SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dexamethasone 1 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mg tablet contains 1 mg dexamethasone.

Excipient(s) with known effect

Lactose monohydrate 73mg/ tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Uncoated tablet.

Round, biplanar, white to off-white tablets with bevelled edges and single break-mark. Dexamethasone 1 mg is embossed with ‘D | 1’.

The tablet can be divided into equal doses.

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.

Dexamethasone 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.

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.
- **For the treatment of Covid-19**
    - Adult patients 6 mg PO, once a day for up to 10 days.
    - *Paediatric population:* Paediatric patients (adolescents aged 12 years and older) are recommended to take 6mg/dose PO 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.

The dose and administration frequency varies with the therapeutic protocol and the associated treatment(s). Dexamethasone administration should follow instructions for dexamethasone administration when described in the Summary of Product Characteristics of the associated treatment(s). If this is not the case, local or international treatment protocols and guidelines should be followed. Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

<u>Renal impairment</u>
Patients undergoing active hemodialysis may show an increased clearance of drug via the dialysate and thus require an adjustment of steroid dose.

<u>Hepatic impairment</u>
In patients with severe liver disease dose adjustment may be necessary. In patients with a severe liver impairment, the biological effects of dexamethasone may be potentiated due to its slower metabolism (prolonged plasma half-life) and hypoalbuminaemia (increased plasma levels of free drug), which may also cause more side effects.

<u>Elderly</u>
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 (osteoporosis, diabetes mellitus, hypertension, reduced immunity, psychological changes). In such patients, the plasma concentrations of dexamethasone may be higher and its excretion slower than in younger patients, therefore its dose should be reduced accordingly.

Paediatric population
The usual dose is 0.01-0.1 mg/kg of body weight daily. The excretion of dexamethasone is approximately equal in children and adults if dosage is adjusted to their body area. Dosage should be planned bearing in mind possible effects upon growth and development and for signs of adrenal suppression.

Long term treatment
For the long-term treatment of several conditions, after initial therapy, glucocorticoid treatment should be switched from dexamethasone to prednisone/prednisolone to reduce suppression on the function of the adrenal cortex.

Discontinuation of treatment
Acute adrenocortical failure may occur after abrupt discontinuation of long-term treatment with large doses of glucocorticoids. Therefore, glucocorticoid doses should be gradually reduced in such cases and treatment should be discontinued gradually. (see section 4.4)

Method of administration
Dexamethasone should be taken with or after food to minimise irritation to the gastrointestinal tract. Drinks containing alcohol or caffeine should be avoided.
Dexamethasone is in the form of tablets 1 mg and 4 mg. The tablets can be divided into equal halves.
When alternate-day therapy is not possible, the entire daily dose of glucocorticoid can usually be administered as a single morning dose; however, some patients will require divided daily doses of glucocorticoids.

4.3 Contraindications

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

Systemic infection unless specific anti-infective therapy is employed.

Stomach ulcer or duodenal ulcer.

Avoid live vaccines in patients receiving immuno suppressive doses (serum antibody response diminished).

In general no contraindications apply in conditions where the use of glucocorticoids may be life saving.

4.4 Special warnings and precautions for use

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. Patients 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.

Adrenocortical insufficiency
An adrenocortical insufficiency, which is caused by glucocorticoid treatment, can, depending on the dose and length of treatment, remain for many months, and in some cases more than a year, after discontinuation of treatment. During treatment with dexamethasone for specific physical stress conditions (trauma, surgery, childbirth, etc.), a temporary increase in dose may be required. Because of the possible risk in stressful conditions, a corticosteroid ID should be made for patients undergoing long-term treatment. Even in cases of prolonged adrenocortical insufficiency after discontinuation of treatment, the administration of glucocorticoids can be necessary in physically stressful situations. An acute therapy-induced adrenocortical insufficiency can be minimized by slow dose reduction until a planned discontinuation time.

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
- Approx. 8 weeks prior through 2 weeks after vaccinations with live vaccines (see section 4.3 and 4.5)
- Systemic mycoses and parasitosis (e.g. Nematodes)
- Poliomyelitis
- Lymphadenitis after BCG vaccination
- Acute and chronic bacterial infections
- With a history of tuberculosis (reactivation risk) use only under tuberculostatic protection
- Known or suspected Strongyloidiasis (threadworm infestation). Treatment with glucocorticoids may lead to lead to Strongyloides hyperinfection and dissemination with widespread larval migration.

In addition, treatment with dexamethasone should only be implemented under strong indications and, if necessary, additional specific treatment must be implemented for:
- Gastrointestinal ulcers
- Severe osteoporosis (as corticosteroids have a negative effect on the calcium balance)
- Difficult to regulate high blood pressure
- Difficult to regulate diabetes mellitus
- Psychiatric disorders (including history)
- Angle closure glaucoma and wide-angle glaucoma
- Corneal ulcerations and corneal injuries

- Severe heart failure

Anaphylactic reaction
Serious anaphylactic reactions may occur.

Tendinitis
The risk of tendinitis and tendon rupture is increased in patients treated concomitantly with glucocorticoids and fluoroquinolones.

Myasthenia gravis
Pre-existing myasthenia gravis may initially deteriorate in the beginning of dexamethasone treatment.

Ocular disorders
Systemic treatment with glucocorticoids can induce chorioretinopathy which may result in impaired vision including loss of vision.
Prolonged use of corticosteroids may cause posterior subcapsular cataracts, glaucoma with possible damage to the optic nerve and can increase the risk of secondary ocular infections due to fungi or viruses.
Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

Intestinal perforation
Because of the risk of an intestinal perforation, dexamethasone must only be used under urgent indication and under appropriate monitoring for:
- Severe ulcerative colitis with threatened perforation
- Diverticulitis
- Entero-anastomosis (immediately postoperative)

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

Diabetes
A higher need for insulin, or oral antidiabetics, must be taken into consideration when administering dexamethasone to diabetics.

Cardiovascular disorders
Regular blood pressure monitoring is necessary during treatment with dexamethasone, particularly during administration of higher doses and with patients with difficult to regulate high blood pressure. Because of the risk of deterioration, patients with severe cardiac insufficiency should be carefully monitored.
Bradycardia may occur in patients treated with high doses of dexamethasone.
Caution should be exercised when using corticosteroids in patients who have recently suffered myocardial infarction as myocardial rupture has been reported.

Infections
Treatment with dexamethasone can conceal the symptoms of an existing, or developing infection thereby making a diagnosis more difficult. The prolonged

use of even small amounts of dexamethasone leads to an increased risk of infection, even by microorganisms which otherwise rarely cause infections (so-called opportunistic infections).

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.

Vaccination
Vaccinations with inactivated vaccine are always possible. However, it should be noted that the immune reaction and thereby the success of inoculation, can be affected by higher doses of corticoids.
Regular checkups with doctors (including vision checkups in three-month intervals) are advised during long-term treatment with dexamethasone.

Metabolic disorders
At high doses, sufficient calcium intake and sodium restriction, as well as serum potassium levels should be monitored. Depending on the length and dosage of the treatment, a negative influence on calcium metabolism can be expected, so that an osteoporosis prophylaxis is recommended. This applies, above all, to co-existing risk factors like familial disposition, increased age, after menopause, insufficient protein and calcium intake, heavy smoking, excessive alcohol intake, as well as insufficient exercise. Prevention consists of sufficient calcium and vitamin D intake and physical activity. Additional medical treatment should be considered in the event of pre-existing osteoporosis.

Corticosteroids should be used cautiously in patients with migraine, as corticosteroids may cause fluid retention.

Psychological changes
Psychological changes are manifested in various forms, the most common being euphoria. Depression, psychotic reactions and suicidal tendencies may also appear.
These illnesses can be serious. Usually they start within a few days or weeks of starting the medicine. They are more likely to happen at high doses. Most of these problems go away if the dose is lowered or the medicine is stopped. However, if problems do happen, they might need treatment. In a few cases, mental health problems have happened when doses are being lowered or stopped.

Cerebral oedema or increased intracranial pressure
Corticosteroids should not be used in conjunction with a head injury since they will probably not be of benefit or may even do harm.

Discontinuation of treatment
Glucocorticoid doses should be gradually reduced.
The following risks should be considered upon interruption or discontinuation of long-term glucocorticoid administration:

- Exacerbation or recurrence of the underlying disease, acute adrenal insufficiency, corticosteroid withdrawal syndrome (A 'withdrawal syndrome' may include fever, muscle and joint pain, inflammation of the nose lining (rhinitis), weight loss, itchy skin and inflammation of the eye (conjunctivitis)).
- Certain viral diseases (chickenpox, measles) in patients treated with glucocorticoids, may be very severe.
- Children and immunocompromised persons without previous chickenpox or measles infection are particularly at risk. If these people have contact with people infected with measles or chickenpox while undergoing treatment with dexamethasone, a preventative treatment should be introduced if necessary.

Other
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.

Paediatric population

Corticosteroids cause a dose-dependent inhibition of growth in infancy, childhood, and adolescence since corticosteroids may give rise to early closing of the epiphyses, which may be irreversible. Therefore, during long-term treatment with dexamethasone, the indication should be very strongly presented in children and their growth rate should be checked regularly. 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/hg twice daily.

Elderly

The adverse effects of systemic corticosteroids can have serious consequences especially in old age, mainly osteoporosis, hypertension, hypokalemia, diabetes, susceptibility to infection and skin atrophy. Close clinical monitoring is required to prevent life-threatening reactions.

Influence of diagnostic tests

Glucocorticoids can suppress skin reaction to allergy testing. They can also affect the nitroblue tetrazolium test for bacterial infections and cause false-negative results.

Note on doping

The use of doping tests when taking dexamethasone can lead to positive results.

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

4.5 Interaction with other medicinal products and other forms of interaction

Prior to the use of Dexamethasone in combination with any other medicinal product, reference should be made to the Summary of Product Characteristics of that product.

Pharmacodynamic interactions

Patients taking NSAIDs should be monitored, as NSAIDs may increase the incidence and/or severity of gastric ulcers. Acetylsalicylic acid should be used carefully in combination with corticosteroids in hypoprothrombinaemia.

The renal clearance of salicylates is increased by corticosteroids. Therefore, the dosage of salicylates may be reduced once the steroids are discontinued. Steroid withdrawal may result in salicylate intoxication due to the increase of salicylate concentration in the serum.

Corticosteroids reduce the effect of antidiabetic agents such as insulin, sulfonylurea, and metformin. Hyperglycaemia and diabetic ketoacidosis may occur occasionally. Therefore, at the beginning of treatment, diabetics should have more frequent blood and urine tests.

The hypokalemic effect of acetazolamide, loop diuretics, thiazide diuretics, kaliuretics, amphotericin B injections (glucomineral)-corticosteroids, tetracosactide and laxatives will increase. Hypokalemia promotes cardiac arrhythmias, especially torsade de pointes, and increases the toxicity of cardiac glycosides. Before the start of corticosteroid treatment, hypokalemia should be corrected and patients should be monitored clinically, for electrolytes and by electrocardiography. Furthermore, there are case reports in which the simultaneous use of amphotericin B and hydrocortisone led to an enlarged heart and heart failure.

Antiulcer drugs: Carbenoxolone increases the risk of hypokalemia.

Chloroquine, hydroxychloroquine and mefloquine: Increased risk of myopathies and cardiomyopathies.

Concomitant administration of ACE inhibitors creates an increased risk of blood disorders.
The blood pressure-lowering effects of antihypertensive drugs may be affected by corticosteroids. The dose of the anti-hypertensive treatment may have to be adjusted during the treatment with dexamethasone.

Thalidomide: Great care should be taken during co-administration with thalidomide, a there have been reported cases of toxic epidermal necrolysis.

The effect of vaccinations may be reduced during treatment with dexamethasone.
Vaccination with live vaccines during treatment with large therapeutic doses of dexamethasone (and other corticosteroids) is contraindicated due to the possibility of viral infection. In this case, vaccination should be postponed for at least 3 months after the completion of treatment with corticosteroids. Other types of immunisation during treatment with large therapeutic doses of corticosteroids are dangerous due to the risk of neurological complications and decreased or absent increase in the antibody titers (in comparison with expected values) and therefore a smaller protective effect. However, patients who have received corticosteroids locally (parenteral) or for a short period of time (less than 2 weeks), in smaller doses may be immunised.

Cholinesterase inhibitors: Concomitant use of cholinesterase inhibitors and corticosteroids may cause serious muscle weakness in patients with myasthenia gravis. If possible, cholinesterase inhibitors should be discontinued at least 24 hours before the start of corticosteroid therapy.

The risk of tendinitis and tendon rupture is increased in patients treated concomitantly with glucocorticoids and fluoroquinolones.

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.

<u>Pharmacokinetic interactions</u>

<u>Effects of other medicinal products on dexamethasone:</u>

Dexamethasone is metabolized via the cytochrome P450 3A4 (CYP3A4).
The administration of dexamethasone with inducers of CYP3A4, such as ephedrine, barbiturates, rifabutin, rifampicin, phenytoin, and carbamazepine can lead to reduced plasma concentrations of dexamethasone, so the dose must be increased.

Aminoglutethimide can accelerate the reduction of dexamethasone and reduce its efficacy. If necessary, the dexamethasone dosage should be adjusted.

Bile acid resins, such as cholestyramine, may decrease the absorption of dexamethasone.
Topically applied gastrointestinal drugs, antacids, activated charcoal: Decreased glucocorticoid resorption has been described during co-administration of prednisolone and dexamethasone. Therefore, the administration of glucocorticoids and topically applied gastrointestinal drugs, antacids, activated charcoal should be postponed (with an interval of at least two hours).

The administration of dexamethasone with inhibitors of CYP3A4, such as azoleantifungals (e.g. ketoconazole, itraconazole), HIV protease inhibitors (e.g. ritonavir) and macrolide antibiotics (e.g. erythromycin) may lead to increased plasma concentrations and reduced clearance of dexamethasone. If required, the dexamethasone dose should be reduced.

Ketoconazole may not only increase the plasma concentration of dexamethasone by inhibition of CYP3A4, but also suppress adrenal corticosteroid synthesis and cause adrenal insufficiency upon discontinuation of corticosteroid treatment.

Estrogens, including oral contraceptives, may inhibit the metabolism of certain corticosteroids and thus enhance their effect.

Effects of dexamethasone on other medicinal products

Dexamethasone is a moderate inducer of CYP3A4. The administration of dexamethasone with substances metabolized by CYP3A4 can lead to increased clearance and decreased plasma concentrations of these substances.

Tuberculostatics: A reduction of isoniazid plasma concentrations was observed during concurrent use of prednisolone. Patients taking isoniazid should be monitored closely.

Cyclosporine: Concomitant administration of cyclosporine and corticosteroids may lead to an increased effect of both substances. There is an increased risk of cerebral seizures.

Praziquantel: Reduced praziquantel plasma concentrations create a risk of treatment failure due to the increased hepatic metabolism of dexamethasone.

Oral anticoagulants (coumarin): Concomitant corticosteroid therapy may either potentiate or lead to a weakening of the effect of oral anticoagulants. In case of high doses or of treatment lasting over 10 days there is a risk of bleeding specific to corticosteroid therapies (gastrointestinal mucosa, vascular fragility). Patients who use corticosteroids combined with oral anticoagulants should be closely monitored (controls on day 8, then every two weeks during and after treatment).

Atropine and other anticholinergics: Intraocular pressure increases may be noted during co-administration with dexamethasone.

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

Somatotropin: the effect of the growth hormone can be reduced.

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

4.6 Fertility, Pregnancy and lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs, however, dexamethasone readily crosses the placenta.
Administration of corticosteroids to pregnant animals can cause abnormalities of fetal 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 (see also section 5.3). However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Breast-feeding

Corticosteroids may pass into breast milk, although no data are available for dexamethasone. Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression.
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.

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.

Dexamethasone may cause confusional state, hallucinations, dizziness, somnolence, fatigue, syncope and blurred vision (see section 4.8). If affected, patients should be instructed not to drive, use machines or perform hazardous tasks while being treated with dexamethasone.

4.8 Undesirable effects

Summary of the safety profile

The incidence of anticipated adverse effects correlates with the relative potency of the substance, dose, time of day of administration and duration of treatment. During a short-term therapy, in compliance with the dosage recommendations and close monitoring of patients, the risk of side effects is low.

The usual side effects of short-term dexamethasone treatment (days/weeks) include weight gain, psychological disorders, glucose intolerance and transitory adrenocortical insufficiency. Long-term dexamethasone treatment (months/years) usually causes central obesity, skin fragility, muscle atrophy, osteoporosis, growth retardation and long-term suprarenal insufficiency. (see also section 4.4 Special warnings and precautions for use)

Tabulated list of adverse reactions

System Organ Class	**Frequency Not known (cannot be estimated from the available data)**
Infections and infestations	Increased susceptibility to, or exacerbation of, (latent) infections* (including septicaemia, tuberculosis, eye infections, chickenpox, measles, fungal and viral infections) with masking of clinical symptoms, opportunistic infections
Blood and lymphatic system disorders	Leukocytosis, lymphopenia, eosinopenia, polycythemia, abnormal coagulation
Immune system disorders	Hypersensitivity reactions including anaphylaxis, immunosuppression (see also under “Infections and parasitic diseases”)
Endocrine disorders	Suppression of the hypothalamic-pituitary-adrenal axis and induction of Cushing's syndrome (typical symptoms: full-moon face, plethora, truncal obesity), secondary adrenal and pituitary insufficiency* (especially in stress such as trauma or surgery), growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea, hirsutism
Metabolism and nutrition disorders	Weight gain, negative protein and calcium balance*, increased appetite, sodium and water retention*, potassium loss* (caution: rhythm disorders), hypokalemic alkalosis, manifestation of latent diabetes mellitus, impaired carbohydrate tolerance with increased dose requirements of antidiabetic therapy*, hypercholesterolemia, hypertriglyceridaemia
Psychiatric disorders*	Psychological dependence, depression, insomnia, aggravated schizophrenia, mental illness, from euphoria to manifest psychosis
Nervous system disorders	Increased intracranial pressure with papilloedema in children (pseudotumor cerebri) usually following discontinuation of treatment; manifestation of latent epilepsy, increased seizures in overt epilepsy, vertigo, headache

Eye disorders	Elevated intraocular pressure, glaucoma*, papilloedema, cataract*, mainly with posterior subcapsular opacity, corneal and scleral atrophy, increased ophthalmic viral, fungal and bacterial infections, worsening of symptoms associated with corneal ulcers*, chorioretinopathy
Cardiac disorders	Cardiac muscle rupture after recent history of myocardial infarction, congestive heart failure in predisposed patients, cardiac decompensation*
Vascular disorders	Hypertension, vasculitis, increased atherosclerosis and risk of thrombosis/thromboembolism (increase in coagulability of blood may lead to thromboembolic complications)
Respiratory, thoracic and mediastinal disorders	Hiccough
Gastrointestinal disorders	Dyspepsia, abdominal distension*, gastric ulcers with perforation and bleeding, acute pancreatitis, ulcerative esophagitis, oesophageal candidiasis, flatulence, nausea, vomiting
Skin and subcutaneous tissue disorders	Hypertrichosis, skin atrophy, telangiectasia, striae, erythema, steroid acne, petechiae, ecchymosis, allergic dermatitis, urticaria, angioneurotic oedema, thinning hair, pigment disorders, increased capillary fragility, perioral dermatitis, hyperhidrosis, tendency to bruise
Musculoskeletal and connective tissue disorders	Premature epiphyseal closure, osteoporosis, fractures of the spine and long bones, aseptic necrosis of the femoral and the humeral bones, tendon tears*, proximal myopathy, muscle weakness, loss of muscle mass
Reproductive system and breast disorders	Impotence
General disorders and administration site conditions	Reduced response to vaccination and skin tests. Delayed wound healing, discomfort, malaise, steroid withdrawal syndrome: a too rapid reduction in corticosteroid dose after prolonged treatment can lead to acute adrenal insufficiency, hypotension, and death. A withdrawal syndrome may present with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss.

* see also section 4.4 Special warnings and precautions for use

Description of selected adverse reactions

Adrenocortical insufficiency
An adrenocortical insufficiency, which is caused by glucocorticoid treatment, can, depending on the dose and length of treatment, remain for many months and in some cases more than a year, after discontinuation of treatment. (see section 4.4 Special warnings and precautions for use)

Psychological changes

Psychological changes are manifested in various forms, the most common being euphoria. Depression, psychotic reactions and suicidal tendencies may also appear. These illnesses can be serious. Usually they start within a few days or weeks of starting the medicine. They are more likely to happen at high doses. Most of these problems go away if the dose is lowered or the medicine is stopped. (see section 4.4 Special warnings and precautions for use)

Infections
Treatment with dexamethasone can conceal the symptoms of an existing, or developing infection thereby making a diagnosis more difficult and can lead to an increased risk of infection. (see section 4.4 Special warnings and precautions for use)

Intestinal perforation
Corticosteroids can be associated with an increased risk of colonic perforation in severe ulcerative colitis with threatened perforation, diverticulitis and entero-anastomosis (immediately postoperative).
Signs of peritoneal irritation after gastrointestinal perforation may be absent in patients receiving high doses of glucocorticoids. (see section 4.4 Special warnings and precautions for use)

Cardiovascular disorders
Bradycardia, deterioration of severe cardiac insufficiency and difficult to regulate high blood pressure may occur. Caution should be exercised when using corticosteroids in patients who have recently suffered myocardial infarction as myocardial rupture has been reported. (see section 4.4 Special warnings and precautions for use)

Paediatric population
Corticosteroids cause a dose-dependent inhibition of growth in infancy, childhood, and adolescence since corticosteroids may give rise to early closing of the epiphyses, which may be irreversible. (see section 4.4 Special warnings and precautions for use)

Elderly
The adverse effects of systemic corticosteroids can have serious consequences especially in old age, mainly osteoporosis, hypertension, hypokalemia, diabetes, susceptibility to infection and skin atrophy. (see section 4.4 Special warnings and precautions for use)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Reports of acute toxicity and/or deaths following overdose with glucocorticoids are rare.

Overdose or prolonged use may exaggerate glucocorticoid adverse effects.

Management

No antidote is available. Treatment should be symptomatic and supportive with the dosage of dexamethasone being reduced or slowly withdrawn where possible. 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: corticosteroids for systemic use, glucocorticoids, ATC code: H02AB02.

Mechanism of action
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.

Its 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.

The RECOVERY trial

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 the primary endpoint the greatest effect regarding discharge within 28 days was seen among patients who were receiving invasive mechanical ventilation at randomization (rate ratio 1.48; 95% CI 1.16, 1.90), followed by

[1] www.recoverytrial.net

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).

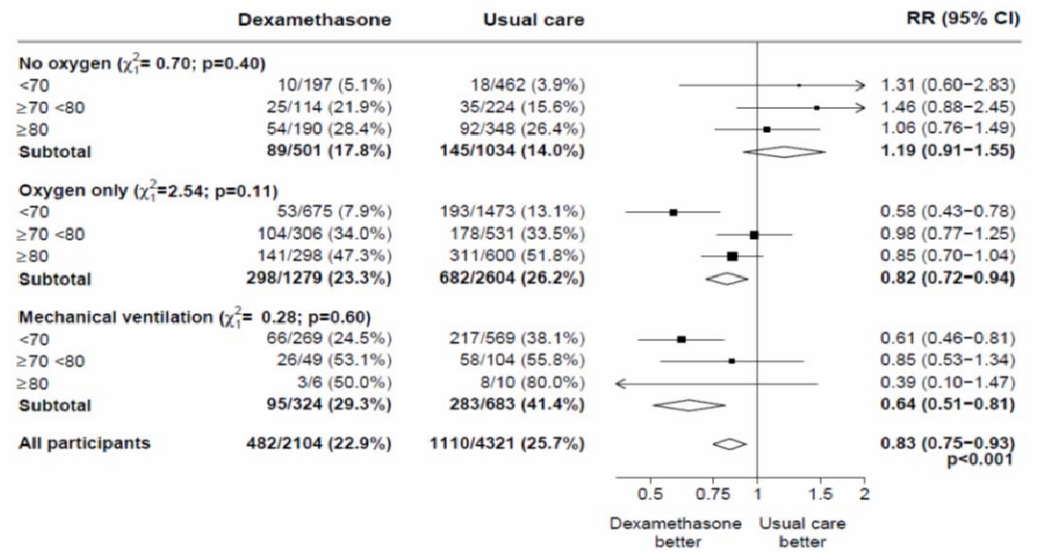
Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
tality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
harged from hospital in 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
sive mechanical llation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
sive mechanical llation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
h	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.

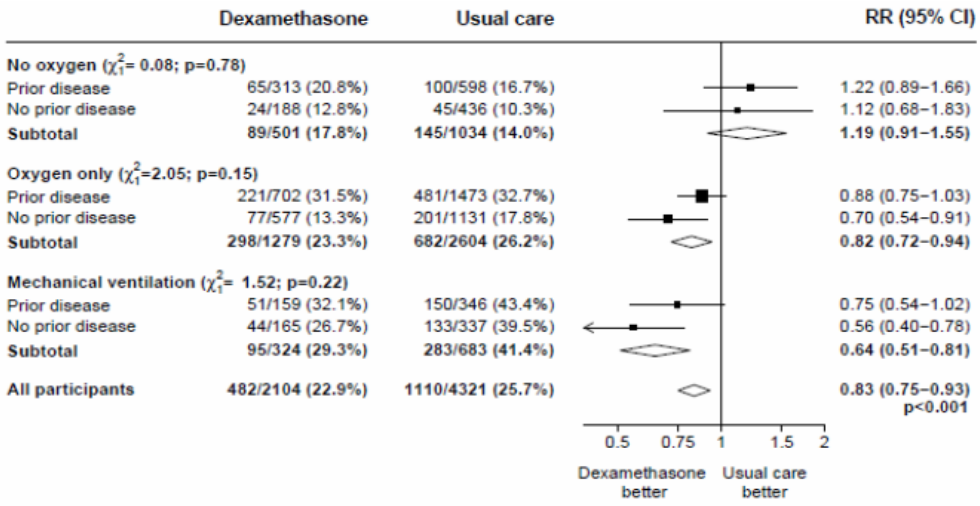
Safety
There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved.

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

[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)



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



5.2 Pharmacokinetic properties

Absorption and Distribution

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 ± 0.9 h. 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. They cross the placenta and may be excreted in small amounts in breast milk.

Biotransformation
Dexamethasone is metabolised mainly in the liver but also in the kidney.

Elimination
Dexamethasone and its metabolites are excreted in the urine.

5.3 Preclinical safety data

Studies in animals have shown that glucocorticoids increase the incidence of cleft palate, spontaneous abortions and intrauterine growth retardation. In some cases these divergences were combined with defects of the central nervous system and of the heart. In non-human primates, minor cranial skeletal abnormalities were observed. These effects were observed after use of high doses of dexamethasone.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C and in the original pack to protect from light.

6.5 Nature and contents of container

Thermoformed unit-dose blisters (PVC/PVDC film) sealed with Aluminium lidding foil. Each unit-dose blister contains 10 tablets.
10 x 1, 20 x 1, 30 x 1, 40 x 1, 50 x 1, 60 x 1 and 100 x1, in a box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Limited
Dashwood House,
69 Old Broad Street,
London,
EC2M 1QS,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0617

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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