Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dexamethasone Phosphate 4 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 millilitre (ml) of solution for injection contains 3.32 mg of dexamethasone base (as dexamethasone sodium phosphate) which is equivalent to 4.00 mg of dexamethasone phosphate or 4.37 mg dexamethasone sodium phosphate.

Each 2 millilitres (ml) of solution for injection contains 6.64 mg of dexamethasone base (as dexamethasone sodium phosphate) which is equivalent to 8.00 mg of dexamethasone phosphate or 8.74 mg dexamethasone sodium phosphate.

Excipients with known effect:
This medicine contains 20 mg of propylene glycol per 1 ml – see sections 4.2, 4.4, 4.6 and 4.8.
This medicine contains 0.42 mg of sodium per 1 ml - see section 4.4.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)

Clear and colourless solution, free of visible particles.
pH 7.5 – 8.7

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous or Intramuscular administration
Dexamethasone phosphate 4 mg/ml solution for injection is recommended for systemic administration by intravenous or intramuscular injection when oral therapy is not feasible or desirable in the following conditions:

- *Cerebral oedema caused by cerebral tumour, neurosurgical interventions, cerebral abscess, bacterial meningitis*
- *Posttraumatic shock* and prevention of *posttraumatic acute respiratory distress syndrome* (ARDS)
- *Coronavirus disease 2019 (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.*
- *Anaphylactic shock* (following initial epinephrine injection)
- Severe acute *asthma attack*
- *Initial parenteral treatment of extensive, acute, severe skin diseases, such as erythroderma, pemphigus vulgaris, acute eczema*
- Initial parenteral treatment of *autoimmune diseases*, such as systemic lupus erythematosus (in particular visceral forms)
- *Active rheumatoid arthritis* with a severe progressive course, e.g. rapidly destructive forms and/or with extraarticular manifestations

- Severe *infectious diseases* with toxic states (e.g. tuberculosis, typhus, brucellosis) only with appropriate anti-infective therapy

- *Palliative therapy* for *malignant tumours*

- Prophylaxis and therapy of *postoperative or cytostatic-induced vomiting* in the context of antiemetic regimens

Subcutaneous administration

- *Palliative therapy* for malignant tumours and prevention and treatment of *chemotherapy-induced nausea and vomiting* (CINV)

In palliative care, patients receiving corticosteroids for symptoms such as fatigue, anorexia, refractory nausea and vomiting or adjuvant analgesia and symptomatic treatment of cord compression or raised intracranial pressure, Dexamethasone phosphate 4 mg/ml solution for injection may be administered subcutaneously (see section 4.2) as an alternative to the oral route when the latter is unacceptable or no longer feasible.

Local administration

- Intraarticular injections for persistent inflammation in one or several joints after general treatment of chronic inflammatory joint disease, activated arthrosis, acute forms of periarthropathia humeroscapularis
- Infiltration therapy (when strictly indicated) for non-bacterial tendovaginitis and bursitis, periarthropathy, insertional tendinopathy

4.2 Posology and method of administration

Posology
Dose must be individualised depending on the disease, severity of the disease and on the individual patient's response to treatment. In general, relatively high initial doses should be used, with significantly higher doses required for the management of acute severe conditions than for chronic diseases.
The following dosage schedules are recommended:

Systemic use
Intravenous or intramuscular administration
Adults

- *Cerebral oedema*

Initially 8-10 mg (up to 80 mg) IV, then 16-24 mg (up to 48 mg)/day IV in 3-4 (6) individual doses over 4-8 days. A long-term administration of Dexamethasone phosphate 4 mg/ml solution for injection at lower doses may be necessary during irradiation and as a part of conservative therapy of inoperable cerebral tumours.
Cerebral oedema due to bacterial meningitis: 0.15 mg/kg of body weight every 6 hours over 4 days.

- *Posttraumatic shock and prevention of posttraumatic ARDS*

Initially 40-100 mg IV repeated after 12h. Alternatively 16 – 40 mg every 6 hours over 2 – 3 days.

- *T*reatment of COVID-19

6 mg 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.

- *Anaphylactic shock*

40-100 mg IV following an initial intravenous epinephrine injection. The dose can be repeated if necessary.

- *Severe acute asthma attack*

8-20 mg IV as early as possible. The injection can be repeated where necessary at a dose of 8 mg every 4 hours. Intravenous aminophylline may be administered additionally.

- *Acute skin diseases*

Daily doses of 8-40 mg IV, in individual cases up to 100 mg followed by oral treatment at decreasing doses.

- Active phases of *systemic rheumatic disease* such as *systemic lupus erythematosus*

Daily doses of 6-16 mg.

- *Active rheumatoid arthritis with a severe progressive course*

Daily doses of 12-16 mg for the management of rapidly progressing disease. Daily doses of 6-12 mg are recommended in case of extraarticular manifestations.

- *Severe infectious disease* with toxic states (e.g. tuberculosis, typhus) only as an adjunct to anti-infective therapy)

Daily doses of 4-20 mg IV. In individual cases (e.g. typhus) initially up to 200 mg.

- *Palliative therapy for malignant tumours*

Initially 8-16 mg/day, in the case of longer-term treatment, 4-12 mg/day.

- *Prophylaxis and therapy of cytostatic-induced vomiting in the context of antiemetic regimens*

10-20 mg IV before the start of chemotherapy, then, where necessary, 2 to 3 times daily 4-8 mg over 1-3 days (moderately emetogenic therapy) or up to 6 days (highly emetogenic chemotherapy).

- *Prophylaxis and therapy of postoperative vomiting*

Individual dose of 8-20 mg IV before the start of the operation.

Subcutaneous administration

- *Palliative therapy* for malignant tumours, prevention and treatment of *chemotherapy-induced nausea and vomiting* (CINV)

In palliative care, subcutaneous Dexamethasone phosphate 4 mg/ml solution for injection may be administered by injection or Continuous Subcutaneous Infusion (CSCI). Doses usually range between 4.8 mg to 19.3 mg over 24 hours, taking into consideration local clinical guidelines, and should be titrated according to the response.

Paediatric population

- *Cerebral oedema* due to bacterial meningitis

0.4 mg/kg of body weight in children every 12 hours over 2 days, starting before the first administration of antibiotics.

- *Posttraumatic shock and prevention of posttraumatic ARDS*

Initially 40 mg IV in children repeated after 12h.

- *Treatment of COVID-19*

Adolescents aged 12 years and older are recommended to be given 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.

- *Anaphylactic shock*

40 mg IV in children following an initial intravenous epinephrine injection, the dose can be repeated if necessary.

- *Severe acute asthma attack*

0.15-0.3 mg/kg of body weight IV or 1.2 mg/kg of body weight as a bolus, then followed by 0.3 mg/kg every 4-6 hours.
Intravenous aminophylline may be administered additionally.

- *Prophylaxis and therapy of postoperative vomiting*

0.15-0.5 mg/kg of body weight in children older than 2 years old with a maximum dose of 16 mg.

Dexamethasone phosphate 4 mg/ml solution for injection is generally not recommended for use in pre-term or full-term neonates (see sections 2 and 4.4).
Dexamethasone phosphate 4 mg/ml solution for injection contains propylene glycol (20 mg per ml) therefore it should be used with **caution** in infants and children younger than 5 years old especially if high doses are required or prolonged treatment is considered (see sections 2 and 4.4).

Local use
The usual dose recommended for local infiltration or intraarticular administration is 4-8 mg. A lower dose of 2 mg is usually needed for an injection into a small joint.

Use in patients with hepatic or renal impairment
Due to the propylene glycol content of the product, medical monitoring is required in patients with impaired hepatic or renal function (see sections 2 and 4.4).

In the case of hypothyrosis or liver cirrhosis, comparatively low doses can suffice, or a dose reduction may be necessary.

Method of administration
The duration of the administration depends on the indication.
Dexamethasone phosphate 4 mg/ml solution for injection can be given without mixing or dilution.

Intravenous, intramuscular, intraarticular injection or infiltration.
Alternatively, Dexamethasone phosphate 4 mg/ml solution for injection can be added, without loss of potency, to sodium chloride 0.9%, glucose 5% or Ringer's solution and given by intravenous infusion:

- continuously or intermittently or via drip tubing in adults
- over 15 – 20 minutes in children.

In palliative care, Dexamethasone phosphate 4 mg/ml solution for injection can be diluted with sodium chloride 0.9% solution and given by Continuous Subcutaneous Infusion (CSCI).
Infusion mixtures must be used within 24 hours and the usual aseptic techniques for injections should be observed.

Intraarticular injection should be administered under strict aseptic conditions. A single intraarticular injection in general suffices to successfully relieve symptoms. If a further injection is considered necessary, this should be given 3-4 weeks later at the

earliest. The number of injections per joint should be limited to 3-4. In particular, after each consecutive injection, medical examination of the joint is indicated.
Local infiltration should be carried out under rigorous aseptic conditions into the area of the most severe pain or tendon attachments. Caution should be exercised not to give the injection directly into the tendon. Administration at short intervals should be avoided.
In case high doses are required for a single treatment, use of dexamethasone medicinal products with higher strengths/volume should be considered.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- For local intraarticular injection: infection within the joint or close proximity to the joint being treated, bacterial arthritis, unstable joints, bleeding disorders (spontaneous or due to anticoagulants), periarticular calcification, avascular bone necrosis, tendon rupture, Charcot joint.
- For local infiltration therapy: infection at the administration site not treated primarily with anti-infective therapy.

4.4 Special warnings and precautions for use

In individual patients, following an administration of Dexamethasone phosphate 4 mg/ml solution for injection, severe anaphylactic reactions have been observed, with circulatory failure, cardiac arrest, arrythmias, bronchospasm, and/or a fall or rise in blood pressure.

Due to immunosuppression, treatment with Dexamethasone phosphate 4 mg/ml solution for injection can lead to an increased risk of bacterial, viral, parasitic, opportunistic, and fungal infections. Symptoms of an existing or developing infection can be masked, hampering diagnosis. Latent infections, such as tuberculosis or hepatitis B, can be reactivated.

If, during treatment with Dexamethasone phosphate 4 mg/ml solution for injection, unusually stressful situations or physical stress arise (trauma, surgical procedure, childbirth, etc.) a transient increase in dose may be necessary.
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.

Special precautions:
Therapy with Dexamethasone phosphate 4 mg/ml solution for injection should be considered only when strictly necessary and with additional targeted anti-infective therapy, in case of the following diseases:

- Acute viral infections (hepatitis B, *Herpes zoster, Herpes simplex,* chickenpox, herpes keratitis)
- HBsAg-positive chronic active hepatitis
- Approximately 8 weeks before and up to 2 weeks after immunisations using live vaccines
- Systemic fungal infections
- Parasitoses (e.g. nematodes)
- In case of patients suspected of or with confirmed strongyloidiasis (threadworm infection), glucocorticoids can lead to activation and large-scale proliferation of parasites
- Poliomyelitis
- Lymphadenitis after BCG immunisation
- Acute and chronic bacterial infections
- In case of tuberculosis in the medical history, use only with tuberculostatic protection

Therapy with Dexamethasone phosphate 4 mg/ml solution for injection should be considered only when strictly necessary and with additional specific therapy in case of the following diseases:

- Gastrointestinal ulcers
- Osteoporosis
- Severe heart failure
- Poorly/inadequately controlled hypertension
- Poorly/inadequately controlled diabetes mellitus

- Psychiatric illness (including previous history of the condition), including suicidal tendencies. Neurological or psychiatric monitoring is recommended.
- Narrow- and wide-angle glaucoma. Ophthalmological monitoring and concomitant anti-glaucoma treatment are recommended.
- Corneal ulceration and corneal injuries. Ophthalmological monitoring and concomitant therapy are recommended.

Visual disturbances
In case of the systemic and topical use of corticosteroids, visual disturbances can occur. If a patient presents with symptoms such as blurred vision or other visual disturbances, referral to an ophthalmologist to assess possible causes should be considered. These include cataract, glaucoma, or rare diseases, e.g. central serous chorioretinopathy (CSC), which have been reported after the use of systemic or topic corticosteroids.
Due to a risk of intestinal perforation, Dexamethasone phosphate 4 mg/ml solution for injection may only be used when strictly necessary and careful monitoring should be ensured in case of the following concurrent conditions:

- Severe ulcerative colitis with a risk of perforation, possibly also without peritoneal irritation
- Diverticulitis
- Enteroanastomoses (immediately postoperatively)

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.

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

During therapy with Dexamethasone phosphate 4 mg/ml solution for injection, in diabetic patients, increased requirements for insulin or oral antidiabetics should be taken into account.

During treatment with Dexamethasone phosphate 4 mg/ml solution for injection, in particular when high doses are used and in patients with poorly controlled hypertension, regular blood pressure measurements are necessary.

Patients with severe heart failure must be carefully monitored, as there is a risk of deterioration.

There is a risk of bradycardia if high dexamethasone doses are used.

Severe anaphylactic reactions can also occur.

The risk of tendon-related symptoms, tendonitis, and tendon ruptures is increased when fluoroquinolone and glucocorticoids are administered together.

Pre-existing *myasthenia gravis* can deteriorate during treatment with Dexamethasone phosphate 4 mg/ml solution for injection.

Immunisations with inactivated (killed) vaccines may be undertaken in principle. However, it must be taken into account that the immune response and thus the success of the immunisation can be impaired if higher doses of corticosteroids are used.
If high doses of corticosteroid are used, sufficient potassium intake should be ensured and dietary restriction of sodium intake may be necessary. The serum potassium level should be monitored.
Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Abrupt discontinuation of Dexamethasone phosphate 4 mg/ml solution for injection administered for more than approximately 10 days can lead to exacerbation or recurrence of the underlying disease and to the occurrence of acute adrenal failure/cortisone withdrawal syndrome. Therefore, when discontinuation is anticipated, the dose should be reduced slowly.

Some viral diseases such as chickenpox or measles may have a particularly serious course in patients being treated with glucocorticoids. Immunosuppressed patients without a definite history of chickenpox or measles are at particular risk. If during

therapy with Dexamethasone 4 mg/ml solution for injection these patients come into contact with individuals suffering from measles or chickenpox, preventative treatment should be started, where necessary.

In post marketing experience, tumour lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

In case of intravenous administration, the injection should be given slowly over 2-3 minutes. Following a too rapid administration, short and essentially harmless undesirable effects in the form of unpleasant tingling or paraesthesias, lasting up to 3 minutes can occur.

Dexamethasone phosphate 4 mg/ml solution for injection is intended for a short-term use only. If this medicinal product is administered over a long period, further warnings and precautions must be taken into account/ considered as for medicinal products containing glucocorticoids intended for long-term use.

Following local administration, possible systemic adverse effects and interactions have to be taken into account.

The intraarticular administration of glucocorticoids increases the risk of joint infections. Longer-term and repeated use of glucocorticoids in weight-bearing joints can lead to a deterioration of wear-related lesions due to possible overload of the joint following a reduction in pain or other symptoms.

Children and adolescents
In the growth phase of children, the benefit-risk ratio of therapy with Dexamethasone phosphate 4 mg/ml solution for injection should be considered carefully.
Premature neonates
Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours) of premature infants with chronic lung disease at starting doses of 0.25mg/kg twice daily.

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).

Propylene glycol content
Due to the propylene glycol content of the product (20 mg per ml), caution should be exercised when high doses of Dexamethasone phosphate 4 mg/ml solution for injection are used in infants and children younger than 5 years old and/or for prolonged period of time (see sections 2 and 4.2). The following paediatric population groups are particularly at risk of developing propylene glycol toxicity:

- *Neonates (new born infants less than 4 weeks old)*

Dexamethasone phosphate 4 mg/ml solution for injection is not recommended for use in pre-term or full-term neonates. However, following a careful individual assessment, the product might be considered for a neonate if in the opinion of the health care professional/ at a discretion of a prescriber benefits of using the product outweigh potential risks.
When doses higher than 0.05 ml/kg/day of Dexamethasone phosphate 4 mg/ml solution for injection are required in neonates, the corresponding dose of propylene glycol may exceed the **1mg/kg/day** safety threshold. Exceeding this safety threshold in neonates may induce serious adverse effects when co-administered with any substrate for alcohol dehydrogenase such as ethanol, particularly if they receive other medicines that contain propylene glycol or alcohol. Close medical monitoring for any signs of toxicity is necessary.

- *Infants (children older than 4 weeks old) and children younger than 5 years old*

When doses higher than 2.5 ml/kg/day of Dexamethasone phosphate 4 mg/ml solution for injection are required, the corresponding dose of propylene glycol may exceed the **50 mg/kg/day** safety threshold. The co-administration of propylene glycol at doses of 50 mg/kg/day and above with any substrate for alcohol dehydrogenase (such as ethanol) may induce serious

adverse effects in **infants** and **children younger than 5 years old,** particularly if they receive other medicines that contain propylene glycol or alcohol. Dexamethasone phosphate 4 mg/ml solution for injection should therefore be used with caution in this population.
In the growth phase in children, the benefit-risk ratio of therapy with Dexamethasone 4 mg/ml solution for injection should be carefully considered.

Elderly
As elderly patients are at greater risk of osteoporosis, the benefit-risk ratio of the therapy with Dexamethasone 4 mg/ml solution for injection should be carefully weighed up.

Hepatic and renal impairment
Due to the propylene glycol content of the product frequent medical monitoring is necessary in patients with renal insufficiency or with liver failure because various adverse effects attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction (see sections 2 and 4.2). Daily exposure to propylene glycol in those patients should not exceed **50 mg/kg**, corresponding to 2.5 ml/kg/day of Dexamethasone phosphate 4 mg/ml solution for injection.

The use of Dexamethasone phosphate 4 mg/ml solution for injection can result in positive results of doping tests.

Sodium
This medicinal product contains up to 1.9 mmol (43 mg) sodium per maximum single dose of the medicinal product (350 mg for a person with 70 kg bodyweight), equivalent to 2.15% 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

There is an increased risk of gastrointestinal ulcerations and bleeding when used with non-steroidal anti-inflammatory drugs (NSAIDs), salicylates, and indometacin.

The half-life of glucocorticoids can be increased when used with estrogens (e.g. ovulation inhibitors) and therefore the corticoid effect can be enhanced.

Medicines that induce CYP3A4 such as phenytoin, barbiturates, carbamazepine, primidone, rifampicin may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and reduced physiological activity, the dosage may have to be adjusted.

CYP3A4 inhibitors (including ketoconazole, itraconazole, and cobicistat) can reduce dexamethasone clearance, which can lead to an increased effect and adrenal suppression/Cushing's syndrome. The combination should be avoided, unless the benefit outweighs the increased risk of systemic corticosteroid side effects. In this case, patients should be monitored for systemic corticosteroid effects.

Ephedrine may increase metabolism of glucocorticoids and thus may reduce their effect.

Concomitant therapy with angiotensin-converting enzyme (ACE) inhibitors may increase a risk of blood count changes.

Digoxin (cardiac glycosides) toxicity can be precipitated by corticosteroids via the effect of electrolyte imbalance (potassium deficiency).

When corticosteroids are administered concomitantly with potassium-depleting diuretics or laxatives, patients should be observed closely for development of hypokalaemia due to increased potassium excretion.

The efficacy of coumarin anticoagulants may be changed by concurrent corticosteroid treatment. The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time, in order to avoid spontaneous bleeding. A dose adjustment of the anticoagulant can be necessary in the case of concomitant use.

The desired effects of hypoglycaemic agents (including insulin) are antagonised by corticosteroids.

In case of concomitant use of glucocorticoids with atropine or other anticholinergics, intraocular pressure may increase.

Prolonged muscle relaxation can occur when non-depolarising muscle relaxants are used concomitantly with glucocorticoids.

Corticosteroids can reduce praziquantel concentration in the blood.

There is an increased risk of myopathies and cardiomyopathies when dexamethasone is used concomitantly with chloroquine, hydroxychloroquine and mefloquine.

Following administration of protirelin, thyroid stimulating hormone (TSH) rise can be reduced.

When administered concomitantly with other immunosuppressants there is an increased susceptibility to infections and possible deterioration or manifestation of latent infections. Additionally in combination with cyclosporine, the level of cyclosporine in blood is increased and a risk of cerebral seizures is also increased.
Concomitant use with fluoroquinolones can increase the risk of tendon-related symptoms.

Skin reactions to allergy tests can be suppressed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Dexamethasone crosses the placenta.
During pregnancy, especially in the first trimester, dexamethasone may be considered for use only following a careful benefit-risk assessment. Corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks.

When administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intrauterine growth retardation.

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.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intrauterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man (see section 5.3).

If glucocorticoids are administered at the end of pregnancy, the foetus is at risk of adrenal cortex atrophy, which may necessitate a tapering substitution treatment in neonate.

Dexamethasone phosphate 4 mg/ml solution for injection contains propylene glycol. Although propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus Dexamethasone phosphate 4 mg/ml solution for injection should be used with caution during pregnancy. Careful assessment of the potential benefits and associated risks of treatment with steroids and propylene glycol administration should be made on individual basis.

Breast-feeding
Dexamethasone is excreted in breast milk. No harm to the infant has ever been reported.

Dexamethasone phosphate 4 mg/ml solution for injection should be used with caution in breast-feeding women only when strictly necessary. A careful assessment of the potential benefits and associated risks of treatment has to be made on individual basis.

If higher doses are necessary for the treatment of a disease, breast-feeding should be discontinued.

Dexamethasone phosphate 4 mg/ml solution for injection contains propylene glycol which was also detected in breast milk. Although propylene glycol has not been shown to cause reproductive or developmental toxicity in animals and humans Dexamethasone phosphate 4 mg/ml solution for injection should be used with caution by breast-feeding women. Careful assessment of the potential benefits and associated risks of treatment with steroids and propylene glycol administration should be made on an individual basis.

4.7 Effects on ability to drive and use machines

Dexamethasone phosphate 4 mg/ml solution for injection has no, or negligible influence, on the ability to drive and use machines; the same applies to work in a hazardous setting.

4.8 Undesirable effects

The risk of undesirable effects is low during short-term dexamethasone therapy. However, in case of short-term and high-dose parenteral therapy, the risk of electrolyte changes, oedema, possible increase in blood pressure, heart failure, cardiac arrhythmias, or seizures must be considered, and the clinical manifestations of infection should also be anticipated. Clinicians should be alert to the possibility of gastrointestinal ulcers which are often stress-related, and which can be relatively asymptomatic during corticosteroid treatment, and a reduction in glucose tolerance.

The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression, correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see section 4.4).

The frequency of the adverse reactions is listed according to the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Rare (≥1/10000 to <1/1000)
Very rare (<1/10000)
Not known (cannot be estimated from the available data)

System organ class	Frequency	Undesirable effects
Infections and infestations	Not known	Masking of infections, manifestation, exacerbation, or reactivation of viral infections, fungal infections, bacterial, parasitic, and opportunistic infections, activation of strongyloidiasis (see section 4.4).
Blood and lymphatic system disorders	Not known	Moderate leukocytosis, lymphopenia, eosinopenia, polycythaemia.
Immune system disorders	Not known	Hypersensitivity reactions (e.g. drug-induced exanthema), severe anaphylactic reactions, such as arrhythmias, bronchospasms, hypertension or hypotension, circulatory collapse, cardiac arrest, weakening of the immune system.
Endocrine disorders	Not known	Cushing's syndrome (typical symptoms: moon face, abdominal obesity, and plethora), adrenal suppression (see section 4.4).
Metabolism and nutrition disorders	Not known	Sodium retention with oedema, increased potassium loss (beware of arrhythmias), weight gain, reduced glucose tolerance, diabetes mellitus, hypercholesterolaemia and hypertriglyceridaemia, appetite increase.
Psychiatric disorders	Not known	Depressions, irritation, euphoria, increased drive, psychoses, mania, hallucinations, affect lability, feelings of anxiety, sleep disturbances, suicidal tendency.
Nervous system disorders	Not known	Pseudotumour cerebri, manifestation of latent epilepsy, increase in the likelihood of a seizure in case of manifest epilepsy.
Eye disorders	Not known	Cataract, in particular with posterior subcapsular opacification, glaucoma, deterioration of symptoms in the case of corneal ulcer, increased risk of viral, fungal, and bacterial infections of the eye, deterioration of bacterial inflammations of the cornea, ptosis, mydriasis, chemosis, iatrogenic scleral perforation, chorioretinopathy. In rare cases, reversible exophthalmos. Blurred vision (see also section 4.4).
Cardiac disorders	Not known	Hypertrophic cardiomyopathy in prematurely born infants (see section 4.4).
Vascular disorders	Not known	Hypertension, increase risk of arteriosclerosis and

		thrombosis, vasculitis (also as withdrawal syndrome after long-term therapy), increased capillary fragility.
Gastrointestinal disorders	Not known	Gastrointestinal ulcers, gastrointestinal bleedings, pancreatitis, gastric symptoms.
Skin and subcutaneous tissue disorders	Not known	Striae rubrae, atrophy, teleangiectasias, petechiae, ecchymoses, hypertrichosis, steroid acne, rosacea-like (perioral) dermatitis, changes in skin pigmentation.
Musculoskeletal and connective tissue disorders	Not known	Myopathy, muscular atrophy and weakness, steroid myopathy, osteoporosis (dose-dependent also possible after a short treatment only), aseptic bone necrosis, tendon-related symptoms, tendinitis, tendon rupture, epidural lipomatosis, growth inhibition in children.
Reproductive system and breast disorders	Not known	Disturbances in sexual hormone secretion (causing irregular menstruation through to amenorrhoea, hirsutism, impotence).
General disorders and administration site conditions	Not known	Delayed wound healing.

Local use:
Local irritations and intolerances are possible (sensation of heat, relatively persistent pain). The development of skin atrophy and atrophy of subcutaneous tissue at the injection site cannot be excluded if corticosteroids are not injected carefully into a 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 the national reporting system: HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

Symptoms:
Acute intoxications with dexamethasone have never been reported. In case of chronic overdose, intensified adverse effects (see section 4.8), in particular in relation to the endocrine system, metabolism, and electrolyte balance, are expected.
No antidote is available. Treatment is probably not indicated for reactions due to chronic poisoning, unless the patient has a condition that would render a patient to be unusually susceptible to experience adverse effects from corticosteroids. In this case, symptomatic treatment should be instituted as necessary.

Anaphylactic and hypersensitivity reactions may be treated with adrenaline, positive-pressure artificial respiration and aminophylline.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code: H02AB02

Pharmacodynamic effects
Dexamethasone is a mono-fluorinated glucocorticoid with marked antiallergic, antiphlogistic, and membrane-stabilising properties and effects on the carbohydrate, protein, and fat metabolism.

Dexamethasone possesses the actions and effects of other basic glucocorticoids and is among the most active members of its class.
Dexamethasone has an approximately 7.5-fold greater glucocorticoid effect than prednisolone and prednisone, and its effect is 30 times more potent than that of hydrocortisone; there are no mineralocorticoid effects.

The biological effect of glucocorticoids such as dexamethasone stems from activation of the transcription of corticosteroid-sensitive genes. The anti-inflammatory, immunosuppressive, and antiproliferative effects are elicited, amongst other mechanisms, by reduced formation, release, and activity of inflammatory mediators and through inhibition of the specific functions and the migration of inflammatory cells. In addition, the effect of sensitised T-lymphocytes and macrophages on target cells by corticosteroids is possibly prevented.

If long-term corticoid medication is necessary, the possible induction of transient adrenal insufficiency must be taken into account. The suppressibility of the hypothalamus-pituitary-adrenal axis depends in part on individual factors.

Clinical efficacy and safety – COVID-19

Clinical efficacy

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% 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, 1.90), followed by oxygen only (rate ratio, 1.15 ;95% CI 1.06-1.24) with no beneficial effect in patients not receiving oxygen (rate ratio, 0.96; 95% CI 0.85-1.08).

Outcome	Dexamethasone (N = 2104)	Usual Care (N = 4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

*Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.

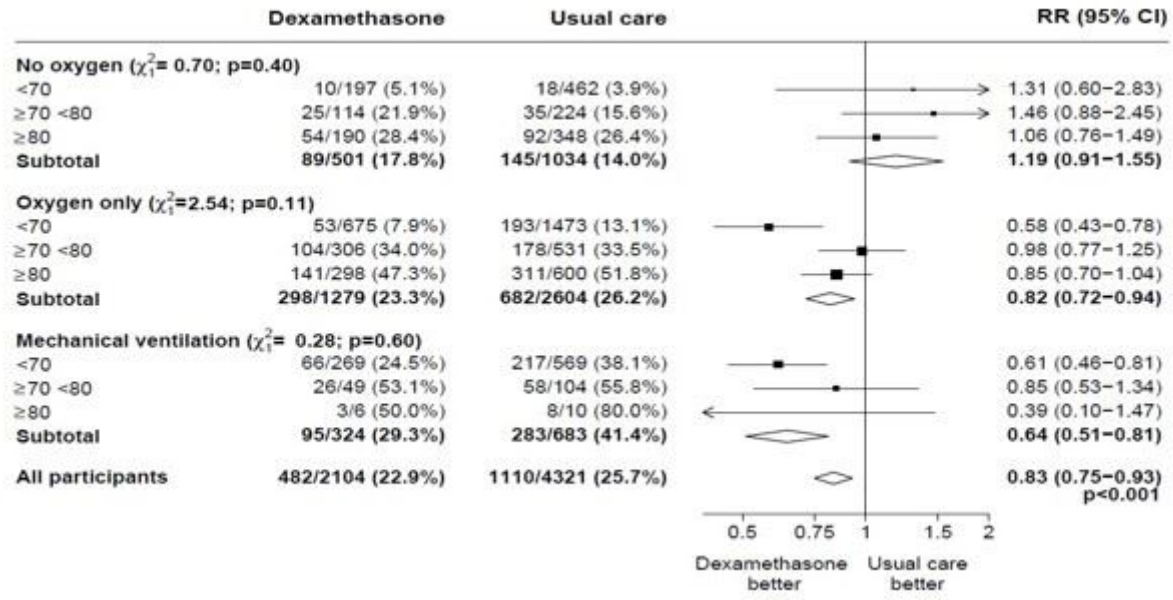
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

Safety

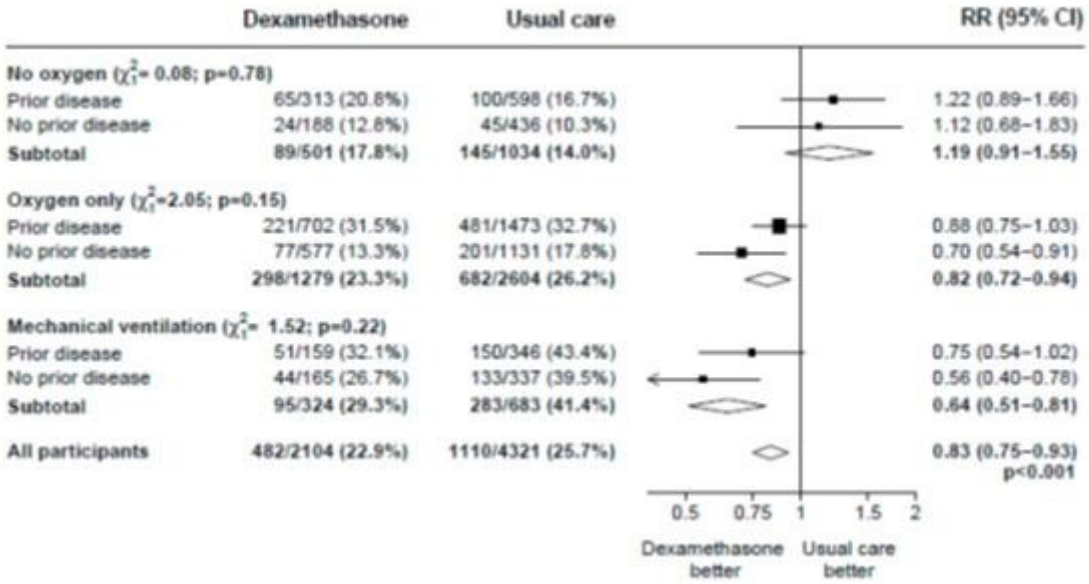
There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved.

Subgroup analyses

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



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



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

5.2 Pharmacokinetic properties

Distribution
Binding of dexamethasone to plasma proteins is less than for most other corticosteroids and is estimated to be about 77%. Dexamethasone binds to plasma proteins in a dose-dependent fashion. At very high doses, most circulates freely in the blood. In the case of hypoalbuminaemia, the proportion of unbound (active) corticoid increases. After intravenous application of radioactively marked dexamethasone in humans, maximum dexamethasone levels were measured in the cerebrospinal fluid, namely approximately 1/6 of the corresponding plasma concentration. The plasma half-life of dexamethasone is about 190 minutes.

With a biological half-life of over 36 hours, dexamethasone is one of the very long-acting glucocorticoids. Due to the protracted action, continual daily doses can therefore lead to accumulation and overdose.

Elimination

The (serum) elimination half-life of dexamethasone, in adults, averages approximately 250 minutes (+ 80 minutes).

Excretion is largely renal, in the form of free dexamethasone alcohol. Some metabolism takes place, and the metabolites are excreted chiefly as glucuronates or sulfates, likewise largely through the kidneys. Up to 65% of a dose is excreted in the urine in 24 hours. Disturbances in renal function do not affect the elimination of dexamethasone substantially. On the other hand, the elimination half-life is extended in the case of severe liver disease.

5.3 Preclinical safety data

Acute toxicity:
The LD_{50} for dexamethasone after a single oral application within the first 7 days in mice is 16 g/kg of body weight and in rats is more than 3 g/kg of body weight. After a single subcutaneous application, the LD50 in mice is more than 700 mg/kg of body weight and in rats is approximately 120 mg/kg of body weight within the first 7 days. Observed over a period of 21 days, these values drop, which is interpreted as a consequence of severe infection-released diseases, caused by hormone-induced immunosuppression.

Chronic toxicity:
There is no information on chronic toxicity in humans or animals. Corticoid-induced manifestations of intoxication have never been reported. In the case of relatively long-term therapy with doses above 1.5 mg /day, marked side effects must be anticipated (see section 4.8).

Mutagenic and carcinogenic potential:
Available study results for glucocorticoids reveal no evidence of clinically relevant genotoxic properties.

Reproductive toxicity:
In experimental animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs, and primates, but not in horses or sheep. In some cases, these abnormalities were combined with defects of the central nervous system and the heart. In primates, after exposure, changes were observed in the area of the brain. In addition, intrauterine growth can be delayed. All of these effects were observed when high doses were administered.

Environmental risk assessment (ERA):
Based on endocrine mechanism of action of dexamethasone a risk to aquatic compartment(s) cannot be excluded (See section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Disodium edetate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Dexamethasone is physically incompatible with daunorubicin, doxorubicin, vancomycin, diphenhydramine (with lorazepam and metoclopramide) and metaraminol bitartrate and should not be admixed with solutions containing these drugs. It is also incompatible with doxapram and glycopyrrolate in syringe and with ciprofloxacin, idarubicin and midazolam in Y-site injections (1:1 mixture).

Compatibility data of dexamethasone given continuously over 24 hours via SC syringe driver:

- Compatible with metoclopramide and morphine
- Possible incompatibility with octreotide (somatostatin analogue)
- Precipitates with the following: cyclizine, midazolam, haloperidol, levomepromazine.

6.3 Shelf life

Unopened ampoules: 2 years

Opened ampoules: The product should be used immediately after first opening.

Diluted solution:
Chemical and physical in-use stability of dilutions has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the 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

Store below 25°C. Do not freeze.
Keep the ampoule in the outer carton in order to protect from light.

For storage conditions after first opening or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless neutral glass one-point-cut (OPC) ampoules type I, with a nominal volume of 1 ml or 2 ml.
Package contains 5 or 10 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When Dexamethasone phosphate 4 mg/ml solution for injection is given by intravenous infusion, glucose 5%, sodium chloride 0.9% and Ringer's solution are recommended as diluents. The exact concentration of dexamethasone per infusion container should be determined by the desired dose, patient fluid intake and drip rate required.

In palliative care, Dexamethasone phosphate 4 mg/ml solution for injection can be diluted with sodium chloride and given by Continuous Subcutaneous Infusion (CSCI).

The solution should be visually inspected prior to use. Only clear solutions practically free from particles should be used.
For single use only.

This medicinal product may pose a risk to the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Inselstraße 1
31787 Hameln
Germany

8 MARKETING AUTHORISATION NUMBER

PA2237/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th August 2021
Date of last renewal: 28th April 2026

10 DATE OF REVISION OF THE TEXT

November 2025