Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dexamethasone phosphate 4 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 4 mg of dexamethasone phosphate (as 4.37 mg of dexamethasone sodium phosphate, equivalent to 3.3 mg of dexamethasone base).

Excipient with known effect:
Each 1 ml ampoule contains 3.2 mg of sodium (as trisodium citrate dihydrate and disodium edetate dihydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear and colourless solution, free of visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dexamethasone Phosphate 4 mg/ml solution for injection is indicated in the following situations:

SYSTEMIC USE

The indications are:
The same as for oral corticosteroids, in situations in which the oral route is unavailable (vomiting, altered consciousness);
Conditions that require a rapid therapeutic effect:

Shock of haemorrhagic, traumatic, surgical or septic origin

Autoimmune inflammatory diseases: Lupus erythematosus, Dermatomyositis, Polyarteritis nodosa, Thrombocytopenic purpura, Pemphigus vulgaris, Rheumatoid arthritis

Allergies: Acute bronchial asthma, Severe angioedema (in combination with antihistamines), Anaphylactic shock (in association with adrenaline), Imminent allograft rejection

Infections:
Severe typhoid fever, especially if associated with altered consciousness, shock, coma
Stridulous laryngitis (pseudocroup) in children.

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.

Neurological conditions: Cerebral oedema following tumours, abscesses, cerebral toxoplasmosis.

ORL: Laryngeal dyspnoea

Oncological conditions:
In combination with other medicines, treatment of symptomatic multiple myeloma, acute lymphocytic leukaemia, acute lymphoblastic leukaemia, Hodgkin's disease and non-Hodgkin's lymphoma Prophylaxis and treatment of cytostatic drug-induced vomiting
Compression of the spinal cord due to metastatic lesions

LOCAL USE

The same as for topical corticosteroids where the condition justifies strong local concentration. All prescriptions for loco-regional injections must take into account the danger of infection, particularly the risk of facilitating bacterial proliferation.

This product is indicated in:

Dermatological conditions: Keloids

Rheumatological conditions
Periarticular injections: tendonitis, bursitis
Soft tissue injections: heel pain, carpal tunnel syndrome, Dupuytren's contracture.

4.2 Posology and method of administration

N. B. All doses are expressed in mg of dexamethasone phosphate
The lowest effective dose for the shortest possible period should be used and this should be monitored frequently to adjust the dose appropriately to the intensity of the disease (see section Warnings and precautions).
Dexamethasone Phosphate 4 mg/ml solution for injection can be administered directly intramuscularly (IM), intra-articularly or intravenously (IV), by intravenous infusion or soft tissue infiltration.

SYSTEMIC USE

Intravenous and intramuscular administration: the dose for IM or IV administration of dexamethasone is variable, depending on the condition to be treated. It generally ranges from 0.4 to 24 mg (0.1 to 6 ml) daily. The duration of treatment depends on the patient's clinical response and, as soon as improvements appear, the dose should be adjusted to the minimum necessary to maintain the desired clinical response. Discontinuation of the medicinal product after the completion of treatment should be gradual.

Shock: A single IV injection of 2 to 6 mg/kg body weight (0.5 to 1.5 ml/kg), which can be repeated in 2-6 hours if shock persists. High dose treatment should be continued only until the patient's condition has stabilized and usually for no more than 48-72 hours. This bolus injection can be followed by a continuous intravenous infusion of 3 mg/kg body weight (0.75 ml/kg) for 24 hours. Dexamethasone Phosphate 4 mg/ml solution for injection can be diluted with the following solutions for infusion: 0.9% Sodium Chloride, 5% Glucose or Ringer (see section 6.6).

Cerebral oedema: an initial dose of 10 mg (2.5 ml), IV, followed by 4 mg (1.0 ml) IM every 6 hours until symptoms of oedema decrease (usually after 12 to 24 hours). After 2 to 4 days, the dose should be reduced and discontinued gradually over a period of 5 to 7 days. In patients with recurrent or inoperable neoplasms, maintenance therapy can be effective at doses of 2 mg (0.5 ml) IM or IV, 2-3 times a day.

Life-threatening cerebral oedema:

Dose schedule for high dosage (all doses are expressed in mg dexamethasone phosphate):

	Adults	**Children > 35 kg**	**Children < 35 kg**
Starting dose	50 mg (12.5 ml) IV	25 mg IV (6.25 ml)	20 mg (5.0 ml) IV
1st day	8 mg (2.0 ml) IV every 2 hours	4 mg (1.0 ml) IV every 2 hours	4 mg (1.0 ml) IV every 3 hours
2nd day	8 mg (2.0 ml) IV every 2 hours	4 mg (1.0 ml) IV every 2 hours	4 mg (1.0 ml) IV every 3 hours
3rd day	8 mg (2.0 ml) IV every 2 hours	4 mg (1.0 ml) IV every 2 hours	4 mg (1.0 ml) IV every 3 hours
4th day	4 mg (1.0 ml) IV every 2 hours	4 mg (1.0 ml) IV every 4 hours	4 mg (1.0 ml) IV every 6 hours
5th - 8th day	4 mg (1.0 ml) IV every 4 hours	4 mg (1.0 ml) IV every 6 hours	2 mg (0.5 ml) IV every 6 hours
After 8 days	Decrease: daily reduction of 4 mg (1.0 ml)	Decrease: daily reduction of 2 mg (0.5 ml)	Decrease: daily reduction of 1 mg (0.25 ml)

Note: The intravenous and intramuscular routes of administration of dexamethasone should only be used in case of acute illness or in life-threatening situations.
Replacement with oral therapy should be performed as soon as possible.

For the treatment of Covid-19:

Adult patients 6 mg IV, 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 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

Intra-articular and soft tissue injections

The dose varies according to the degree of inflammation and the size and location of the affected area. Injections can be repeated once every 3-5 days (for example, for bursas) up to once every 2-3 weeks (for joints).

	Injection site	**Dose**
1.	Large joints	2 mg to 4 mg (0.5 ml to 1.0 ml)
2.	Small joints	800 micrograms to 1 mg (0.2 ml to 0.25 ml)
3.	Bursas	2 mg to 3 mg (0.5 ml to 0.75 ml)
4.	Tendon sheaths	400 micrograms to 1 mg (0.1 ml to 0.25 ml)
5.	Infiltration into soft tissues	2 mg to 6 mg (0.5 ml to 1.5 ml)
6.	Ganglia	1 mg to 2 mg (0.25 ml to 0.5 ml)

SPECIAL POPULATIONS

Paediatric population

The required doses are variable and may need to be adjusted according to individual needs. Normally, the daily dose ranges from 200 micrograms/kg body weight to 400 micrograms/kg body weight (0.05 ml/kg body weight to 0.1 ml/kg body weight).

Corticosteroids cause growth retardation in childhood and adolescence, which can be irreversible. Treatment should be limited to the minimum dose for the shortest possible time. In order to minimise the suppression of the hypothalamic-pituitary-adrenal axis and growth delay, treatment should be limited, as far as possible, to a single dose every other day.

The growth and development of infants and children on long-term treatment with corticosteroids should be carefully monitored.

Elderly

The treatment of elderly patients, especially in the long term, should be planned, taking into account the most serious consequences in old age. Such effects include osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thin, fragile skin. Careful clinical supervision is necessary to avoid potentially fatal reactions.

4.3 Contraindications

Except in life-threatening situations, systemic administration of corticosteroids is generally contraindicated in patients with systemic infections (unless specific antimicrobial treatment is used).
Hypersensitivity to the active substance or to any of the excipients mentioned in the section 6.1.

4.4 Special warnings and precautions for use

An Information Leaflet must be provided with this product.

Patients with 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.

The patients and/or their carers should be advised that potentially serious psychiatric adverse effects can occur with the use of systemic steroids (see section 4.8). Symptoms usually appear within a few days or weeks after starting treatment. The risks may be higher with high doses/systemic exposure (see also section 4.5 pharmacokinetic interactions that may increase the risk of side effects), although dose levels do not allow to predict the onset, type, severity or duration of the effects. Most side effects reverse after a dose reduction or discontinuation, although specific treatment may be required. Patients/caretakers of patients should be encouraged to seek medical advice if worrying psychological symptoms develop, especially in case of suspected depression or suicidal thoughts. Patients/patient caretakers should also be aware of possible psychiatric disorders that may occur during or immediately after the gradual dose reduction/discontinuation of systemic steroids, although these interactions have been reported infrequently.

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.

Special care is needed when considering the use of systemic corticosteroids in patients with a current or previous personal history of severe affective disorder, or in their first-degree relatives. These include depression or manic depression and previous steroid psychosis.

The lowest effective dose of corticosteroids should be used to control the condition under treatment, for the minimum possible period. Frequent assessment of the patient is necessary to properly adjust the dose to the intensity of the disease (see dosage section). When dose reduction is possible, it should be performed gradually. If the reduction in the dose of dexamethasone after prolonged treatment is too rapid, it can lead to acute adrenal insufficiency, hypotension and death.

There may also be a "withdrawal syndrome" with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful/itchy lumps on the skin and weight loss.

Adrenal suppression: adrenal cortical atrophy develops during prolonged therapy and may persist for several years after stopping treatment. The discontinuation of corticosteroids after prolonged treatments should, therefore, be gradual to avoid acute adrenal insufficiency, with gradual reduction over weeks or months, according to the dose and duration of treatment. During prolonged treatment, any intercurrent illness, trauma or surgical procedure will require a temporary dose increase; if corticosteroid treatment has been discontinued after prolonged therapy, it may need to be restarted temporarily.

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.

There is a lack of evidence to support the prolonged use of corticosteroids in septic shock. Although these may be useful in the initial treatment, they may not influence overall survival.

Severe anaphylactic reactions have occurred after parenteral administration of corticosteroids, particularly in patients with a history of allergy. Relevant precautions must be taken before administration.

Note that the absorption rate is slower after intramuscular injection.

Corticosteroids, when administered intra-articularly, are associated with a substantially increased risk of an inflammatory response in the joint, especially bacterial infections introduced during injection. Special care is required, and all intra-articular injections of corticosteroids should be performed in an aseptic environment. Charcot-type arthropathies have been reported, particularly after repeated injections.

Before an intra-articular injection, the joint fluid must be examined to exclude any septic process. A significant increase in pain, accompanied by local swelling, additional restriction of joint movement, fever and general malaise may suggest septic arthritis. If this complication occurs and sepsis is confirmed, appropriate antimicrobial therapy should be started.

Patients should be seriously alerted to the importance of not overloading the joints in which symptomatic improvement has been achieved, but in which the inflammatory process remains active.

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical situation can consist of atypical and severe infections, such as septicaemia and tuberculosis, which could remain hidden and reach an advanced stage before being detected.

Chickenpox is of particular concern as this usually minor illness can be fatal in immunosuppressed patients. Patients (or parents of the child) without a confirmed history of chickenpox should be advised to avoid personal contact with chickenpox or shingles and, if exposed, should seek medical advice urgently. Passive immunisation with varicella zoster immunoglobulin (VZIG) is necessary for exposed non-immune patients who are receiving systemic dexamethasone or who have received it during the last 3 months; this should be given within 10 days after exposure to chickenpox. If the diagnosis of chickenpox is confirmed, the disease will require specialised care and urgent treatment. Dexamethasone should not be stopped and the dose may need to be increased.

Live vaccines should not be administered to individuals with an impaired immune response. Antibody response to other vaccines may be decreased.

The tetrazolium nitro blue test for bacterial infections may show false negative results.

Special care should be taken when treating patients with the following conditions and frequent monitoring of the patient is necessary:

- Liver failure, chronic renal failure, congestive heart failure, high blood pressure, epilepsy, migraine.
- Osteoporosis, since corticosteroids increase calcium excretion. Postmenopausal women are particularly at risk.
- Latent tuberculosis, since corticosteroids can cause reactivation.
- Hypothyroidism or cirrhosis, as these patients often show an exaggerated response to corticosteroids.
- Latent amoebiasis, since corticosteroids can cause reactivation. Before treatment, amoebiasis should be excluded in any patient with unexplained diarrhoea or who has recently been in the tropics.
- Herpes simplex ocular, as corticosteroids can cause perforation of the cornea.

Corticosteroids should also be used with caution in patients with diabetes mellitus (or a family history of diabetes), affective disorders (especially in previous cases of steroid psychosis), glaucoma (or a family history of glaucoma), peptic ulcer, or previous myopathy induced by corticosteroids.

Dexamethasone has been used "off-label" in the treatment and prevention of chronic lung disease in premature infants. Clinical trials have shown a short-term benefit in reducing ventilator dependence, but no long-term benefit in reducing the time to discharge, the incidence of chronic lung disease or mortality. Available data suggest long-term adverse effects on neurological development after early treatment (<96 hours) of premature infants with chronic lung disease, at initial doses of 0.25 mg/kg twice daily. Recent studies have suggested a connection between the use of dexamethasone in premature infants and the development of cerebral palsy. In view of this possible safety issue, an assessment of the risk-benefit balance for the patient should be made on a case-by-case basis.

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).

In post-marketing experience, situations of tumour lysis syndrome (TLS) have been observed in patients with haematological diseases, after the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patients with a high risk of TLS, such as patients with a high proliferative index, high tumour burden and high sensitivity to cytotoxic agents should be strictly monitored, and special precautions should be taken.

This medicinal product contains 3.2 mg sodium per ml, equivalent to 0.16% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Liver enzyme-inducing medicinal products such as barbiturates, ephedrine, rifampicin, rifabutin, carbamazepine, phenytoin, primidone and aminoglutethimide can enhance the metabolism of corticosteroids, resulting in decreased pharmacological action, and a need for adjustment of the dose.

The efficacy of coumarin anticoagulants can be increased by concomitant corticosteroid therapy, requiring strict monitoring of prothrombin time or INR to prevent spontaneous bleeding. Corticosteroids can affect glucose tolerance and increase the required dose of glucose-lowering agents (including insulin).

The incidence of gastrointestinal ulceration increases in patients receiving concomitant therapy with non-steroidal anti-inflammatory agents and corticosteroids.

Renal clearance of salicylates increases with corticosteroids and discontinuation of steroids can result in salicylate poisoning.

Diuretics are antagonised by corticosteroids and the potassium-lowering effect of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone is enhanced. In patients receiving potassium-depleting corticosteroids and diuretics and/or cardiac glycosides, hypokalaemia should be monitored. This is of particular importance in patients receiving cardiac glycosides, as hypokalaemia increases the toxicity of these medicinal products. The effects of antihypertensive medicinal products are also antagonised by corticosteroids.

4.6 Fertility, pregnancy and lactation

Pregnancy
The ability of corticosteroids to cross the placenta varies, however, dexamethasone easily crosses the placental barrier.

The administration of corticosteroids to animals in gestation can cause abnormalities in foetal development, including cleft palate, delayed intrauterine growth and effects on brain growth and development. There is no evidence that treatment with corticosteroids results in an increased incidence of congenital abnormalities, such as cleft palate/lip in humans. See also section 5.3 of the SmPC. However, when administered for prolonged periods or several times during pregnancy, corticosteroids may increase the risk of delayed intrauterine growth. Hypoadrenalism may, in theory, occur in the newborn after prenatal exposure to corticosteroids, but it usually resolves spontaneously after birth and is rarely of clinical importance. As with all medicines, corticosteroids should only be prescribed when the benefits for the mother and child outweigh the risks. However, when corticosteroids are essential, patients with normal pregnancies can be treated as if they were not pregnant.

Babies born to mothers who received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of adrenal insufficiency.

Patients with pre-eclampsia or fluid retention require careful monitoring.

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.

Breastfeeding
Corticosteroids can pass into breast milk, although there are no data available on dexamethasone. Babies of mothers who take high doses of systemic corticosteroids for long periods of time, may have a degree of adrenal suppression. Growth suppression or other adverse effects may occur.

Fertility
Animal studies have shown reductions in female fertility (see section 5.3). Data on male fertility are not available.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Adverse reactions
A wide range of psychiatric effects have been reported, including affective disorders (such as irritable, euphoric, depressed and labile moods, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and worsening schizophrenia), behavioural disorders, irritability, anxiety, sleep disorders and cognitive impairment including confusion and

amnesia. The effects are common and can occur in both adults and children. In adults, the frequency of serious effects was estimated at 5-6%. Psychological effects have been reported with the discontinuation of corticosteroids; the frequency is unknown.
The occurrence of foreseeable undesirable effects, including suppression of the hypothalamic-pituitary-adrenal axis, is correlated with the relative potency of the medicinal product, dosage, time of administration and duration of treatment (see other special warnings and precautions for use).

High doses of dexamethasone sodium phosphate are intended for short-term treatment and therefore adverse effects are not common. However, peptic ulceration and bronchospasm may occur.

With the exception of hypersensitivity, the following side effects have been associated with prolonged use of systemic corticosteroids.

Endocrine and metabolic disorders:
Suppression of the hypothalamic-pituitary-adrenal axis; cushingoid syndrome, hirsutism and weight gain; growth suppression in babies, children and adolescents; absence of secondary adrenocortical response, particularly in times of stress, such as surgery or trauma; menstrual irregularities and amenorrhea; impaired glucose tolerance with increased need for antidiabetic therapy; hyperglycaemia; negative protein/nitrogen balance and calcium balance; increased appetite.
Metabolic: Electrolyte imbalance (sodium and water retention, with oedema and hypertension); nitrogen depletion; hyperglycaemia; hypokalaemic alkalosis; increased potassium and calcium excretion and hypertension.
Anti-inflammatory and immunosuppressive effects: increased susceptibility to infections and their severity with suppression of clinical signs and symptoms; opportunistic infections; reactivation of latent tuberculosis (see section Precautions).
Musculoskeletal: muscle atrophy, proximal myopathy, premature epiphyseal closure, osteoporosis, avascular osteonecrosis, muscle weakness, tendon rupture, spinal compression and long bone fractures.
Gastrointestinal: Dyspepsia, peptic ulcer with perforation and haemorrhage, oesophageal ulcers, acute pancreatitis and candidiasis.
Dermatological: poor wound healing; atrophy of the skin; bruises; telangiectasis and stretch marks; petechiae and bruises; erythema; increased sweating; possible suppression of skin tests; burning or tingling; wounds; allergic dermatitis; hives, candidiasis, acne.
Neurological: mental disorders, psychological dependence, euphoria, depression, insomnia, headaches, convulsions, vertigo. Worsening of epilepsy and schizophrenia. Increased intracranial pressure with papilloedema in children (cerebral pseudo-tumour), usually after discontinuing treatment.
Eye disorders: posterior subcapsular cataract or increased intraocular pressure can result in glaucoma or occasionally damage to the optic nerve; exophthalmos and papilloedema; thinning of the cornea or sclera; exacerbation of ophthalmic viral or fungal diseases; chorioretinopathy, vision, blurred (frequency not known; see also section 4.4).
Others: hypersensitivity has been reported, including anaphylaxis; blindness associated with intralesional therapy on the face and neck; hyperpigmentation; hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; post-injection "flare" (after intra-articular injection): Charcot-type arthropathy, leucocytosis, thromboembolism.

Discontinuation
Abrupt discontinuation of treatment with systemic corticosteroids, which has lasted up to 3 weeks, is appropriate if relapse of the disease is considered to be unlikely. An abrupt discontinuation of dexamethasone doses up to 6 mg after 3 weeks is likely to lead to clinically relevant suppression of the HPA axis in most patients. In the following patient groups, gradual discontinuation of systemic corticosteroids should be considered, even for treatments lasting 3 weeks or less:
• Patients who have had repeated treatment with systemic corticosteroids, especially if for more than 3 weeks,
• When a short-term treatment has been prescribed within one year after cessation of the long-term treatment (months or years),
• Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy,
• Patients who received doses of systemic corticosteroids greater than 6 mg dexamethasone daily,
• Patients repeatedly taking doses at night.

Withdrawal signs and symptoms: reducing the dose of corticosteroids too quickly after prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. (see section Precautions). There may also be "withdrawal symptoms" with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful / pruritic nodules on the skin and weight loss.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continuous 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

Treatment of anaphylaxis with adrenaline and positive pressure ventilation. Other supportive measures intended to stabilize the patient's state.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: 8.2.2 – Hormones and medicinal products used to treat endocrine disorders. Corticosteroids. Glucocorticoids
ATC code: H02AB02.

The pharmacology of corticosteroids is complex and these medicinal products affect almost every system in the body. Maximum pharmacological activity appears after peaks in blood concentration, suggesting that most effects of the medicinal product result from the modification of enzyme activity, rather than its direct action.

The RECOVERY trial (Randomised Evaluation of COVid-19 thERapY) 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 randomisation, 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 randomisation (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 randomisation (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 randomisation.

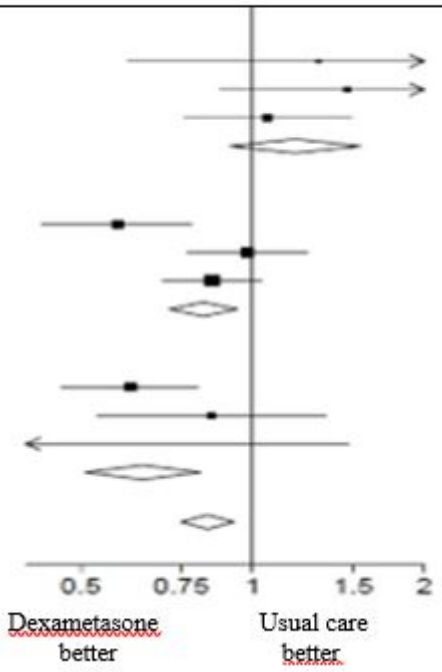
Safety

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

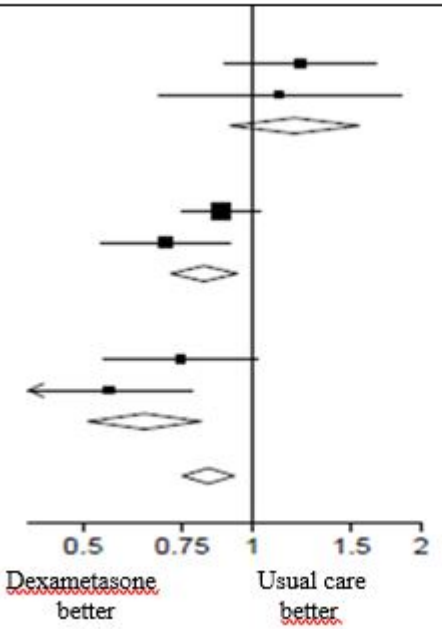
Effects of allocation to DEXAMETHASONE on 28−day mortality, by age and respiratory support received at randomisation

	Dexametasone	Usual care	RR (95% CI)
No oxygen (χ^2_1 = 0,70; p=0,40)			
< 70	10/197 (5,1%)	16/462 (3,9%)	1,31 (0,60-2,83)
≥ 70 <80	25/114 (21,9%)	35/224 (15,6%)	1,46 (0,88-2,45)
≥ 80	54/190 (28,4%)	92/348 (26,4%)	1,06 (0,76-1,49)
Subtotal	**89/501 (17,8%)**	**145/1034 (14,0%)**	**1,19 (0,91-1,55)**
Oxygen only (χ^2_1 = 2,54; p=0,11)			
< 70	53/675 (7,9%)	193/1473 (13,1%)	0,58 (0,43-0,78)
≥ 70 <80	104/306 (34,0%)	178/531 (33,5%)	0,98 (0,77-1,25)
≥ 80	141/298 (47,3%)	311/600 (51,8%)	0,85 (0,70-1,04)
Subtotal	**298/1279 (23,3%)**	**682/2604 (26,2%)**	**0,82 (0,72-0,94)**
Mechanical ventilation (χ^2_1 = 0,28; p=0,60)			
< 70	66/269 (24,5%)	217/569 (38,1%)	0,61 (0,46-0,81)
≥ 70 <80	26/49 (53,1%)	58/104 (55,8%)	0,85 (0,53-1,34)
≥ 80	3/6 (50,0%)	8/10 (80,0%)	0,39 (0,10-1,47)
Subtotal	**95/324 (29,3%)**	**283/683 (41,4%)**	**0,64 (0,51-0,81)**
All participants	**482/2104 (22,9%)**	**1140/4321 (25,7%)**	**0,83 (0,75-0,93) P<0,001**



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

	Dexametasone	Usual care	RR (95% CI)
No oxygen (χ^2_1 = 0,08; p=0,78)			
Prior disease	65/313 (20,8%)	100/598 (16,7%)	1,22 (0,89-1,66)
No prior disease	24/188 (12,8%)	45/436 (10,3%)	1,12 (0,68-1,83)
Subtotal	**89/501 (17,8%)**	**145/1034 (14,0%)**	**1,19 (0,91-1,55)**
Oxygen only (χ^2_1= 2,05; p=0,15)			
Prior disease	221/702 (31,5%)	481/1473 (32,7%)	0,88 (0,75-1,03)
No prior disease	77/577 (13,3%)	201/1131 (17,8%)	0,70 (0,54-0,91)
Subtotal	**298/1279 (23,3%)**	**682/2604 (26,2%)**	**0,82 (0,72-0,94)**
Mechanical ventilation (χ^2_1 =1,52 ; p=0,22)			
Prior disease	51/159 (32,1%)	150/346 (43,4%)	0,75 (0,54-1,02)
No prior disease	44/165 (26,7%)	133/337 (39,5%)	0,56 (0,40-0,78)
Subtotal	**95/324 (29,3%)**	**283/683 (41,4%)**	**0,64 (0,51-0,81)**
All participants	**482/2104 (22,9%)**	**1140/4321 (25,7%)**	**0,83 (0,75-0,93) P<0,001**



5.2 Pharmacokinetic properties

Intramuscular injections of dexamethasone phosphate result in maximum plasma concentrations of dexamethasone after 1 hour. Dexamethasone is readily absorbed from the gastrointestinal tract. The biological half-life in plasma is about 190 minutes. The binding of dexamethasone to plasma proteins is less than for most other corticosteroids. Dexamethasone penetrates tissue fluids and cerebrospinal fluids. The metabolism of the medicinal product takes place in the kidneys and liver and the excretion through urine.

5.3 Preclinical safety data

Glucocorticoids have low acute toxicity. Data on carcinogenicity and chronic toxicity are not available. Observations regarding genotoxicity have been shown to be caused by artefacts. In reproductive toxicity studies in mice, rats, hamsters, rabbits and dogs, dexamethasone caused embryofoetal malformations, such as an increase in the number of cases of cleft palate and skeletal defects, decreased weight of the thymus, spleen and adrenal gland, abnormalities in the lungs, liver and kidneys and inhibition of growth. The evaluation of the postnatal development of animals treated in the prenatal period demonstrated the occurrence of decreased glucose tolerance and insulin sensitivity, behavioural changes and reduced brain and body weight. In males, fertility may decrease due to apoptosis of germ cells and defects in spermatogenesis. The existing data on female fertility are contradictory.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Creatinine
Trisodium citrate dihydrate
Disodium edetate dihydrate
1M sodium hydroxide (for pH adjustment)
Water for injections.

6.2 Incompatibilities

Dexamethasone sodium phosphate is physically incompatible with daunorubicin, doxorubicin, vancomycin, diphenhydramine (with lorazepam and metoclopramide) and metaraminol bitartrate and should not be mixed with solutions containing these medicinal products. It is also incompatible with doxapram and glycopyrrolate in syringes and with ciprofloxacin, idarubicin and midazolam in Y- system injections (mixture 1:1).

6.3 Shelf life

Closed packaging: 2 years

Shelf life after dilution:
The physical-chemical stability after dilution of the solution for injection in 0.9% Sodium Chloride, 5% Glucose or Ringer solution was demonstrated for 24 hours at a temperature below 25ºC and when protected from light.
From a microbiological point of view, the product should be used immediately. If not used immediately, then in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store below 25ºC.
Store in the outer carton in order to protect from light.

6.5 Nature and contents of container

Type I amber glass ampoules, containing 1 ml solution for injection.
1 ml ampoules in packs of 10 or 50.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Dexamethasone Phosphate 4 mg/ml solution for injection can be diluted with the following solutions for infusion:
Sodium Chloride 0.9%
Glucose 5%
Ringer solution

For single use. Dispose any remaining unused solution. Only clear, particle-free solutions should be used.

Any unused medicine or waste must be disposed in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kroener Strasse 1
Bad Homburg v.d.H 61352
Germany

8 MARKETING AUTHORISATION NUMBER

PA2059/077/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd July 2022
Date of last renewal: 03rd August 2022

10 DATE OF REVISION OF THE TEXT

November 2023