated to the individual response and the nature of the disease. In order to minimise side effects, the lowest effective possible dosage should be used (see 'Side effects').
The initial dosage varies from 0.5 – 9mg a day depending on the disease being treated. In more severe diseases, doses higher than 9mg may be required. The initial dosage should be maintained or adjusted until the patient's response is satisfactory.
Both the dose in the evening, which is useful in alleviating morning stiffness, and the divided dosage regimen are associated with greater suppression of the hypothalamo-pituitary-adrenal axis. If satisfactory clinical response does not occur after a reasonable period of time, discontinue treatment with dexamethasone and transfer the patient to another therapy.
If the initial response is favourable, the maintenance dosage should be determined by lowering the dose gradually to the lowest dose required to maintain an adequate clinical response. Chronic dosage should preferably not exceed 1.5mg dexamethasone daily.
Patients should be monitored for signs that may require dosage adjustment. These may be changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness and the effect of stress (e.g. surgery, infection, trauma). During stress it may be necessary to increase dosage temporarily.
If the drug is to be stopped after more than a few days of treatment, it should be withdrawn gradually.
The following equivalents facilitate changing to dexamethasone from other glucocorticoids:
Milligram for milligram, dexamethasone is approximately equivalent to betamethasone, 4 to 6 times more potent than methylprednisolone and triamcinolone, 6 to 8 times more potent than prednisone and prednisolone, 25 to 30 times more potent than hydrocortisone, and about 35 times more potent than cortisone.

Acute, self-limiting allergic disorders or acute exacerbations of chronic allergic disorders.
The following dosage schedule combining parenteral and oral therapy is suggested:
First day: Dexamethasone sodium phosphate injection 4mg or 8mg (1ml or 2ml) intramuscularly.
Second day: 1mg (2.5ml) Dexamethasone Oral Solution twice a day.
Third day: 1mg (2.5ml) Dexamethasone Oral Solution twice a day.

Fourth day: 500micrograms (1.25ml) Dexamethasone Oral Solution twice a day.
Fifth day: 500micrograms (1.25ml) Dexamethasone Oral Solution twice a day.
Sixth day: 500micrograms (1.25ml) Dexamethasone Oral Solution.
Seventh day: 500micrograms (1.25ml) Dexamethasone Oral Solution.
Eighth day: Re-assessment.

If a dose of less than 5ml is required, an oral dosing device should be employed.
This schedule is designed to ensure adequate therapy during acute episodes whilst minimising the risk of overdosage in chronic cases.
Raised intracranial pressure: Initial therapy is usually by injection. When maintenance therapy is required, this should be changed to dexamethasone oral solution as soon as possible. For the palliative management of patients with recurrent or inoperable brain tumours, maintenance dosage should be calculated individually. A dosage of 2mg two or three times a day may be effective. The smallest dosage necessary to control symptoms should always be used.

Dexamethasone suppression tests:

1. Tests for Cushing's syndrome:
2mg (5ml) Dexamethasone Oral Solution should be administered at 11pm. Blood samples are then taken at 8am the next morning for plasma cortisol determination.
If greater accuracy is required, 500 micrograms (1.25ml) Dexamethasone Oral Solution should be administered every 6 hours for 48 hours. Blood should be drawn at 8am for plasma cortisol determination on the third morning.
24-hour urine collection should be employed for 17-hydroxycorticosteroid excretion determination.

2. Test to distinguish Cushing's syndrome caused by pituitary ACTH excess from the syndrome induced by other causes:
2mg (5ml) Dexamethasone Oral Solution should be administered every 6 hours for 48 hours. Blood should be drawn at 8am for plasma cortisol determination on the third morning.
24-hour urine collection should be employed for 17-hydroxycorticosteroid excretion determination.

**Childhood Croup:**
A single dose of 0.15mg/kg Dexamethasone Oral Solution is recommended. A second dose may be administered after 12 hours, if considered necessary by the treating physician.

Doses of up to 0.6mg/kg dexamethasone have been used safely in clinical studies. However, a maximum dose of 10mg (25ml Dexsol Oral Solution) is recommended.

The following dosage chart should be followed for the treatment of childhood croup at a dose of 0.15mg/kg.

| Approximate age (mths/yrs) | | Approximate weight (kg) | | Volume of Dexsol (ml) |
|---|---|---|---|---|
| Min | Max | Min | Max | |
| 0 | 2 mths | 4 | 5.5 | 2 |
| 3 mths | 6 mths | 5.6 | 7.9 | 3 |
| 6 mths | 12 mths | 8 | 10.5 | 4 |
| > 12 mths | 2 yrs | 10.6 | 13.3 | 5 |
| > 2 yrs | 4 yrs | 13.4 | 16.2 | 6 |
| > 4 yrs | 7 yrs | 16.3 | 22 | 8 |
| > 7 yrs | 9 yrs | 22.1 | 27 | 10 |
| > 9 yrs | 12 yrs | 27.1 | 41 | 15 |
| > 12 yrs | 14 yrs | 42 | 55 | 20 |
| > 14 yrs | | 56 | 68 | 25 |

**For the treatment of Covid-19**

Adult patients 6 mg orally, once a day for up to 10 days.

*Paediatric population*
Paediatric patients (adolescents aged 12 years and older with body weight at least 40kg) are recommended to take 6mg orally, once a day for up to 10 days.

Duration of treatment should be guided by clinical response and individual patient requirements.

*Elderly, renal impairment, hepatic impairment*
No dose adjustment is needed.

**Elderly:**
Treatment of elderly patients, particularly if long term, should be planned bearing in mind the more serious consequences of the common side effects of corticosteroids in old age.

**Paediatric population:**
Dosage should be limited to a single dose on alternate days to lessen retardation of growth and minimize suppression of hypothalamo-pituitary-adrenal axis.

Method of administration
For oral use
Alternatively, this product is suitable for administration via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes. For further information see section 6.6.

**4.3 Contraindications**

- Hypersensitivity to dexamethasone or any of the excipients listed.
- Systemic infection unless specific anti-infective therapy is employed.
- Systemic fungal infections.
- Stomach ulcer or duodenal ulcer
- Infection with tropical worms

**4.4 Special warnings and precautions for use**

**A patient information leaflet should be supplied with this product.**
Patients should carry 'steroid treatment' cards, which give clear guidance on the precautions to be taken to minimise risk, and which provides details of prescriber, drug, dosage and the duration of treatment.

Undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose or whenever possible as a single morning dose on alternative days. Frequent patient review is required to appropriately titrate the dose against disease activity. When reduction in dosage is possible, the reduction should be gradual (Refer to 'Posology and Administration).

**Anti-inflammatory/Immunosuppressive effects/Infection**

Corticosteroids may exacerbate systemic fungal infections and should not be used unless they are needed to control drug reactions due to amphotericin. There have also been reports in which concomitant use of amphotericin and hydrocortisone was followed by cardiac enlargement and heart failure.

If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained.

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation may be atypical, and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised.
Appropriate anti-microbial therapy should accompany glucocorticoid therapy when necessary e.g. in tuberculosis and viral and fungal infections of the eye.
There may be decreased resistance and inability to localise infection in patients on corticosteroids.

The results of a randomised, placebo-controlled study suggest an increase in mortality if methylprednisolone therapy starts more than two weeks after the onset of Acute Respiratory Distress Syndrome (ARDS). Therefore, treatment of ARDS with corticosteroids should be initiated within the first two weeks of onset of ARDS (see also section 4.2.).

*Chickenpox is of particular concern, since this normally minor illness may be fatal in immunosuppressed patients.* Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster, and if exposed they should seek urgent medical attention. Passive immunisation with varicella/zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous three months; this should be given within ten days of exposure to chickenpox. *If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.*
Measles can have a more serious or even fatal course in immunosuppressed patients. In such children or adults particular care should be taken to avoid exposure to measles. If exposed, prophylaxis with intramuscular pooled immunoglobulin (IG) may be indicated. Exposed patients should be advised to seek medical advice without delay.

Corticosteroids may activate latent amoebiasis or strongyloidiasis or exacerbate active disease. Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis or Toxoplasma. It is recommended that these are ruled out before initiating corticosteroid therapy particularly in those patients who have spent time in the tropics or those with unexplained diarrhoea.

A report shows that the use of corticosteroids in cerebral malaria is associated with a prolonged coma and an increased incidence of pneumonia and gastro-intestinal bleeding and therefore corticosteroids should not be used in cerebral malaria.

*Eye disorders*
Prolonged use of corticosteroids may produce subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses. Particular care is needed when treating patients with glaucoma (or family history of glaucoma) as well as when treating patients with ocular herpes simplex, because of possible corneal perforation.

*Electrolyte disturbances*
Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, retention of salt and water, and increased excretion of potassium, but these effects are less likely to occur with synthetic derivatives, except when used in large doses.Dietary salt restriction and potassium supplementation may be necessary with corticosteroid therapy. All corticosteroids increase calcium excretion.
Particular care is needed when treating patients with renal impairment, hypertention and congestive heart failure.

*Adrenal Suppression*
Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment. In patients who have received more than physiological doses of systemic corticosteroids (approximately 1 mg dexamethasone) for greater than 3 weeks, withdrawal should not be abrupt.

How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal.
If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about HPA suppression, the dose of systemic corticosteroids may be reduced rapidly to physiological doses. Once a daily dose of 1mg dexamethasone is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it is considered that the disease is unlikely to relapse.

Abrupt withdrawal of doses of up to 6 mg daily of dexamethasone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression in the majority of patients.

In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be considered even after courses lasting 3 weeks or less:

• Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks.
• When a short course has been prescribed within one year of cessation of long term therapy (months or years).
• Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
• Patients receiving doses of systemic corticosteroid greater than 6 mg daily of dexamethasone.
• Patients repeatedly taking doses in the evening.

*Intercurrent illness and stress*
During prolonged therapy, any intercurrent illness, trauma , stressor surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced. Patients under stress may require increased doses of corticosteroids prior, during and after the period of stressful situation.

*Withdrawal symptoms*
Stopping corticosteroids after prolonged therapy may cause withdrawal symptoms including fever, myalgia, arthralgia and malaise. This may occur in patients even without evidence of adrenal insufficiency.

*Treatment of Covid-19*
Systemic corticosteroids should not be stopped for patients who are already treated with systemic (oral) corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease) but not requiring supplemental oxygen.

*General*
In addition to the information given under the other headings, particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary:
- diabetes mellitus (or a family history of diabetes)
- osteoporosis (especially post-menopausal females)
- hypertension or congestive heart failure
- existing or previous history of severe affective disorders (especially previous steroid psychosis)
- history of tuberculosis
- glaucoma (or a family history of glaucoma)
- previous corticosteroid-induced myopathy
- myasthenia gravis
- non-specific ulcerative colitis, diverticulitis or fresh intestinal anastomosis
- peptic ulceration
- liver failure
- renal insufficiency
- hypothyroidism
- epilepsy
- migraine
- history of allergy to corticosteroids
- herpes simplex

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

Fat embolism has been reported as a possible complication of hypercortisonism.

Large doses of corticosteroids may mask the symptoms of gastro-intestinal perforation.

Reports in the literature suggest an apparent association between use of corticosteroids and left-ventricular free-wall rupture after a recent myocardial infarction; therefore, corticosteroids should be used with great caution in these patients.

In rare cases, decrease or withdrawal of orally administered corticosteroids could reveal underlying disease that is accompanied by eosinophilia (e.g. Churg Strauss Syndrome) in patients with asthma.

*Hypersensitivity*
Rare cases of anaphylactoid or hypersensitivity reactions such as glottis oedema, urticaria and bronchospasm have been reported especially with parenteral administration of corticosteroids and in patients with a history of allergy. Prophylactic measures should be taken especially if the patient has a history of allergic reactions to medicines.
If such anaphylactoid reaction occurs, the following measures are recommended:

immediate slow intravenous injection of 0.1-0.5ml of adrenaline (solution of 1:1000:0.1-0.5mg adrenaline dependent on body weight), intravenous administration of aminophyline and artificial respiration if necessary.

*Psychiatric reactions*
Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 pharmacokinetic interactions that can increase the risk of side effects), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary.
Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

*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.

*Pheochromocytoma crisis*
Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

**Use in Children and Adolescents**

Corticosteroids cause growth retardation. On prolonged administration glucocorticoids may accelerate epiphyseal closure. Treatment should be limited to the minimum dose for the shortest period.
Children and adolescents on prolonged therapy should be carefully monitored.

*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.

*Use in the Elderly*
The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

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.

**Excipient Warnings**

This product contains:

- Propylene glycol (E1520) – This medicine contains 450.6 mg propylene glycol per 5ml dose. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates and in children less than 5 years old.

- Liquid maltitol (E965)– Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- Sorbitol (E420). This medicine contains 490mg sorbitol in each 5ml dose. The additive effect of concomitantly administered products containing sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
- Benzoic acid (E210) – This medicine contains 5mg benzoic acid in each 5ml dose. Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).
- Sodium. This medicine contains less than 1mmol sodium (23mg) per 5ml dose, that is to say essentially 'sodium-free'.

**4.5 Interaction with other medicinal products and other forms of interaction**

Effects of other medicinal products on dexamethasone:

Dexamethasone is metabolized via cytochrome P450 3A4 (CYP3A4). Concomitant administration of dexamethasone with inducers of CYP3A4, such as phenytoin, barbiturates (e.g. primidone and phenobarbital), ephedrine, rifabutin, carbamazepine and rifampicin may lead to decreased plasma concentrations of dexamethasone and the dose may need to be increased.

Dexamethasone reduces the plasma concentration of the antiviral drugs indinavir and saquinavir.

Patients taking methotrexate and dexamethasone have an increased risk of haematological toxicity.

Concomitant administration of inhibitors of CYP3A4 such as ketoconazole, ritonavir and erythromycin may lead to increased plasma concentrations of dexamethasone.
These interactions may also interfere with dexamethasone suppression tests, which therefore should be interpreted with caution during administration of substances that affect the metabolism of dexamethasone.

Ketoconazole may increase plasma concentrations of dexamethasone by inhibition of CYP3A4, but may also suppress corticosteroid synthesis in the adrenal and thereby cause adrenal insufficiency at withdrawal of corticosteroid treatment.

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.

Ephedrine may increase the metabolic clearance of corticosteroids, resulting in decreased plasma levels. An increase of the corticosteroid dose might be necessary.

False-negative results in the dexamethasone suppression test inpatients being treated with indometacin have been reported.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Colestyramine: Colestyramine may decrease the absorption of dexamethasone.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect

Aminoglutethimide: Decrease of dexamethasone efficacy, due to its metabolism increase. An adjustment of dexamethasone dosage may be required.

Gastrointestinal topicals, antacids, charcoal: A decrease in digestive absorption of glucocorticoids have been reported with prednisolone and dexamethasone. Therefore, glucocorticoids should be taken separately from gastrointestinal topicals, antacids or charcoal, with an interval between treatment of at least two hours.

Effects of dexamethasone on other medicinal products

Dexamethasone is a moderate inducer of CYP3A4. Concomitant administration of dexamethasone with substances that are metabolised via CYP3A4 could lead to increased clearance and decreased plasma concentrations of these substances.

The renal clearance of salicylates is increased by corticosteroids and therefore, salicylate dosage should be reduced along with steroidal withdrawal.

The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids.
The hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics**,** amphotericin B injection, potassium depleting agents, corticosteroids (gluco-mineralo), tetracosactideand carbenoxolone are enhanced. Hypokalaemia predisposes to cardiac arrhythmia especially "torsade de pointes" and increase the toxicity of cardiac glycosides. Hypokalemia should be corrected before corticosteroid treatment initiation. In addition, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Sultopride has been linked to ventricular arrhythmias, especially torsade de pointes. This combination is not recommended. Patients taking NSAID's should be monitored since the incidence and/or severity of gastro-ulceration may increase. Aspirin should also be used cautiously in conjunction with corticosteroids in hypoprothrombinaemia.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

Ciclosporin: Increased activity of both ciclosporin and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Thalidomide: Co-administration with thalidomide should be employed cautiously, as toxic epidermal necrolysis has been reported with concomitant use.

Corticosteroids may affect the nitrobuletetrazolium test for bacterial infection and produce false-negative results.

Vaccines attenuated live
Risk of fatal systemic disease

Praziquantel:
Decrease in praziquantel plasmatic concentrations, with a risk of treatment failure, due to its hepatic metabolism increased by dexamethasone.

Oral anticoagulants:
Possible impact of corticosteroid therapy on the metabolism of oral anticoagulants and on clotting factors. At high doses or with treatment for more than 10 days, there is a risk of bleeding specific to corticosteroid therapy (gastrointestinal mucosa, vascular fragility). Patients taking corticosteroids associated with oral anticoagulants should be closely monitored (biological investigations on 8$^{th}$ day, then every 2 weeks during treatment and after treatment discontinuation)

Insulin, sulfonylureas, metformin:
Increase in blood glucose, with sometimes diabetic ketosis, since corticosteroids impair carbohydrate tolerance. Therefore, blood and urine self-monitoring should be reinforced by the patient, in particular at the start of treatment.

Isoniazid:
A decrease in plasma isoniazid levels have been reported with prednisolone. The suggested mechanism is an increase in hepatic metabolism of isoniazid and a decrease in the hepatic metabolism of isoniazid and a decrease in the hepatic metabolism of glucocorticoids. Patients taking isoniazid should be closely monitored.

**4.6 Fertility, pregnancy and lactation**

Since adequate human reproduction studies have not been performed with corticosteroids, dexamethasone should not be used during pregnancy for maternal indications, unless it is clearly necessary. The lowest effective dose needed to maintain adequate disease control should be used.

Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

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

Placental transfer in considerable: foetal serum concentrations are similar to maternal concentrations.

Corticosteroids are excreted in small amounts in breast milk and may suppress growth, interfere with endogenous corticosteroid production or cause other unwanted effects. A decision on whether to continue/discontinue breast feeding or to continue/discontinue therapy with dexamethasone should be made taking into account the benefit of breast feeding to the child and the benefit of dexamethasone therapy to the woman.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intrauterine 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. See also section 5.3 of the SmPC.

**4.7 Effects on ability to drive and use machines**

There are some side effects associated with this product that may affect some patients' ability to drive or operate machinery (see section 4.8 undesirable effects).

**4.8 Undesirable effects**

The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (refer to Special Warnings and Precautions).

The following side effects have been reported; there frequency is unknown.

| **System Organ Class** | |
|---|---|
| Infections and infestations | Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis. Decreased resistance to infection |
| Blood and lymphatic system disorders | Leucocytosis |
| Immune system disorders | Hypersensitivity including anaphylaxis has been reported. |
| Endocrine disorders | Menstrual irregularities and amenorrhoea, suppression of the hypothalamic-pituitary-adrenal axis, premature epiphyseal closure, development of Cushingoid state, hirsutism, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery or illness). Negative protein and calcium balance. |
| Metabolism and nutrition disorders | Sodium retention, fluid retention, potassium loss, hypokalaemic alkalosis, increased calcium excretion. Increased appetite. Impaired carbohydrate tolerance with increased requirement for anti-diabetic therapy. |
| Nervous system disorders | Convulsions and aggravation of epilepsy, vertigo, headache, increased intra-cranial pressure with papilloedema in children (Pseudotumour |

| | |
|---|---|
| | cerebri), usually after treatment withdrawal, psychological dependence, depression, insomnia, aggravation of schizophrenia and psychic disturbances ranging from euphoria to frank psychotic manifestations. A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown. |
| Eye disorders | Posterior subcapsular cataracts, increased intra-ocular pressure, glaucoma, papilloedema, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases, exopthalmos. Frequency rare: Vision blurred (see also section 4.4)<br>Frequency not known: Chorioretinopathy |
| Cardiac disorders | congestive heart failure in susceptible patients |
| Vascular disorders | Thromboembolism, hypertension |
| Gastrointestinal disorders | Dyspepsia, peptic ulceration with perforation and haemorrhage, acute pancreatitis, candidiasis. Abdominal distension and vomiting. Ulcerative oesophagitis. Perforation of the small and large bowel particularly in patients with inflammatory bowel disease. Nausea, hiccups. |
| Skin and subcutaneous tissue disorders | Impaired wound healing, thin fragile skin, petechiae and ecchymoses, erythema, striae, telangiectasia, acne, increased sweating, suppressed reaction to skin tests, other cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic oedema, thinning scalp hair. |
| Musculoskeletal and connective tissue disorders | Osteoporosis, vertebral and long bone fractures, avascular necrosis, tendon rupture. Proximal myopathy. Muscle weakness, aseptic necrosis of femoral and humeral heads, loss of muscle mass. Growth suppression in children and adolescents. |
| General disorders and administration site conditions | Malaise, abnormal fat deposits. |
| Investigations | Increased or decreased motility and number of spermatozoa, weight gain. |

Withdrawal symptoms and signs

Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (See 'Special Warnings and Precautions').
A 'withdrawal syndrome' may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

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 professional are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2. Tel: +353 16764971, Fax: +353 16762517. Website: www.hpra.ie e-mail: medsafety@hpraie.

**4.9 Overdose**

Reports of acute toxicity and/or deaths following overdosage with glucocorticoids are rare. No antidote is available. Treatment is probably not indicated for reactions due to chronic poisoning unless the patient has a condition that would render him unusually susceptible to ill effects from corticosteroids. In this case, the stomach should be emptied and symptomatic treatment should be instituted as necessary. Anaphylactic and hypersensitivity reactions may be treated with epinephrine (adrenaline), positive-pressure artificial respiration and aminophylline. The patient should be kept warm and quiet. The biological half life of dexamethasone in plasma is about 190 minutes.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Corticosteroid, ATC Code: H02A B02

Dexamethasone is a highly potent and long-acting glucocorticoid with negligible sodium retaining properties and is therefore, particularly suitable for the use in patients with cardiac failure and hypertension. It's anti-inflammatory potency is 7 times greater than prednisolone and like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive properties.
Dexamethasone has a biological half life of 36 - 54 hours and therefore is suitable in conditions where continuous glucocorticoid action is required.

Covid-19

The RECOVERY trial (Randomised Evaluation of COVID-19 thERapY,)[1] is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19.

The trial was conducted at 176 hospital organizations in the United Kingdom.

There were 6425 Patients randomised to receive either dexamethasone (2104 patients) or usual care alone (4321 patients). 89% of the patients had laboratory-confirmed SARS-CoV-2 infection.

At randomization, 16% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non invasive ventilation), and 24% were receiving neither.

The mean age of patients was 66.1+/-15.7 years. 36% of the patients were female. 24% of patients had a history of diabetes, 27% of heart disease and 21% of chronic lung disease.

**Primary endpoint**

Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%), respectively (rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001).

In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and in those receiving supplementary oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94).

There was no clear effect of dexamethasone among patients who were not receiving any respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

**Secondary endpoints**

Patients in the dexamethasone group had a shorter duration of hospitalization than those in the usual care group (median, 12 days vs. 13 days) and a greater probability of discharge alive within 28 days (rate ratio, 1.10; 95% CI, 1.03 to 1.17).

In line with theprimary endpoint the greatest effect regarding discharge within 28 days wasseen among patients who were receiving invasive mechanical ventilation atrandomization (rate ratio 1.48; 95% CI 1.16, 1.90), followed by oxygen only(rate ratio, 1.15 ;95% CI 1.06-1.24) with no beneficial effect in patients not receiving oxygen (rate ratio, 0.96 ; 95% CI 0.85-1.08).

| Outcome | Dexamethasone (N=2104) | Usual Care (N=4321) | Rate or Risk Ratio (95% CI)* |
|---|---|---|---|
| | no./total no. of patients (%) | | |
| **Primary outcome** | | | |
| Mortality at 28 days | 482/2104 (22.9) | 1110/4321 (25.7) | 0.83 (0.75–0.93) |
| **Secondary outcomes** | | | |
| Discharged from hospital within 28 days | 1413/2104 (67.2) | 2745/4321 (63.5) | 1.10 (1.03–1.17) |
| Invasive mechanical ventilation or death† | 456/1780 (25.6) | 994/3638 (27.3) | 0.92 (0.84–1.01) |
| Invasive mechanical ventilation | 102/1780 (5.7) | 285/3638 (7.8) | 0.77 (0.62–0.95) |
| Death | 387/1780 (21.7) | 827/3638 (22.7) | 0.93 (0.84–1.03) |

* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

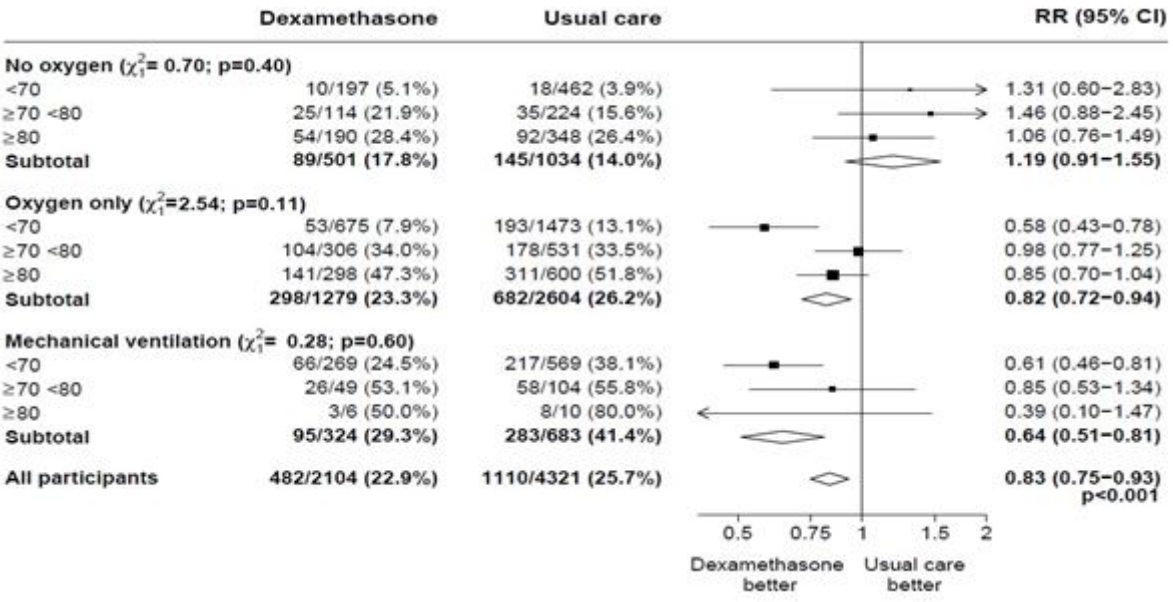
www.recoverytrial.net

**Safety**

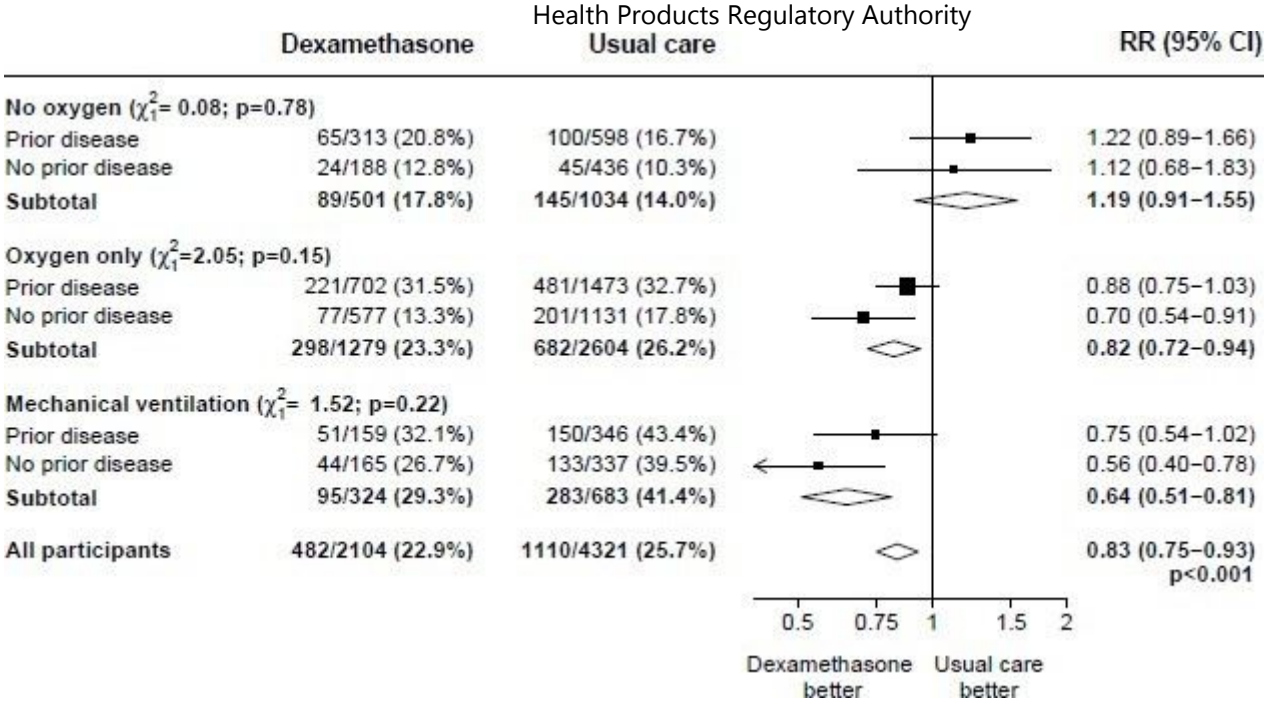
There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved.

**Subgroup analyses**

***Effects of allocation to DEXAMETHASONE on 28−day mortality, by age and respiratory support received at randomisation[2]***




***Effects of allocation to DEXAMETHASONE on 28−day mortality, by respiratory support received at randomisation and history of any chronic disease.[3]***




[2,3] (source: Horby P. et al., 2020; https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1; doi: https://doi.org/10.1101/2020.06.22.20137273)

**5.2 Pharmacokinetic properties**

Dexamethasone is well absorbed when given by mouth; peak plasma levels are reached between 1 and 2 hours after ingestion and show wide interindividual variations. The mean plasma half life is 3.6 ± 0.9h. Dexamethasone is bound (to about 77%) to plasma proteins, mainly albumins. Percentage protein binding of dexamethasone, unlike that of cortisol, remains practically unchanged with increasing steroid concentrations. Corticosteroids are rapidly distributed to all body tissues. Dexamethasone is metabolised mainly in the liver but also in the kidney. Dexamethasone and its metabolites are excreted in the urine.

**5.3 Preclinical safety data**

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, inter-uterine growth can be delayed. All these effects were seen at high doses.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Benzoic acid (E420), propylene glycol (E1520), citric acid monohydrate, liquid maltitol (E965), garden mint flavour (containing isopropanol and propylene glycol (E1520)), sorbitol, liquid (non-crystallising) (E420), sodium citrate and purified water.

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

Shelf Life: 2 years
Shelf life after first opening the container:3 months

**6.4 Special precautions for storage**

Do not store above 25°C. Do not refrigerate.

The storage at temperatures higher than 25°C could allow precipitation inside the solution. Do not use the product if solid particles are observed inside the solution.
This product is sensitive to light. Store in the original package.

**6.5 Nature and contents of container**

Bottles: 75ml and 150ml in Amber (Type III) glass.

Closures: HDPE, EPE wadded, tamper evident, child resistant closure.

**6.6 Special precautions for disposal and other handling**

No special requirement for disposal.

Instructions for administration via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes.

Dexsol Oral Solution is suitable for use with the following type of NG and PEG tubes:

| Material | External Bore Size (Fr Unit) | Internal Diameter (mm) | Maximum Length (cm) | Recommended flush volume (ml) |
|---|---|---|---|---|
| Silicone | 4 | 0.80 | 125 | 5 |
| | 6 | 1.00 | 125 | 5 |
| | 10 | 2.00 | 125 | 5 |
| PVC | 4 | 0.80 | 125 | 5 |
| | 8 | 1.50 | 125 | 5 |
| | 12 | 2.50 | 125 | 5 |
| Polyurethane | 4 | 0.80 | 125 | 5 |
| | 8 | 1.50 | 125 | 5 |
| | 12 | 2.60 | 125 | 5 |
| | 18 | 4.00 | 125 | 5 |

Ensure that the enteral feeding tube is free from obstruction before administration.

1. Flush the enteral tube with water, a minimum flush volume of 5 ml is required.
2. Administer the required dose of Dexsol Oral Solution with a suitable measuring device.
3. Flush the enteral tube with water again, using a minimum volume of 5ml of water.

With respect to tubal administration, this product should be administered with silicone, PVC, polyurethane NG or PEG tubes only.

Healthcare professional should be aware that with air flushing procedure there is a risk of under dosing (up to 50%). It is therefore recommended that only water flush is used.

**7 MARKETING AUTHORISATION HOLDER**

Taw Pharma (Ireland) Ltd
104 Lower Baggot Street
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Dublin
D02 Y940
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA23081/006/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 3rd February 2006
Date of last renewal: 8 March 2010

## 10 DATE OF REVISION OF THE TEXT

January 2023