SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dexamethasone 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg dexamethasone

Excipients with known effect

Each tablet contains 72.5 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, flat bevelled tablets of about 6.0 mm in diameter and 2.5-2.8mm, thickness, debossed ‘D’ on top and ‘2’ underneath on one side and plain on the other side.

4.1 Therapeutic indications

Neurology

Cerebral oedema caused by a brain tumour, neuro-surgical, bacterial meningitis, brain abscess.

Pulmonary and respiratory diseases

Sever acute asthma attack.

Dermatology

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

Autoimmune disorders/rheumatology

Oral initial treatment of autoimmune disorders like systemic lupus erythematodes (especially visceral forms).

Severe progressive form of active rheumatoid arthritis, e.g. rapidly destructive forms and/or extraarticular manifestations.

Infectology

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

Oncology

Palliative treatment of neoplastic diseases.

Endocrinology

Congenital adrenogenital syndrome in adulthood.

COVID-19

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

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 phase of rheumatic system disorders: -Systemic lupus erythematosus 6 -16 mg/day.
- Severe progressive form of active rheumatoid arthritis: -In rapidly destructive forms 12-16 mg / day, with 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 prolong 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 extrem stress (e.g. birth) a 10 fold increase.

Treatment of Covid-19:

Adult patients 6 mg IV or PO, 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 IV or 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.
Method of administration

The tablets should be taken during or after meal They should be swallowed whole, with a sufficient amount of liquid. The daily dose should be administered as a single dose in the morning, if possible (circadian therapy). In patients who require a high-dose therapy because of their disease, multiple daily dosing is often required to achieve maximum effect.
Depending on the underlying disease, clinical symptoms and response to therapy, the dose can be reduced at a faster or slower rate and the therapy stopped, or the patient is stabilised on a maintenance dose as low as possible and, if necessary, adrenal axis monitored. Basically, the dose and duration of treatment should be kept as high and long as necessary, but as low and short as possible. In principle, the dose should be reduced gradually.
In long-term therapy which is deemed necessary following initial treatment, patients should be switched to prednisone/prednisolone, because this leads to lower adrenal suppression.
In hypothyroidism or liver cirrhosis, low doses may be sufficient or a dose reduction may be necessary.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Depending on the dose and duration of therapy, an adrenocortical insufficiency caused by glucocorticoid therapy can continue for serveral months, and in individual cases more than a year, after cessation of therapy. In cases particular physical stress conditions (trauma, surgery, childbirth, etc.) during treatment with dexamethasone, a temporary increase in dose may be required. Because of the potential risk in stressful situation, patients on extended therapy should be issued a steroid card. Also in cases of prolonged adrenal insufficiency after cessation of treatment, the administration of glucocorticoids may be necessary in physically stressful situations. In case case of intended withdrawal, treatment -induced acute adrenal insufficiency may be minimized by slow dose reduction.
Through immunosuppression, treatment with Dexamethasone can lead to an increased risk of bacterial, viral, parasitic, opportunistic and fungal infections. It can mask the symptoms of an existing or developing infection, thereby making a diagnosis more difficult. Latent infections, like tuberculosis or hepatitis B, can be reactivated.
Treatment with dexamethasone should only be implemented in the event of the strongest indications and, if necessary, additional targeted anti-infective treatment administered for the following illnesses:

- Acute viral infections (Herpes zoster, Herpes simplex, Varicella, herpetic keratitis)
- HBsAG-positive chronic active hepatitis

- Approximately 8 weeks prior through 2 weeks after vaccinations with live vaccines
- Systemic mycoses and parasitosis (e.g. Nematodes)
- In patients with suspected or confirmed Strongyloidiasis (infection with threadworm), glucocorticoids can lead to lead activation and mass proliferation of these parasites.
- Poliomyelitis
- Lymphadenitis after BCG vaccination
- Acute and chronic bacterial infections
- In a history of tuberculosis (reactivation risk) use only under tuberculostatic protection

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

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

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

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

Signs of peritoneal irritation after gastrointestinal perforation may be absent in patients receiving high doses of glucocorticoids.
The possibility of a higher need for insulin, or oral antidiabetics, must be taken into consideration when administering dexamethasone to diabetics.
Regular blood pressure monitoring is necessary during treatment with dexamethasone, particularly during administration of higher doses and in patients with high blood pressure that 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.
Serious anaphylactic reactions may occur.
The risk of tendon disorder, tendinitis and tendon rupture is when glucocorticoids and fluoroquinolones are administered together.

A concurrent myasthenia gravis may initially worsen during treatment with Dexamethasone .
Vaccinations with inactivated vaccine are always possible. However, it should be noted that the immune response and thus the vaccine may be compromised at higher doses of corticosteroids.
During long-term treatment with dexamethasone, regular check-ups with doctors (including opthalmologic 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 the treatment, a negative influence on calcium metabolism can be expected, therfore, the prevention of osteoporosis is recommended. This applies especially to patients with concomitant risk factors, such as familial predisposition, advance age, postmenopausal, 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 glucocorticoid, the following risk must be taken account: exacerbation or relapse of the underlying disease, acute adrenal insufficiency, corticosteroid 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 people have contact with people infected with measles or chickenpox while undergoing treatment with dexamethasone, a preventative treatment should be introduced if necessary.
In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.
Visual disturbance

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

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

Therapy should be of limited duration or in case of long-term therapy, it should be carried out alternatingly. .
Preterm neonates: Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours) of premature infants with chronic lung disease at starting doses of 0.25 mg/kg twice daily.
Elderly

Because elderly patients are at an increased risk of osteoporosis, the benefit-risk balance of treatment with Dexamethasone should be carefully weighed.Influence of diagnostic tests
Note
The use dexamethasone can lead to positive results in doping controls.
Dexamethasone tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Ostrogens (e.g. oral contraceptives), The half-life of glucocorticoids may be prolonged. Therefore, the effect of corticoids may be increased.
Antacids: Concomitant administration of aluminum hydroxide or magnesium hydroxide can lead to a reduction in the absorption of glucocorticoids with reduced efficacy of
Dexamethasone. There should be a 2-hour interval between the intake of one and the other drug.
Drug that inducers of CYP3A4, such as barbiturates, rifabutin, rifampicin, phenytoin, primidone and carbamazepine: the effectof corticoids may be reduced.
Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.
Drug that inhibition of CYP3A4, such as Ketoconazole and itraconazole: The effect of corticoids may be increased.
Ephedrine: The metabolism of glucocorticoids may be accelerated and thus their effectiveness reduced.
ACE inhibitors : increased risk of blood count changes.
Cardiac glycosides: The effect of glycosides may be increased by potassium deficiency.

Saluretics/laxatives: Potassium excretion may be increased.

Antidiabetics: The hypoglycaemic effect may be reduced

Coumarin derivatives: The anticoagulants effect mey be reduce or increased. Dosage adjustment of the anticoagulant may be necessary when co-administred.

Nonsteroidal anti-inflammatory drug (NSAIDs), salicylated and indomethacin: The risk of gastrointestinal ulcer and bleeding is increased.

Non-depolarizing muscle relaxants: the muscle relaxing effect may last longer.
Atropine and other anticholinergics: additional intraocular pressure increases are possible during concomitant use.
Praziquantel: Corticosteroids may cause a fall in praziquantel concentration in the blood.
Chloroquine, hydroxychloroquine and mefloquine: Increased risk of myopathies and cardiomyopathies.
Somatropin: The effect of somatropin may be reduced under long-term therapy.
Protirelin: Reduced increase in TSH may be noted during administration of protirelin.

Immunosuppressive agents: Increased susceptibility to infections and possible aggravation or manifestation of latent infections. Additionally, for ciclosporin: The blood levels of cyclosporine are increased: There is an increased risk of seizures.
Fluoroquinolones may increase the risk of tendon disorders.
Effect on investigation methods: Skin reactions in allergy tests can be suppressed

4.6 Fertility, Pregnancy and lactation

Pregnancy:

Dexamethasone crosses the placenta. During pregnancy, especially in the first trimester, the drug should only be administered benefit-risks assesment. In long-term treatment with glucocorticoids during pregnancy,foetal growth disorder cannot be excluded. Administration of corticosteroids to pregnant animals can cause abnormalities in foetal development,. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man (see Section 5.3). If glucocorticoids are administered towards the end of pregnancy, there is a risk of atrophy of the foetal adrenal cortex, which may necessitate replacement therapy in the newborn, which has to be slowly reduced.
Breast-feeding

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

- Very common (≥ 1/10)

- Common (≥ 1/100 to < 1/10)

- Uncommon (≥ 1/1,000 to < 1/100)

- Rare (≥ 1/10,000 to < 1/1,000)

- Very rare (< 1/10,000)

- Not known (cannot be estimated from the available data)

Hormone replacement therapy:

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

Pharmacotherapy:

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

Tabulated list of adverse reactions

	Not known
Infections and infestations	Masking of infection, manifestation and exacerbation of viral infection, fungal infections, bacterial , parasitic and opportunistic infections, activation of strongyloidiasis.
Blood and lymphatic system disorders	Moderate leukocytosis, lymphopenia, eosinopenia, polycythemia.
Immune system disorders	Hypersensitivity reactions (e.g. drug eruption), severe anaphylaxis reaction, 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, plethora,),
Metabolism and nutrition disorders	Sodium retention with oedema, increase potassium excretion (risk of rhythmias) Weight gain, reduce glucose tolerance, diabetes mellitus, hypercholesterolemia and hypertriglyceridaemia, increased appetite,
Psychiatric disorders	Depression, irritability, euphoria, increased drive, psychoses, mania, hallucination, emotional liability, anxiety, sleep disorder, suicidality.
Nervous system disorders	Pseudotumor cerebri, manifestation of latent epilepsy, increased seizures 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), increase capillary fragility .
Gastrointestinal disorders	Gastrointestinal ulcers, Gastrointestinal bleeding, pancreatitis, stomach discomfort, hiccups
Skin and subcutaneous tissue disorders	Striaerubra, atrophy, telangiectasia, 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, endon 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 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

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

5.1 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 7.5 times greater than prednisolone and, like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive properties.
Glucocorticoids, such as dexamethasone, exert their biological effects by activating the transcription of corticosteroid-sensitive genes. The antiinflammatory, immunosuppressive and anti-proliferative effects are caused by decreased formation, release and activity of inflammatory mediators, by the inhibition of specific functions and the migration of inflammatory cells. In addition, the effect of sensitized T lymphocytes and macrophages on target cells may be prevented by corticosteroids.
Dexamethasone has a biological half-life of 36 - 54 hours and therefore is suitable in conditions where continuous glucocorticoid action is required.

Treatment of COVID-19

The RECOVERY trial (Randomised Evaluation of COVid-19 thERapY,) [Dexamethasone in Hospitalized Patients with Covid-19, N Engl J Med 2021;384:693-704] 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-CoV2 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).

Primary and Secondary Outcomes and Prespecified Subsidiary Clinical Outcomes

Outcome	Dexamethasone (N = 2104)	Usual Care (N = 4321)	Rate or Risk (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Death 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	1416/2104 (67.3)	2748/4321 (63.6)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	462/1780 (26.0)	1003/3638 (27.6)	0.93 (0.85–1.01)
Invasive mechanical ventilation	110/1780 (6.2)	298/3638 (8.2)	0.79 (0.64–0.97)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)
Subsidiary clinical outcomes			
Use of ventilation‡	25/501 (5.0)	65/1034 (6.3)	0.84 (0.54–1.32)
Non-invasive ventilation	20/501 (4.0)	57/1034 (5.5)	0.77 (0.47–1.26)
Invasive mechanical ventilation	9/501 (1.8)	19/1034 (1.8)	1.07 (0.49–2.34)
Successful cessation of invasive mechanical ventilation§	160/324 (49.4)	268/683 (39.2)	1.47 (1.20–1.78)
Renal-replacement therapy¶	89/2034 (4.4)	314/4194 (7.5)	0.61 (0.48–0.76)

* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation. Risk ratios have been adjusted for age with respect to the outcomes of invasive mechanical ventilation or death (and its subcomponents), use of ventilation, and renalreplacement therapy.
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization. ‡ Excluded from this category are patients who were receiving oxygen (since some patients in this category were receiving non-invasive ventilation) or invasive mechanical ventilation at randomization.
§ Excluded from this category are patients who were not receiving invasive mechanical ventilation at randomization.
¶ Excluded from this category are patients who were receiving renal-replacement therapy at randomization

Secondary endpoints

Patients in the dexamethasone group had a shorter duration of hospitalisation 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).

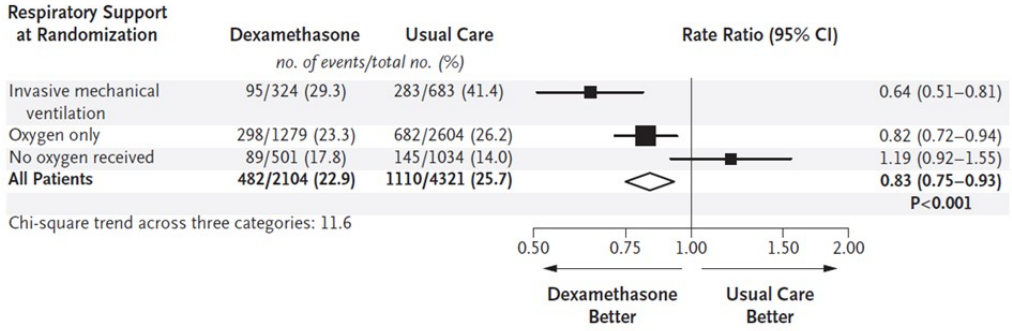
In line with the primary endpoint the greatest effect regarding discharge within 28 days was seen among patients who were receiving invasive mechanical ventilation at randomization (rate ratio 1.48; 95% CI 1.16, 1.90), followed by oxygen only (rate ratio, 1.15 ;95% CI 1.06- 1.24) with no beneficial effect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

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

Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.



Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen with or without non-invasive ventilation, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

Source: Dexamethasone in Hospitalized Patients with Covid-19, N Engl J Med 2021;384:693-704

5.2 Pharmacokinetic properties

Absorption and distribution

After oral administration, dexamethasone is rapidly and almost completely absorbed in the stomach and small intestine. Its bioavailability is 80–90%. Maximum blood levels are reached between 60 and 120 minutes. The binding of dexamethasone to plasma albumins is dose-dependent. At very high doses, the largest portion circulates freely in the blood. In hypoalbuminaemia the proportion of the unbound (active) corticoid rises.

Biotransformation

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

Elimination

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

Renal and hepatic impairment

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

5.3 Preclinical safety data

Acute toxicity:

In mice and rats, the LD50 for dexamethasone after a single oral dose is 16 g/kg body and over 3 g/kg body weight, respectively, within the first 7 days.

Following a single subcutaneous dose, the LD50 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. Corticoidinduced 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 tumorigenic potential:

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

Reproductive toxicity:

In animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates, but 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, intra-uterine growth can be delayed. All these effects were seen at high dosages.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Maize starch

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

Bottle once opened: 100 days

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original container to protect from light and moisture.

6.5 Nature and contents of container

Blister pack: Opaque PVC film and Al foil

Container pack: HDPE container and HDPE lid

Pack sizes:

28, 30, 50, 100 tablets in blister pack

28, 30, 50, 100 tablets in container

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited

11 Boumpoulinas Street

Nicosia 1060 Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0238

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/02/2022

10 DATE OF REVISION OF THE TEXT

03/06/2024