Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dexamethasone phosphate Teva 4 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains 4.37 mg dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.3 mg dexamethasone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Systemic use

Neurology
Cerebral oedema (only with confirmed cerebral symptoms based on CT scan) caused by cerebral tumour, neurosurgical procedures, brain abscess, bacterial meningitis

Emergency treatment
Post-traumatic shock/prevention of post-traumatic acute respiratory distress syndrome

Anaphylactic shock (following primary epinephrine injection)

Lung and respiratory diseases
Severe acute asthma attack, interstitial aspiration pneumonia

Dermatology
Parenteral initial treatment of extensive, severe, acute skin diseases, including erythroderma, pemphigus vulgaris, acute eczema

Autoimmune diseases/Rheumatology
Parenteral initial treatment of autoimmune diseases, including systemic Lupus erythematodes, especially visceral forms

Active phases of systemic vasculitis, including polyarteritis nodosa (duration of treatment should be limited to 2 weeks in the case of simultaneous positive hepatitis B serology)

Severe progressive form of active rheumatoid arthritis, e.g. rapidly destructive forms and/or with extra-articular manifestations

Juvenile idiopathic arthritis with severe systemic variant (Still's syndrome) or iridocyclitis unable to be influenced locally

Rheumatic fever with carditis

Infectiology

Severe infectious diseases with toxic states (e.g. tuberculosis, typhoid, brucellosis; only with concomitant anti-infective therapy)

Oncology
Palliative therapy of malignant tumours

Prevention and treatment of post-operative or cytostatic agent-induced vomiting within the scope of antiemetic regimens.

Treatment of Covid-19
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.

Local use

Intraarticular injection
Persistent inflammation in one or several joints following general treatment of chronic inflammatory joint diseases, activated arthrosis, acute forms of periarthritis humeroscapularis

Infiltration therapy (strict indication)
Non-bacterial tendovaginitis and bursitis, periarthropathies, insertional tendinopathies

Ophthalmology
Subconjunctival administration in cases of non-infectious keratoconjunctivitis, scleritis (with the exception of necrotising scleritis), anterior and intermediate uveitis.
The ampoules with 2 ml solution for injection are not suitable for subconjunctival use.

4.2 Posology and method of administration

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:

Systemic use:
Neurology
Cerebral oedema
Depending on the cause and severity, initial dose of 8–10 mg (up to 80 mg) IV, followed by 16–24 mg (up to 48 mg)/day IV, 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.

Emergency treatment
Post-traumatic shock/prevention of post-traumatic acute respiratory distress syndrome
Initial IV dose of 40–100 mg (children 40 mg) repeated after 12 hours or 16–40 mg every 6 hours for 2–3 days.

Anaphylactic shock
Following primary epinephrine IV injection, 40–100 mg IV (children 40 mg), repeated if required.

Lung and respiratory diseases
Severe acute asthma attack

Adults
8–20 mg IV as soon as possible, then 8 mg injections repeated every 4 hours if required.
Children
0.15–0.3 mg/kg body weight IV or oral or 1.2 mg/kg body weight as an initial bolus followed by 0.3 mg/kg body weight every 4–6 hours.
Aminophylline and secretolytic agents may be administered concomitantly.

Interstitial aspiration pneumonia
Initial IV dose of 40–100 mg (children 40 mg) repeated after 12 hours or 16–40 mg every 6 hours for 2–3 days.

Dermatology

Acute skin diseases

Depending on the nature and extent of the disease, daily doses of 8–40 mg IV, up to 100 mg in individual cases. Followed by oral treatment with decreasing doses.

Autoimmune diseases/Rheumatology

Polyarteritis nodosa

6–15 mg/day (duration of treatment should be limited to 2 weeks in the case of simultaneous positive hepatitis B serology).

Active phases of systemic rheumatic diseases

Systemic lupus erythematosus 6–16 mg/day.

Severe progressive form of active rheumatoid arthritis

In rapidly destructive forms 12–16 mg/day, in extra-articular manifestations 6–12 mg/day.

Juvenile idiopathic arthritis with severe systemic variant (Still's syndrome) or iridocyclitis unable to be influenced locally

12–15 mg IV

Rheumatic fever with carditis

12–15 mg IV

Infectiology

Severe infectious diseases, toxic states (e.g. tuberculosis, typhoid; in addition to corresponding anti-infective therapy only)

4–20 mg/day IV or oral, an initial dose of up to 200 mg in individual cases (e.g. typhoid).

Oncology

Palliative therapy of malignant tumours

Initially 8–16 mg/day, in prolonged treatment 4–12 mg/day.

Prevention and treatment of cytostatic agent-induced vomiting within the scope of antiemetic regimens

10–20 mg IV or oral before initiation of chemotherapy, then 4–8 mg 2–3 times daily as required for 1–3 days (moderately emetogenic chemotherapy) or up to 6 days (highly emetogenic chemotherapy).

Prevention and treatment of post-operative vomiting

A single IV dose of 8–20 mg prior to the operation. In children from 2 years, 0.15–0.5 mg/kg body weight (up to 16 mg).

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 6mg/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.

Local use:

Local infiltration and injection therapy is usually carried out with 4–8 mg; 2 mg dexamethasone phosphate is sufficient if injected into small joints and with subconjunctival administration.

Method of administration

Dexamethasone phosphate Teva is administered as a slow intravenous injection or infusion (2–3 minutes). In the event of vein difficulties and if circulatory function is intact, it may also be administered intramuscularly. Dexamethasone phosphate Teva can also be administered via infiltration or the intraarticular or subconjunctival routes. The duration of treatment depends on the indication.

Direct intravenous injection or injection into the infusion tube should be preferred to administration by infusion.

In hypothyroidism or liver cirrhosis, comparatively low doses may be sufficient or a dose reduction may be necessary.

Intraarticularinjections should be treated like open joint operations and are to be administered only under strict aseptic conditions. In general, a single intraarticular injection is sufficient to successfully alleviate symptoms. If a further injection is deemed necessary, it should be administered after at least 3–4 weeks. No more than 3–4 injections should be administered in each joint. Medical monitoring of the joint is indicated, particularly in the event of repeat injections.

Infiltration
The medicinal product is infiltrated into the area with the strongest pain or the tendon insertion. Caution: must not be injected intratendinously. Injections at short intervals should be avoided and strict aseptic precautionary measures must be complied with.

4.3 Contraindications

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

Intraarticular injection is contraindicated in the following cases:

- infection in or in the immediate vicinity of the joint to be treated
- bacterial arthritis
- instability of the joint to be treated
- predisposition to bleeding (spontaneous or due to anticoagulants)
- periarticular calcification
- avascular bone necrosis
- tendon rupture
- neuropathic arthropathy

Infiltration without causal additional treatment is contraindicated in the event of infection at the administration site. Subconjunctival administration is contraindicated in the event of viral, bacterial and mycotic eye diseases as well as corneal injury and ulceration.

4.4 Special warnings and precautions for use

Individual cases of severe anaphylactic reactions with circulatory collapse, cardiac arrest, arrhythmia, bronchospasm and/or hypotension or hypertension have been observed with dexamethasone.

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.

In cases of particular physical stress situations (trauma, surgery, childbirth, etc.) during treatment with dexamethasone, a temporary dose increase may be required.

Treatment with dexamethasone should only be implemented in the event of the strictest indications and, if necessary, additional targeted anti-infective treatment for the following illnesses:

- acute viral infections (herpes zoster, herpes simplex, varicella, herpetic keratitis)
- HBsAg-positive chronic active hepatitis
- approximately 8 weeks before to 2 weeks after vaccinations with live vaccines
- systemic mycoses and parasitoses (e.g. nematodes)
- in patients with suspected or confirmed strongyloidiasis (infection with threadworms), glucocorticoids can lead to 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 strict indications and, if necessary, additional specific treatment for:

- gastrointestinal ulcers
- osteoporosis
- severe heart failure
- high blood pressure that is difficult to regulate
- diabetes mellitus that is difficult to regulate
- 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

Due to the risk of intestinal perforation, dexamethasone may be administered only under urgent indication and with appropriate monitoring in the following cases:

- severe ulcerative colitis with threatened perforation, possibly without peritoneal irritation
- diverticulitis
- intestinal anastomosis (immediately post-operation)

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 is difficult to regulate.

Because of the risk of deterioration, patients with severe cardiac insufficiency should be carefully monitored.

Bradycardia may occur with high doses of dexamethasone.

Severe anaphylactic reactions may occur.

The risk of tendon disorders, tendinitis and tendon rupture is increased when fluoroquinolones and glucocorticoids are administered together.

Concurrent myasthenia gravis may initially worsen during treatment with dexamethasone.

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

At high doses, sufficient potassium intake and sodium restriction should be ensured and serum potassium levels should be monitored.

Abrupt withdrawal of a treatment that was received for more than approx. 10 days can lead to acute adrenocortical insufficiency/cortisone withdrawal syndrome. Doses should therefore be reduced gradually in the event of planned discontinuation.

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 come into contact with people infected with measles or chickenpox during 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. Patients at high risk of TLS,

such as patients with a high proliferative rate, a high tumour burden and high sensitivity to cytostatic agents, should be monitored closely and appropriate precautions taken.

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.

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 (section 4.8).

Visual disturbances
Visual disturbances 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 (CSC), which have been reported after use of systemic and topical corticosteroids.

Intravenous doses should be administered by slow injection (over 2–3 minutes), as short-term (lasting up to 3 minutes), technically harmless adverse effects such as unpleasant tingling or paraesthesia may occur if injected too rapidly.

Dexamethasone phosphate Teva is a medicine for short-term use. For unintended, long-term use, further warnings and precautions must be taken into account, as described for glucocorticoid-containing medicinal products for long-term use.

Potential systemic adverse effects and interactions should be taken into consideration with local administration.

Intraarticular administration of glucocorticoids increases the risk of joint infections. Long-term and repeat glucocorticoid administration in weight-bearing joints can cause worsening of wear-related changes in the joint. This is potentially caused by an overload of the affected joint after the pain or other symptoms regress.

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

Local application in ophthalmology
Cushing's syndrome and / or adrenal suppression can be linked to the systemic absorption of ophthalmic dexamethasone after intensive or long-term treatment of predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat), may occur. In these cases the treatment should be gradually stopped.

Premature infants
Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours) of premature infants with bronchopulmonary dysplasia at starting doses of 0.25 mg/kg body weight twice daily.

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

Elderly
Because elderly patients are at an increased risk of osteoporosis, the benefit-risk balance of treatment with dexamethasone should be carefully weighed.

Doping
Use of dexamethasone can lead to positive results in anti-doping tests.

Information about excipients

Dexamethasone phosphate Teva contains sodium, but less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that can influence the effect of dexamethasone
Oestrogens (e.g. ovulation inhibitors)
The half-life of glucocorticoids may be prolonged. Therefore, the effect of corticoids may be increased.

CYP3A4 inducers such as rifampicin, phenytoin, carbamazepine, barbiturates and primidone
The effect of corticoids may be reduced.

CYP3A4 inhibitors such as ketoconazole and itraconazole
The effect of corticoids may be increased.

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 adverse reactions, in which case patients should be monitored for systemic corticosteroid adverse reactions.

Ephedrine
The metabolism of glucocorticoids may be accelerated and thus their efficacy reduced.

Dexamethasone influences the effect of the following medicinal products
ACE inhibitors
There is an 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 anticoagulant effect may be reduced. Dosage adjustment of the anticoagulant may be necessary when co-administered.

Non-steroidal anti-inflammatory drugs (NSAIDs), salicylates and indomethacin
The risk of gastrointestinal ulcers and bleeding is increased.

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

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

Praziquantel
Corticosteroids may cause a fall in blood praziquantel concentrations.

Chloroquine, hydroxychloroquine, mefloquine
There is an increased risk of myopathies and cardiomyopathies.

Protirelin
A reduced increase in TSH may be noted during administration of protirelin.

Immunosuppressants
Increased susceptibility to infections and possible aggravation or manifestation of latent infections.

Additionally, for ciclosporin
The blood levels of ciclosporin are increased: There is an increased risk of seizures.

Fluoroquinolones
Fluoroquinolones may increase the risk of tendon disorders.

Effects 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, this medicine should only be administered after careful benefit-risk assessment.
In long-term treatment with glucocorticoids during pregnancy, foetal growth disorders cannot be excluded. Administration of glucocorticoids to pregnant animals can cause abnormalities in foetal development, including cleft palate, intra-uterine growth retardation and effects on brain growth and development. There is no evidence that glucocorticoids result in an increased incidence of congenital abnormalities such as cleft palate/lip in humans (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.

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.

Lactation
Dexamethasone is excreted in breast milk. There are no known cases of harm to the infant. Nevertheless, the indication should be weighed very carefully during breast-feeding. If the disease requires higher doses, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

There is no evidence to date that dexamethasone affects the ability to drive, use machines, or work without safe foothold.

4.8 Undesirable effects

There is a low risk of undesirable effects with short-term dexamethasone therapy. High parenteral doses are an exception to this, as they can lead to electrolyte disturbances, oedema formation and potentially hypertension, heart failure, heart rhythm disorders or seizures. The clinical manifestation of infections must also be taken into account with short-term treatment. Attention should be paid to gastrointestinal ulcers (often stress-induced), because corticosteroid therapy can reduce their symptoms, and to a reduction in glucose tolerance.

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

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, polycythaemia.

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 onset of Cushing's syndrome (typical symptoms include moon face, central obesity and plethora).

Metabolic and nutrition disorders

Sodium retention with oedema, increased potassium excretion (risk of arrhythmias), weight gain, reduced glucose tolerance, diabetes mellitus, hypercholesterolaemia and hypertriglyceridaemia, increased appetite.

Psychiatric disorders
Depression, irritability, euphoria, increased drive, psychoses, mania, hallucinations, affective 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, rare cases of reversible exophthalmos, herpes simplex keratitis with subconjunctival administration, corneal perforation with existing keratitis, chorioretinopathy, blurred vision (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.

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

Respiratory, thoracic and mediastinal disorders
Hiccup.

Gastrointestinal disorders
Gastrointestinal ulcers, gastrointestinal bleeding, pancreatitis, stomach discomfort.

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.

Reproductive system and breast disorders
Disorders of sexual hormone secretion (consequently: irregular menstruation up to amenorrhoea, hirsutism, impotence).

General disorders and administration site conditions
Delayed wound healing.

Local use
Local irritation and intolerability reactions may occur (feeling of heat, persistent pain), especially when used on the eye. Development of skin atrophy and subcutaneous tissue atrophy at the injection site cannot be ruled out if the corticosteroid was 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

Symptoms
Acute intoxications with dexamethasone are not known. In case of chronic overdose, an increase in undesirable effects, especially endocrine, metabolic and electrolyte-related effects, can be expected (see section 4.8).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids
ATC code: H02AB02

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 prednisone, and compared to hydrocortisone it is 30 times more effective, lacking mineralocorticoid effects.

Glucocorticoids, such as dexamethasone, exert their biological effects by activating the transcription of corticosteroid-sensitive genes. The anti-inflammatory, immunosuppressive and anti-proliferative effects are caused by decreased 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 may be prevented by corticosteroids.

When long-term corticoid treatment is required, the possibility 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 in patients hospitalised with COVID-19.

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

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

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

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

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

In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% versus 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% versus 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% versus 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 versus 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).

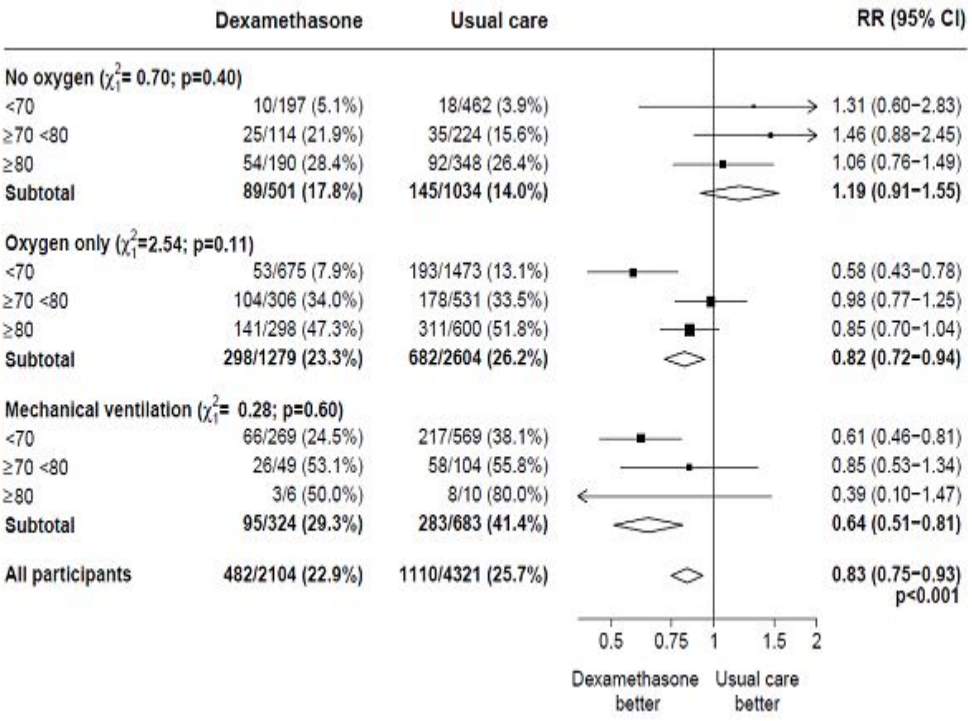
Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10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

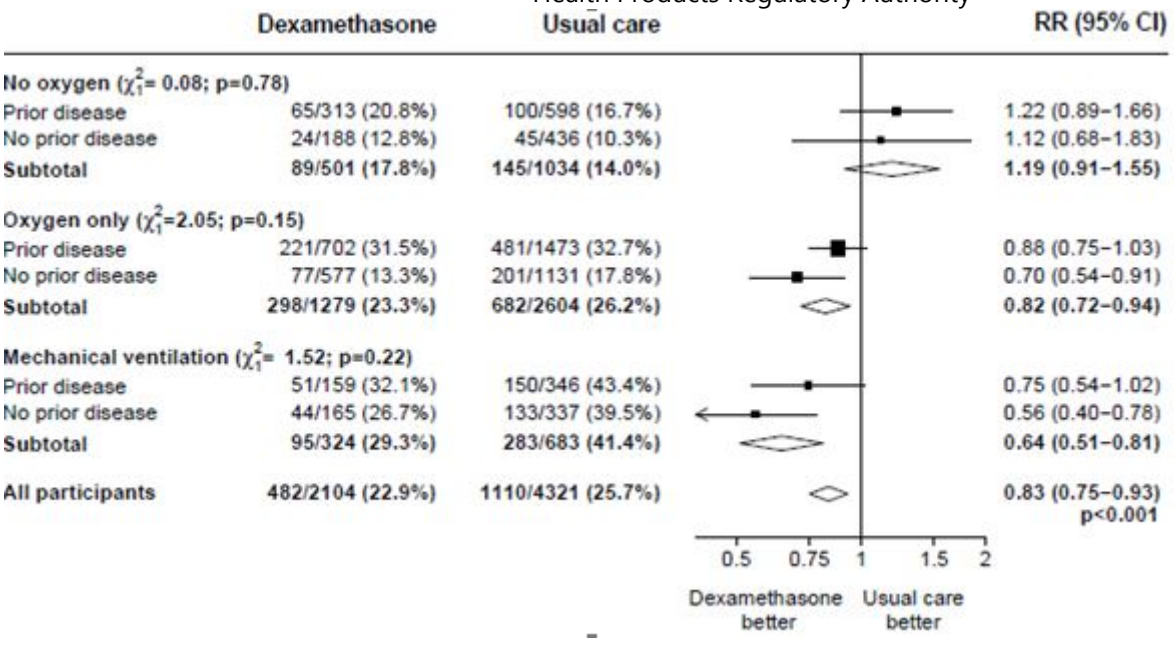
Safety
There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved.

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]



5.2 Pharmacokinetic properties

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. 4 hours after intravenous administration of radio-labelled dexamethasone in humans, peak dexamethasone CSF concentrations were measured at approximately 1/6 of concurrent plasma concentrations.

Dexamethasone has a biological half-life of over 36 hours and is therefore a very long-acting glucocorticoid. Due to the long duration of action, daily continuous administration of dexamethasone can lead to accumulation and overdosing.

The mean (serum) elimination half-life of dexamethasone in adults is 250 minutes (+/- 80 minutes). Elimination is largely renal in the form of free dexamethasone alcohol. Dexamethasone is partly metabolised, and the metabolites are excreted as glucuronates or sulfates, also mainly by the kidneys. 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 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

Sodium edetate (Ph. Eur.)
Sodium chloride
Sodium hydroxide
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

This medicinal product should not be used after the expiry date.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Amber glass ampoules.

Ampoules containing 1 ml solution for injection
Pack of 3 ampoules in 1 ml solution for injection
Pack of 10 ampoules in 1 ml solution for injection
Pack of 30 ampoules in 1 ml solution for injection
Multi-pack of 30 ampoules (3 x 10 ampoules) in 1 ml solution for injection

Ampoules containing 2 ml solution for injection
Pack of 3 ampoules in 2 ml solution for injection
Pack of 10 ampoules in 2 ml solution for injection
Pack of 30 ampoules in 2 ml solution for injection
Multi-pack of 30 ampoules (3 x 10 ampoules) in 2 ml solution for injection

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Only transparent solutions should be used.
The solution must be used immediately after breaking the ampoule. The rest is to be disposed of.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/105/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th January 2022

10 DATE OF REVISION OF THE TEXT

October 2022