Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dexamethasone phosphate 4 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains 3.32 mg of dexamethasone (as dexamethasone sodium phosphate) which is equivalent to 4 mg of dexamethasone phosphate or 4.37 mg dexamethasone sodium phosphate.
Each 2 ml ampoule contains 6.64 mg of dexamethasone (as dexamethasone sodium phosphate) which is equivalent to 8 mg of dexamethasone phosphate or 8.74 mg dexamethasone sodium phosphate.

Excipient with known effect
Each ml of solution contains about 3 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear, colourless solution free from visible particles.
pH of solution between 7.0 – 8.5
Osmolality 270-310 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Systemic use

Dexamethasone phosphate solution for injection/infusion is often used following emergency treatment initiated at high dose:

- Treatment and prophylaxis of cerebral oedema in brain tumours (postoperatively and after X-ray radiation) and after spinal cord trauma.
- State of anaphylactic shock (e.g. contrast medium reaction) in combination with adrenaline, antihistamines and appropriate volume replacement (caution: mixed syringes).
- Polytraumatic shock / prophylaxis of post-traumatic shock lung.
- Severe exacerbations of asthma (only with concomitant sympathomimetics).
- Acute severe dermatosis (e.g. pemphigus vulgaris, erythroderma).
- Severe blood diseases (e.g. acute thrombocytopenic purpura, haemolytic anaemia, as concomitant medication as part of leukaemia treatments).
- As second-line treatment for acute adrenocortical insufficiency (Addisonian crisis).

Dexamethasone phosphate 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.

2. Local use

- Periarticular and infiltrative therapy, e.g. in periarthritis scapulohumeralis, epicondylitis, bursitis, tendovaginitis, styloiditis.
- Intraarticular injection, e.g. in rheumatoid arthritis, if individual joints are affected or respond inadequately to systemic treatment, accompanying inflammatory reactions in rheumatoid arthritis.

4.2 Posology and method of administration

Posology

Posology depends on the severity of pathological symptoms, the patient's individual response and, in intraarticular use, the size of the joint.

Glucocorticoids should only be used for as long – and only at such low doses – as absolutely necessary to achieve and maintain the desired therapeutic effect.

In case high doses are required in a single treatment, use of dexamethasone containing medicinal products with higher strengths/volume should be considered.

All dosage recommendations are given in units of dexamethasone phosphate.

1. Systemic use

For **treatment and prophylaxis of cerebral oedema in brain tumours (postoperatively and after X-ray radiation) and after spinal cord trauma**
Depending on cause and severity the initial dose is 8-10 mg (up to 80 mg) IV, then 16-24 mg (up to 48 mg)/day divided into 3-4 (6) single doses IV over 4-8 days. Long-term, lower-dose administration of dexamethasone phosphate may be necessary during radiation therapy and in the conservative treatment of inoperable brain tumors.

For **anaphylactic shock**, first adrenaline injection IV, then 40-100 mg (children 40 mg) IV injection, repeated as necessary.

Polytraumatic shock / prophylaxis of post-traumatic shock lung
Initially 40-100 mg (children 40 mg) IV, repetition of the dose after 12 hours, or every 6 hours 16-40 mg for 2-3 days.

For **severe exacerbations of asthma**, 8-40 mg IV as early as possible; if needed, repeated injections of 8 mg every 4 hours.

For **acute severe dermatosis** and **severe blood diseases**, initial treatment with 20-40 mg dexamethasone phosphate IV and further treatment depending on the severity of the case, with the same daily dose or lower doses within the first few days and switch to oral therapy.

For treatment of **acute adrenocortical insufficiency** (Addisonian crisis), initiation of therapy with 4-8 mg dexamethasone phosphate IV.

For the treatment of COVID-19
Adult patients: 6 mg IV, once a day for up to 10 days.

Elderly, renal impairment, hepatic impairment (at low dose (6 mg daily) and short duration): No dose adjustment is needed.

Paediatric population: Paediatric patients (adolescents aged 12 years and older with body weight at least 40 kg) are recommended to use 6 mg IV, once a day for up to 10 days.
Duration of treatment should be guided by clinical response and individual patient requirements.

2. Local use

For local infiltrative, periarticular and intraarticular therapy under strictly aseptic conditions, injection of 4 mg or 8 mg dexamethasone phosphate. For injection into a small joint, 2 mg dexamethasone phosphate is sufficient. Depending on the severity of the disease, no more than 3-4 infiltrations or 3-4 injections per joint should be performed. The interval between injections should be not less than 3-4 weeks.

Renal impairment

No dosage adjustment is necessary in patients with impaired renal function (see also section 5.2).

Hepatic impairment

In patients with severe liver disease dose adjustment may be necessary (see also section 5.2).

Paediatric population

In children up to 14 years of age, a 4-day treatment-free interval (intermittent therapy) should be inserted after each 3-day course of treatment, during long-term treatment, due to the risk of growth disorders.

Method of administration

For intravenous, intramuscular, intraarticular or local use (infiltration).
Dexamethasone phosphate solution for injection/infusion is usually administered slowly (2-3 minutes) intravenously in acute diseases, by injection or infusion. However, it can also be administered intramuscularly (only in exceptional cases), as a local infiltration or intraarticularly.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of listed in section 6.1.
- Systemic fungal infection; systemic infection unless specific anti-infective therapy is employed.

Intraarticular injection is contraindicated in cases of:

- infections within or in the immediate vicinity of the joint to be treated;
- bacterial arthritis;
- instability of the joint to be treated;
- bleeding diathesis (spontaneous or due to anticoagulants);
- periarticular calcification;
- avascular osteonecrosis;
- tendon rupture;
- Charcot's joint.

Infiltration without additional causal therapy is contraindicated in the presence of infections within the area of administration.

4.4 Special warnings and precautions for use

Acute adrenocortical insufficiency
Abrupt discontinuation of treatment lasting for more than 10 days can lead to the onset of acute adrenocortical insufficiency. The dose should therefore be reduced slowly if discontinuation is envisaged. Depending on the dose and duration of therapy, adrenocortical insufficiency caused by glucocorticoid therapy may still persist for several months and, in individual cases, for more than one year after discontinuation of therapy.

If particular physical stress situations (e.g. accident, surgery, childbirth) occur during treatment with dexamethasone phosphate, a temporary dose increase may become necessary. Administration of glucocorticoids may also be required in physical stress situations if adrenocortical insufficiency persists after the end of therapy.

Risk of bacterial, viral, fungal, parasitic and opportunistic infections
Treatment with dexamethasone phosphate can increase the risk of bacterial, viral, fungal, parasitic and opportunistic infections due to the immunosuppressive effect.
Symptoms of a manifest or developing infection can be masked, which may make diagnosis more difficult. Particular caution is required in acute viral infections (hepatitis B, herpes zoster, herpes simplex, varicella, herpetic keratitis). In case of acute and chronic bacterial infections, targeted antibiotic therapy should be used.

Latent infections, such as tuberculosis or hepatitis B, may be reactivated. In patients with a history of tuberculosis, dexamethasone should be used only with tuberculostatic prophylaxis.
In case of systemic mycoses, concomitant antifungal therapy should be used.
In case of certain parasitic diseases (amoebic infection, nematodes), concomitant antiparasitic therapy should be used. In patients with known or suspected threadworm infection, glucocorticoids can lead to activation and proliferation.

Simultaneous use of corticosteroids
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.

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.

Special care is required in the following situations:

- Approximately 8 weeks before and up to 2 weeks after prophylactic vaccinations with live vaccines: The course of viral diseases may be particularly severe in patients treated with dexamethasone. Especially at risk are immunocompromised (immunosuppressed) children, as well as individuals who have not yet had measles or chickenpox. If such individuals come into contact with persons with measles or chickenpox during treatment with dexamethasone, they should consult their physician immediately, who may institute preventive treatment as necessary. See also 'Vaccinations' below.
- Osteoporosis: Depending on the dosage and duration of treatment, a negative effect on calcium metabolism must be anticipated; hence, supplementary calcium administration is necessary and vitamin D is recommended. Additional treatment should be considered in patients with pre-existing osteoporosis. In patients with severe osteoporosis, use only in life-threatening situations or over short periods. In elderly patients, a specific benefit/risk analysis should be made and vigilance is required for undesirable effects such as osteoporosis.
- Diabetes mellitus: Clinical surveillance and adjustment of antidiabetic therapy.
- Psychiatric history, including risk of suicide (either past or present): Neurological or psychiatric surveillance is proposed.
- Renal impairment: Concomitant effective therapy of the underlying disease and ongoing monitoring.
- Myasthenia gravis: Initial aggravation of symptoms after corticosteroid administration is possible; hence, careful and cautious selection of the starting dose.

Gastrointestinal disorders
In patients with gastrointestinal ulcers, concomitant treatment with antiulcer agents, as well as careful observation (including X-ray monitoring or gastroscopy) is indicated.

Due to the risk of intestinal perforation, dexamethasone phosphate may be used only when clearly indicated, together with appropriate monitoring, in patients with:

- severe ulcerative colitis with imminent perforation;
- abscess formation or purulent infections;
- diverticulitis;
- intestinal anastomosis (immediately postoperatively).

Signs of peritoneal irritation secondary to gastrointestinal perforation may be absent in patients on high glucocorticoid doses.

Risk of tendon disorders
The risk of tendon disorders, tendinitis and tendon rupture increases with concomitant oral use of fluoroquinolones and corticosteroids.

Vaccinations
In principle, vaccinations with inactivated vaccines are possible. However, it should be remembered that the immune response and hence the success of vaccination at higher corticosteroid dosages may be compromised.

Risk of anaphylactic reactions
Severe anaphylactic reactions may occur.

Long-term therapy
In long-term therapy, regular medical check-ups (including ophthalmological check-ups at three-monthly intervals) are indicated; at comparatively high doses, care should be taken to ensure adequate potassium intake and sodium restriction, and serum potassium levels must be monitored.

Pregnancy
Women should notify their physician if they are or become pregnant.

Cardiovascular disorders
Careful surveillance is indicated in patients with severe heart failure.
In case of difficult-to-control hypertension, combined antihypertensive treatment and regular monitoring is required.
Bradycardia can occur with high dexamethasone doses.
In patients with heart failure, concomitant effective therapy of the underlying disease and ongoing monitoring is required.

Hypertrophic cardiomyopathy
Hypertrophic cardiomyopathy was reported after systemic administration of corticosteroids including dexamethasone to prematurely born infants. In the majority of cases reported, this was reversible on withdrawal of treatment. In preterm infants treated with systemic dexamethasone diagnostic evaluation and monitoring of cardiac function and structure should be performed (see section 4.8).

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

Tumor lysis syndrome (TLS)
In post-marketing experience, tumour lysis syndrome (TLS) has been observed in patients with malignant haematological diseases after the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with a high proliferation rate, high tumour burden and high sensitivity to cytostatics, should be closely monitored and treated with appropriate precautions.

Visual disturbances
Visual disturbances may occur with the systemic and topical use of corticosteroids. If a patient presents with symptoms such as blurred vision or other visual disturbances, consideration should be given to referring the patient to an ophthalmologist for evaluation of possible causes; these may include cataracts, glaucoma or rare diseases, e.g. central serous chorioretinopathy (CSC), which have been reported after the use of systemic or topical corticosteroids.
Special caution should be observed in patients with closed- and open-angle glaucoma. In case of corneal ulceration and injury, close ophthalmological monitoring and therapy is required.

Elderly patients
In elderly patients, a specific benefit/risk analysis should be made and vigilance is required for undesirable effects such as osteoporosis.

Paediatric population
Premature infants: Available data indicate long-term undesirable effects on neuronal development after early treatment (< 96 hours) of premature infants with chronic lung disease at dosages of 0.25 mg/kg twice daily at the start of treatment.
Growing children and adolescents should not be treated unless strictly indicated.

Information related to specific methods of administration
Intramuscular use
Dexamethasone phosphate should only be administered intramuscularly in exceptional cases for the following reasons:

- local intolerability and tissue wasting (adipose tissue and muscle atrophy) are possible;
- uncertainty in dosage: initially excessive dose, later insufficient effect.

Intravenous use
With intravenous use, dexamethasone phosphate should be injected slowly (2-3 minutes), as too rapid administration is more likely to result in brief secondary effects in the form of unpleasant tingling or paraesthesia, which are *per se* harmless and last for up to 3 minutes.

Intraarticular administration
Intraarticular administration of glucocorticoids increases the risk of articular infections. Prolonged and repeated use of glucocorticoids in weight-bearing joints can lead to a worsening of degenerative changes within the joint. One possible cause is overloading of the affected joint after regression of pain or other symptoms.

Local use
In local use, vigilance is required for possible systemic adverse reactions and interactions.

Excipients
This medicinal product contains about 3 mg sodium per ml of solution, equivalent to 0.15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
As this medicinal product may be diluted with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products and other forms of interaction

Digitalis glycosides:	Glycoside effect potentiated due to potassium deficiency
Saluretics:	Additional potassium excretion
Antidiabetics:	Glycaemic reduction decreased
Coumarin derivatives:	Anticoagulant effect attenuated or increased. Dose adjustment is necessary when it is concomitantly administered
Ephedrine:	Corticosteroid effect reduced
Rifampicin, phenytoin, carbamazepine, barbiturates, primidone and other medicinal products that induce CYP3A4:	Corticosteroid effect reduced
Ketoconazole, itraconazole, ritonavir, cobicistat, macrolide antibiotics and other medicinal products that inhibit CYP3A4:	During concomitant treatment with CYP3A inhibitors, including products containing cobicistat, an increased risk of systemic adverse reactions can be anticipated. Such combinations should be avoided, unless the benefit outweighs the increased risk of adverse systemic

	reactions to corticosteroids; in which case, patients should be monitored for systemic corticosteroid effects
Non-steroidal anti-inflammatory drugs/antirheumatic agents (e.g. salicylates and indometacin):	Increased gastrointestinal ulceration and risk of bleeding
Contraceptives containing oestrogen:	Corticosteroid effect increased
Praziquantel:	Reduction in blood praziquantel concentrations possible
ACE inhibitors:	Increased risk for the onset of blood dyscrasias
Chloroquine, hydroxychloroquine, mefloquine:	Increased risk for the onset of myopathy, cardiomyopathy
Somatropin:	Somatropin effect reduced in long-term administration
Laxatives:	Increased potassium loss
Atropine, other anticholinergics:	Additional increase in intraocular pressure not excluded
Non-depolarising muscle relaxants:	Muscle relaxation may be prolonged
Immunosuppressive agents (ciclosporin):	Increased susceptibility to infections and aggravation or manifestation of latent infections. With ciclosporin, there is an additionally increased risk of cerebral seizures
Bupropion:	Co-administration with systemic glucocorticoids can increase the

	risk of seizures
Fluoroquinolones:	Risk of tendon disorders, tendonitis and tendon ruptures is increased

Effect on testing methods:
Skin reactions to allergy tests may be suppressed.
Protirelin: The rise in TSH when protirelin is administered may be reduced.

If glucocorticoid treatment is administered 8 weeks before or up to 2 weeks after active immunisation, attenuation or absence of immunisation can be expected.

4.6 Fertility, pregnancy and lactation

Pregnancy
Dexamethasone crosses the placenta. During pregnancy, especially in the first three months, it should only be used after a careful benefit/risk assessment. Dexamethasone phosphate should be used during pregnancy only in life-threatening situations. In long-term treatment with glucocorticoids during pregnancy, foetal growth disorders cannot be excluded. Administration of corticosteroids to pregnant animals can cause malformations of foetal development, including cleft palates, intrauterine growth retardation and effects on growth and brain development. There are no indications that corticosteroids lead to an increased incidence of congenital abnormalities such as cleft palate/cleft lip in humans. See also section 5.3. If glucocorticoids are given at the end of pregnancy, there is a foetal risk of adrenocortical atrophy, which may necessitate tapered replacement therapy in the neonate. Studies have shown an increased risk of neonatal hypoglycaemia following antenatal administration of a short course of corticosteroids including dexamethasone to women at risk for late preterm delivery.

Breast-feeding
Glucocorticoids are excreted in human milk. No harm to the infant has been reported to date. Nevertheless, they should be used only when strictly indicated during breast-feeding. If higher doses are required on account of the disease, breast-feeding should be discontinued.

Fertility
No fertility studies have been performed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The risk of undesirable effects is low with short-term dexamethasone therapy. However, vigilance is required for gastrointestinal ulcers (often stress-related) which, as a result of the corticosteroid treatment, may produce few symptoms, as well as for signs of reduced glucose tolerance and resistance to infections.

Especially in long-term treatment (longer than about 2 weeks), adverse reactions to glucocorticoids can occur, which, as an exaggerated hormonal effect, are similar to Cushing's syndrome.

The following adverse reactions may occur, which are highly dependent on the dose and duration of therapy and whose frequency is therefore not known (cannot be estimated from the available data):

Infections and infestations
Masking of infections, manifestation, proliferation or reactivation of infections (bacterial, viral, fungal and parasitic and opportunistic infections), threadworm activation (see section 4.4).

Blood and lymphatic system disorders
Blood dyscrasias (moderate leukocytosis, lymphocytopenia, eosinopenia, polycythaemia).

Immune system disorders
Hypersensitivity reactions (e.g. exanthema), severe anaphylactic reactions such as arrhythmias, bronchospasm, hypo- or hypertension, circulatory collapse, cardiac arrest, weakening of the immune system.

Endocrine disorders
Cushing's syndrome (e.g. moon face, truncal obesity), adrenocortical inactivation or atrophy.

Metabolism and nutrition disorders
Sodium retention with oedema formation, increased potassium excretion (caution: arrhythmias), weight gain, reduced glucose tolerance, diabetes mellitus, increased appetite, hypercholesterolemia and hypertriglyceridemia.

Psychiatric disorders
Psychosis, depression, irritability, euphoria, sleep disorders, lability, anxiety, mania, hallucinations, suicidal ideation.

Nervous system disorders
Pseudotumor cerebri, manifestation of latent epilepsy and increased seizure susceptibility in cases of manifest epilepsy.

Eye disorders
Increased intraocular pressure (glaucoma), lens opacity (cataract). Aggravation of corneal ulcer symptoms, promotion of viral, fungal and bacterial eye inflammation, aggravation of bacterial inflammation of the cornea, ptosis, mydriasis, chemosis, iatrogenic scleral perforation, chorioretinopathy. In very rare cases, reversible exophthalmos (see also section 4.4).

Cardiac disorders
Hypertrophic cardiomyopathy in prematurely born infants (see section 4.4).

Vascular disorders
Hypertension, increased risk of atherosclerosis and thrombosis, blood vessel inflammation (vasculitis, also as a withdrawal symptom after long-term therapy), capillary fragility.

Gastrointestinal disorders
Stomach upset, activation and development of gastric ulcer or duodenal ulcer, pancreatitis (in predisposed patients, e.g. due to alcoholism), gastrointestinal bleeding, risk of perforation in ulcerative colitis.

Skin and subcutaneous tissue disorders
Stretch marks (striae rubra), skin thinning (atrophy), pinpoint bleeding under the skin (petechiae), bruising (ecchymosis), steroid acne, perioral dermatitis, telangiectasia, hypertrichosis, changes in skin pigmentation.

Musculoskeletal and connective tissue disorders
Muscle weakness, muscle wasting (atrophy), myopathy, tendon disorders, tendinitis, tendon rupture, osteoporosis, aseptic osteonecrosis, growth retardation in children, epidural lipomatosis.

Reproductive system and breast disorders
Disorders of sex hormone secretion (amenorrhoea, hirsutism, impotence).

General disorders and administration site conditions
Delayed wound healing.

Local use: Local irritation and signs of intolerability are possible (sensations of heat, prolonged pain), especially in ocular use. The development of skin atrophy and subcutaneous tissue atrophy at the injection site cannot be excluded if corticosteroids are not injected carefully into the joint cavity.

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

There are no known cases of acute intoxication with dexamethasone. In the event of overdose, increased adverse reactions (see section 4.8) can be expected, especially on the endocrine system, metabolism and electrolyte balance. There is no known antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Dexamethasone is a monofluorinated glucocorticoid with marked anti-allergic, anti-inflammatory and membrane-stabilising properties, as well as effects on carbohydrate, protein and lipid metabolism.

With a biological half-life of over 36 hours, dexamethasone belongs to the very long-acting glucocorticoids. Due to its long duration of action, dexamethasone can lead to accumulation and overdosing when continuously administered daily.

Dexamethasone possesses a glucocorticoid effect approximately 7.5 times more potent than prednisolone and prednisone; compared with hydrocortisone, it is 30 times more potent; it has no mineralocorticoid effects.

Glucocorticoids such as dexamethasone exert their biological effect by activating the transcription of corticosteroid-sensitive genes. The antiinflammatory, immunosuppressant and antiproliferative effects are induced by factors such as reduced formation, release and activity of inflammatory mediators and by inhibition of specific functions and migration of inflammatory cells. In addition, the effect of sensitised T-lymphocytes and macrophages on target cells by corticosteroids is possibly prevented.

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 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.

[1] www.recoverytrial.net

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 to 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 receipt of invasive mechanical ventilation or death and its subcomponents.

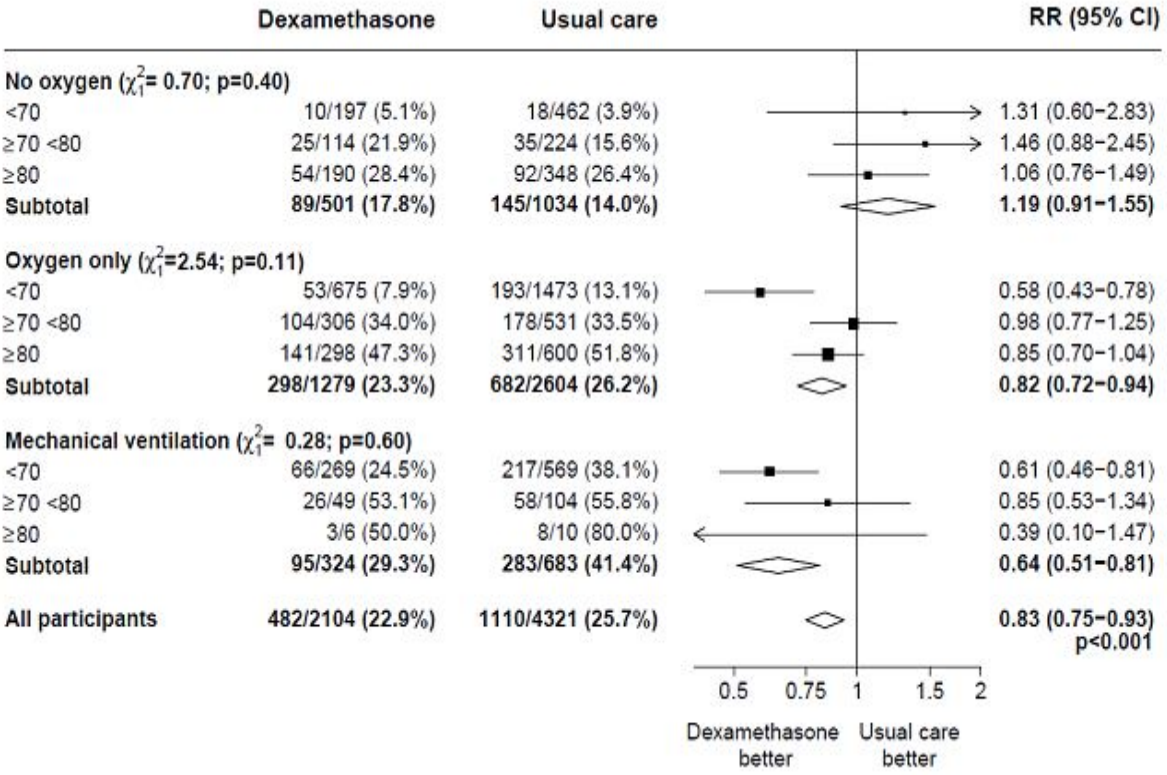
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization..

Safety

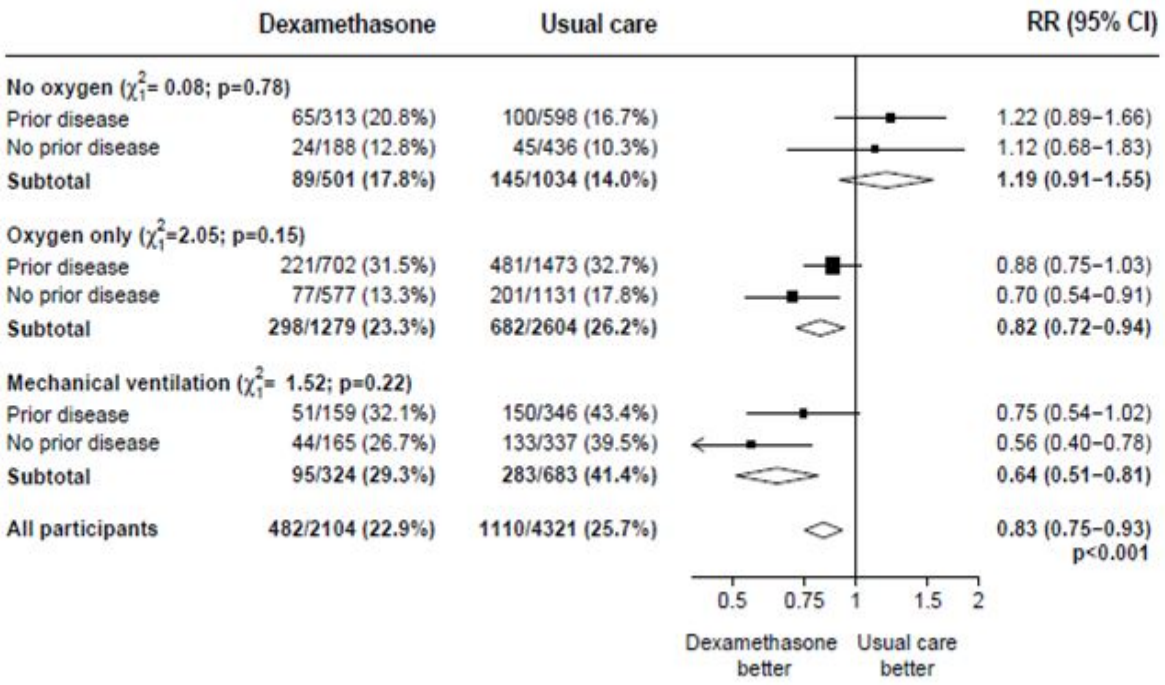
There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved.

Subgroup analyses

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



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



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

5.2 Pharmacokinetic properties

Distribution

Dexamethasone is dose-dependently bound mainly to plasma albumins. At very high concentrations, the major fraction is available freely in blood, i.e. not bound to proteins. In cases of hypoalbuminemia, the fraction of unbound (active) corticosteroid increases.

Cerebrospinal fluid (CSF) penetrability

In humans, peak dexamethasone CSF levels approximately 1/6 of concomitant plasma concentrations are measured four hours after intravenous administration of radioactively labelled dexamethasone.

Placental transfer

Like all glucocorticoids, dexamethasone can cross the placental barrier but, in contrast to most other corticosteroids, it is not metabolised.

Excretion in human milk

No data are available on dexamethasone. Small amounts of glucocorticoids are excreted in human milk, with infant exposure generally less than 1/100 of the dose systemically available in the breast-feeding mother. Nevertheless, with the use of higher doses or during long-term treatment, breastfeeding should be discontinued.

Biotransformation

Following intravenous injection of dexamethasone phosphate, ester cleavage is very rapid. Peak values of the free dexamethasone alcohol are measured after 10 minutes.
It is partly metabolised by conjugation with glucuronic or sulphuric acid in the liver with subsequent excretion mainly via the kidneys.

Elimination

The mean serum elimination half-life of dexamethasone in adult humans is 4.1±1.3 hours. Dexamethasone is largely eliminated via the kidneys in the urine as free dexamethasone alcohol. Kidney damage does not significantly affect dexamethasone elimination. In severe hepatic diseases, e.g. hepatitis, cirrhosis of the liver, as well as during pregnancy and oestrogen administration, the elimination half-life of glucocorticoids is prolonged.
In humans, dexamethasone phosphate is mainly excreted as dexamethasone. To a minor extent, the molecules are hydrogenated or hydroxylated, resulting in the main metabolites 6-hydroxydexamethasone and 20-dihydrodexamethasone. In humans, 30-40% of the amount excreted in the urine is bound to glucuronic acid or sulphuric acid.

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

Reproductive toxicity
In animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates; not in horses and sheep. In some cases these divergences were combined with defects of the central nervous system and 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

Creatinine
Sodium citrate (for pH adjustment)
Disodium edetate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

After opening the ampoule: Once opened, the medicinal product should be used immediately.

Shelf life after dilution
Chemical and physical in-use stability has been demonstrated for 48 hours at 25 °C (protected from light) and 2 to 8 °C.
From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30 °C.
Keep the ampoules in the outer carton in order to protect from light.

For storage conditions after opening of the ampoule, see section 6.3.

6.5 Nature and contents of container

The solution for injection is filled in 1 ml or 2 ml Type I clear colourless glass ampoules with one point cut. Ampoules are marked with a specific colour ring code.
Ampoules are packed in liners. Liners are packed in outer cartons.

Pack sizes:
3, 10, 25, 50 or 100 ampoules of 1 ml
5, 10, 25, 50 or 100 ampoules of 2 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

Once opened, the medicinal product should be used immediately. Any remaining contents should be discarded.

The medicinal product should be visually inspected prior to use. Only clear solutions free from particles should be used.

Dexamethasone phosphate solution for injection/infusion should preferably be administered by the direct intravenous route or injected into the infusion tube. However, the solutions for injection are compatible with the following solutions for infusion (250 ml and 500 ml):

- 9 mg/ml (0.9%) sodium chloride solution
- 50 mg/ml (5%) glucose solution
- Ringer's solution.

When combining with solutions for infusion, information from the respective manufacturers on their solutions for infusion, including data on compatibility, contraindications, undesirable effects and interaction, must be taken into account.

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

7 MARKETING AUTHORISATION HOLDER

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1057
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8 MARKETING AUTHORISATION NUMBER

PA2165/014/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th March 2022

10 DATE OF REVISION OF THE TEXT

April 2023