SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dexamethasone 1 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg of dexamethasone.

Excipient with known effect

Each 1 mg tablet contains 140.05 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

White to off white, round, flat bevelled edge tablet approximately 8 mm in diameter, engraved with DX on one side and 1 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Neurology
Cerebral oedema caused by brain tumours, neurosurgery, bacterial meningitis, brain abscesses.
Pulmonary and respiratory diseases
Severe acute asthma attacks.
Dermatology

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

Autoimmune disorders/rheumatology

Oral initial treatment of autoimmune diseases, such as systemic lupus erythematosus (especially visceral forms). Severe progressive form of active rheumatoid arthritis, e.g. rapidly destructive forms and/or with extra-articular manifestations.

Infectology

Severe infectious diseases with toxic-like conditions (e.g. tuberculosis, typhoid fever) only with concomitant anti-infective therapy.

Oncology

Palliative treatment of malignant tumours.

Endocrinology

Congenital adrenogenital syndrome in adulthood.

COVID-19

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.

Various

Prophylaxis and treatment of emesis induced by cytostatics, emetogenic chemotherapy within antiemetic treatment.

Prevention and treatment of postoperative vomiting, with in antiemetic treatment .

4.2 Posology and method of administration

Posology

Dosage depends on the type and severity of the disease and the individual patient's response to the therapy. In general, relatively high initial doses are used, which must be significantly higher in acute severe courses than in chronic diseases.

Unless otherwise prescribed, the following dosage recommendations apply:

- *Cerebral oedema*
  Depending on 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) single doses over 4 - 8 days. A longer term, lower-dose administration of Dexamethasone tablets may be necessary during radiotherapy and in the conservative therapy of inoperable brain tumours.

- *Cerebral oedema due to bacterial meningitis*
  0.15 mg/kg bodyweight, every 6 hours for 4 days.
  Children: 0.4 mg/kg body weight every 12 hours for 2 days, starting before the first antibiotic administration.

- *Severe acute asthma attacks*
  Adults: 8 - 20 mg, then if required, 8 mg every 4 hours.
  Children: 0.15 - 0.3 mg/kg bodyweight.

- *Acute skin conditions*
  Depending on the type and extent of the disease, daily doses of 8-40 mg. Followed by treatment with decreasing doses.

- *Active phases of systemic rheumatic diseases*
  Systemic lupus erythematosus: 6 – 16 mg daily.

- *Severely progressive form of Active rheumatoid arthritis*
  In rapidly destructive forms 12-16mg/day, in extra-articular manifestations:
  6 - 12 mg/day.

- *Severe infectious diseases, toxic conditions (e.g. tuberculosis, typhoid fever)*
  4 - 20 mg/day for a few days, only with concomitant anti-infective therapy.

- *Palliative treatment of malignant tumours*
  Initially 8 - 16 mg/day, for prolonged treatment 4 - 12 mg/day.

- *Congenital adrenogenital syndrome in adulthood*
  0.25 - 0.75 mg/day, taken as a single dose. If necessary, additional administration of a mineralocorticoid (fludrocortisone). In the case of special physical stress (e.g. trauma, surgery), intercurrent infections, etc., a 2- to 3- fold increase may be required and under extreme stress (e.g. childbirth) a 10- fold increase.

- *For the treatment of Covid-19*
  Adult patients: 6 mg, intravenously or orally, once a day for up to 10 days.
  Paediatric population: Paediatric patients (adolescents aged 12 years and older) are recommended to take 6 mg/dose, intravenously or orally, once a day for up to 10 days.
  The duration of treatment should be guided by the clinical response and the individual patient requirements.
  Elderly, renal impairment, hepatic impairment: No dose adjustment is needed.

- *Prophylaxis and therapy of cytostatic-induced vomiting in the context of antiemetic treatment plans:* 0 - 20 mg before starting chemotherapy,

then 4 - 8 mg up to 2 to 3 times a day for 1 - 3 days (moderately emetogenic chemotherapy) or up to 6 days (highly emetogenic chemotherapy) if necessary.

- *Prophylaxis and treatment of postoperative vomiting*
  Single dose of 8-20 mg before the start of surgery
  Children from 2 years of age and older: 0.15-0.5 mg/kg bodyweight (max. 16 mg).

Method of administration
The tablets should be swallowed whole after a meal and taken with plenty of liquid. The daily dose should be administered as a single dose in the morning if possible (circadian therapy). In patients who require high-dose therapy because of their disease, multiple daily doses are 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 listed in section 6.1.

4.4 Special warnings and precautions for use

Depending on the dose and duration of therapy, adrenalcortical insufficiency caused by glucocorticoid therapy may 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 tablets, 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.

Infections and vaccinations

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 tablets should only be implemented in the event of the strongest indications and if necessary, additional targeted anti-infective therapy administered in the following illnesses:

- acute viral infections (Herpes zoster, Herpes simplex, Varicella, Herpes keratitis)
- HBsAg-positive chronic active hepatitis
- approximately 8 weeks before, or up to 2 weeks after, vaccination with live vaccines;
- systemic mycosis and parasitosis (e.g. nematodes)
- in patients with suspected or confirmed strongyloidiasis (infection with thread worms, as glucocorticoids may lead to activation and mass proliferation of these parasites
- poliomyelitis
- lymphadenitis following BCG vaccination
- acute and chronic bacterial infections
- if there is a history of tuberculosis (reactivation risk), use only under tuberculostatic drugs protection.

In addition, therapy with dexamethasone should only be implemented under strong indications and, if necessary, additional specific treatment must be implemented in the following conditions:

- gastrointestinal ulcers
- osteoporosis
- severe cardiac insufficiency
- high blood pressure that is difficult to regulate
- diabetes mellitus that is difficult to regulate
- psychiatric disorders (including 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.

In COVID-19 infection, 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.

Gastrointestinal disease
Because of the risk of intestinal perforation, Dexamethasone tablets should only be used where there are compelling reasons to do so and under appropriate monitoring in:

- severe ulcerative colitis with an imminent perforation, this may occur without peritoneal irritation
- diverticulitis
- enteroanastomosis (immediately after surgery).

The signs of peritoneal irritation following gastrointestinal perforation may be absent in patients receiving high doses of glucocorticoids.

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

Other conditions:
Regular blood pressure monitoring is necessary during treatment with Dexamethasone tablets, 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 tablets.

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

During long-term therapy with Dexamethasone tablets, regular medical checks (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 tablets, 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.

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.

Paediatric population

In the growth phase of children, the risk-benefit ratio of treatment with Dexamethasone tablets 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 neuro-developmental adverse events, after early treatment (< 96 hours after birth) of premature infants with chronic lung disease at starting doses of 0.25 mg/kg twice daily.

Elderly population:
Because elderly patients are at increased risk of osteoporosis, the benefit-risk ratio of treatment with Dexamethasone tablets should be carefully weighed.

Note:
The use of Dexamethasone tablets can lead to positive results in doping controls.

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Medicines inducing CYP3A4, such as rifampicin, phenytoin, carbamazepine, barbiturates and primidone
The effect of corticoids can be reduced.

CYP3A inhibitors (including ketoconazole, itraconazole, ritonavir and cobicistat)
Co-treatment with CYP3 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, thereby reducing their effectiveness.

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.

Antidiabetic agents
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.

Non-steroidal anti-inflammatory/antirheumatic drugs (NSARs), salicylates and indomethacin
The risk of gastrointestinal ulceration and bleeding is increased.

Non-depolarising muscle relaxants
The muscle-relaxing effect may last longer.

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

Praziquantel
Corticosteroids may cause a reduction of the praziquantel concentration in the blood.

Chloroquine, hydroxychloroquine, mefloquine
There is an increased risk of myopathy and cardiomyopathy.

Somatropin
The effects of somatropin can be reduced during 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 ciclosporin are increased, so there is an increased risk of seizures.

Fluoroquinolones
Fluoroquinolones may increase the risk of tendon disorders.

Influence on investigative methods
Skin reactions in allergy tests can be suppressed.

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

No studies have been conducted on the effects on the ability to drive or to operate machinery.

4.8 Undesirable effects

Hormone replacement therapy
Low risk of side effects if recommended dosages are followed.

Pharmacotherapy
The following side effects may occur, which depend very much on the dose and duration of therapy and whose frequency cannot therefore be stated.

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 (see also section 4.4).
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, hiccups.
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.

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 website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 (see section 4.8).

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-stabilising 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 effect by activating the transcription of corticoid-sensitive genes. The anti-inflammatory, immunosuppressive and antiproliferative effects are caused by decreased formation, release and activity of inflammatory mediators, by the inhibition of the specific functions and migration of inflammatory cells. In addition, the effect of sensitised T lymphocytes and macrophages on target cells may be prevented by corticosteroids.

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

Treatment of 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 for patients hospitalised for COVID-19.

The trial was conducted in 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 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 ration, 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 end points

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 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).

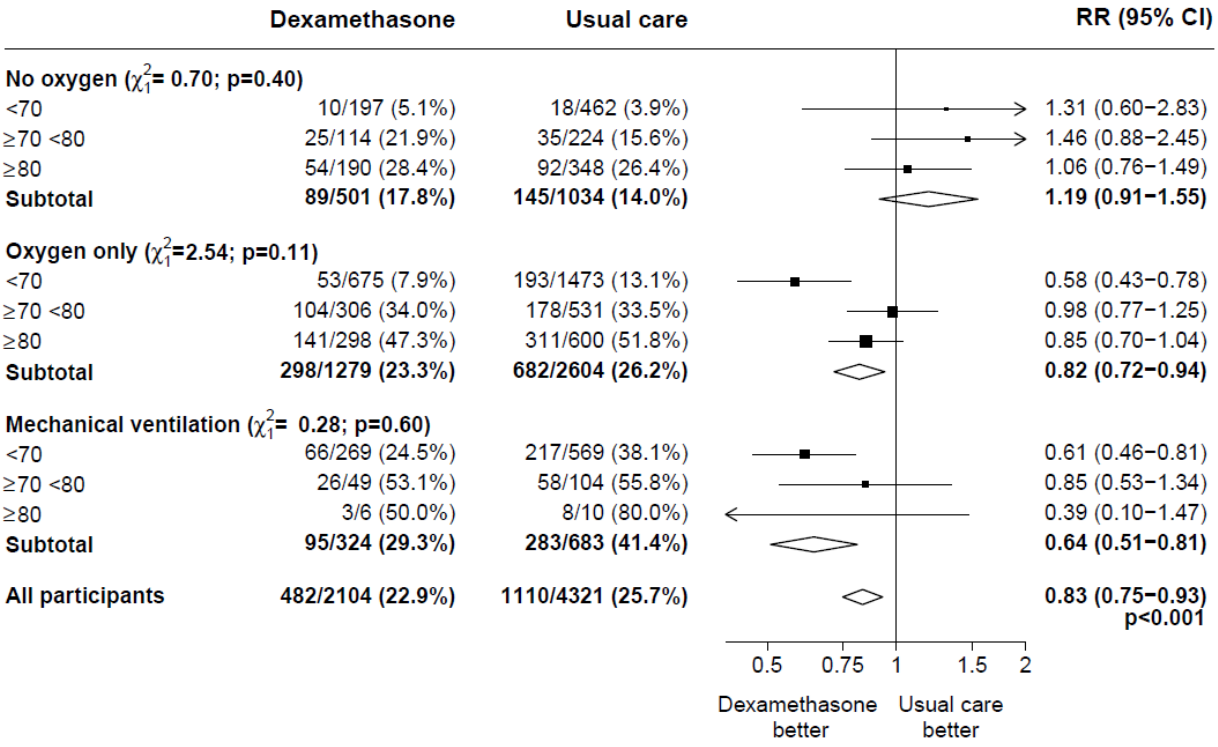
Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (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.

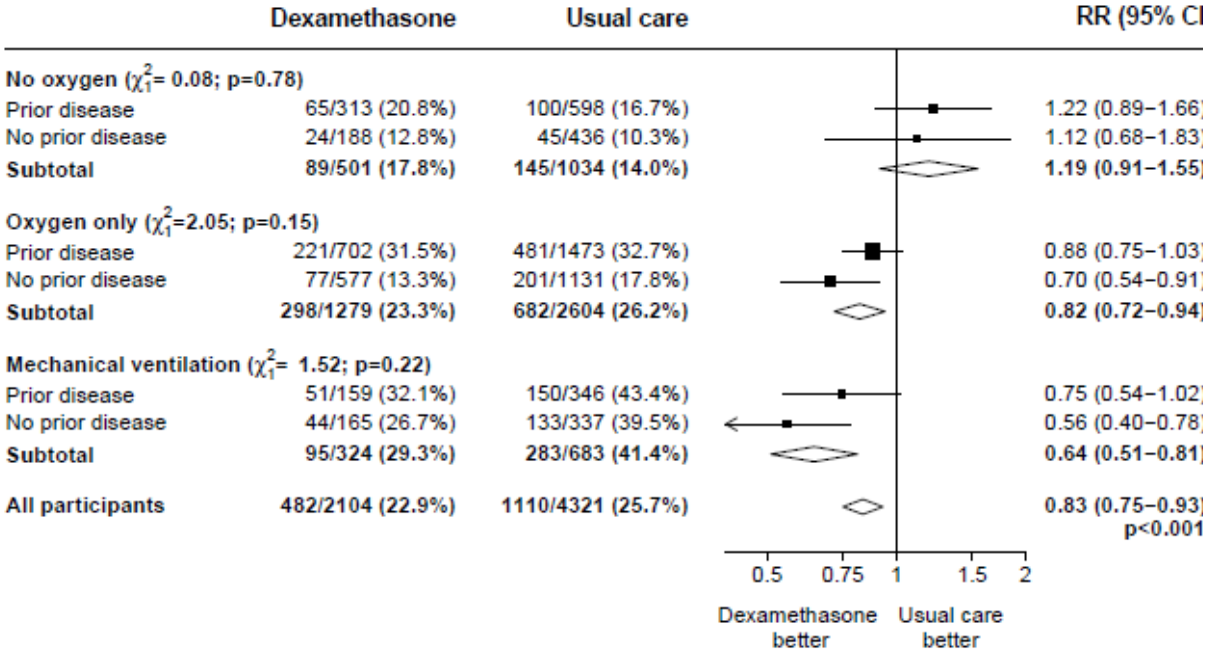
Safety

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]



[1] www.recoverytrial.net

[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

Absorption
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.

Distribution
At very high doses, the largest proportion of the medicine circulates freely in the blood. In hypoalbuminemia, the proportion of unbound (active) corticosteroid increases.

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 Preclinical safety data

Acute toxicity
In mice and rats, the LD_{50} for dexamethasone after a single oral dose is 16 g/kg body weight 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 (see section 4.8)

Mutagenic and tumourigenic potential
The available study findings for glucocorticoids show no evidence of clinically relevant genotoxic properties.

Reproductive toxicity
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
Sorbolac 400
Sodium starch glycolate (Type A)
Magnesium stearate (E572)
Silica, colloidal anhydrous (E551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25ºC. Store in original package in order to protect from light.

6.5 Nature and contents of container

Packed into Alu/PVC/PVDC blisters.

Pack size: 10, 20, 30, 50, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Zentiva Pharma UK Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 17780/1136

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/02/2024

10 DATE OF REVISION OF THE TEXT

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