DEXAMETHASONE
(Dexamethasone Sodium Phosphate)

4mg/mL

Injection

COMPOSITION

Each ml contains:
Dexamethasone Sodium Phosphate U.S.P equivalent to Dexamethasone Phosphate…… 4mg

THERAPEUTIC INDICATIONS
For use in certain endocrine and non-endocrine disorders responsive to dexamethasone therapy

Intravenous or Intramuscular administration

Dexamethasone 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.

Endocrine disorders

Primary or secondary adrenocortical insufficiency

(Hydrocortisone or cortisone is the first choice, but synthetic analogues may be used with mineralocorticoids where applicable and, in infancy, mineralocorticoid supplementation is particularly important)

Non-endocrine disorders

Dexamethasone solution for injection may be used in the treatment of non-endocrine dexamethasone-responsive conditions, including:

Allergy and anaphylaxis

Angioneurotic oedema and anaphylaxis

Coronavirus disease 2019 (COVID-19)

Dexamethasone is indicated in the treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) who require supplemental oxygen therapy.

Gastrointestinal

Crohn's disease and ulcerative colitis

Infection (with appropriate chemotherapy)

Miliary tuberculosis and endotoxic shock

Neurological disorders

Raised intracranial pressure secondary to cerebral tumour and infantile spasms

Respiratory

Bronchial asthma and aspiration pneumonitis

Skin disorders

Toxic epidermal necrolysis

Shock

Adjunctive treatment where high pharmacological doses are needed. Treatment is an adjunct to and not a substitute for, specific and supportive measures the patient may require. Dexamethasone has been shown to be beneficial when used in the early treatment of shock, but it may not influence overall survival.

Subcutaneous administration

In palliative care, patients receiving dexamethasones for symptoms such as fatigue, anorexia, refractory nausea and vomiting or adjuvant analgesia and symptomatic treatment of cord compression or raised intracranial pressure, dexamethasone 3.3mg/ml solution for injection may be administered subcutaneously as an alternative to the oral route when the latter is unacceptable or no longer feasible.

Local administration

for injection is suitable for intraarticular or soft-tissue injection as adjunctive therapy for short-term administration in:

Soft-tissue disorders

Such as carpal tunnel syndrome and tenosynovitis

Intraarticular disorders

Such as rheumatoid arthritis and osteoarthritis with an inflammatory component

Dexamethasone solution for injection may be injected intralesionally in selected skin disorders such as cystic acne vulgaris, localized lichen simplex, and keloids.

DOSAGE AND ADMINISTRATION

*All dosage recommendations are given in units of dexamethasone **base.***

General considerations

Dosage must be individualized on the basis of the disease and the response of the patient. In order to minimize side effects, the lowest possible dosage adequate to control the disease process should be used.

Intravenous and intramuscular injection

Usually, the parenteral dosage ranges are one-third to one-half of the oral dose, given every 12 hours.

The usual initial dosage is 0.4 mg – 16.6 mg (0.12 ml – 5.0 ml) a day. In situations of less severity, lower doses will generally suffice. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosage may be justified. In these circumstances, the slower rate of absorption by intramuscular administration should be recognized.

Both the dose in the evening, which is useful in alleviating morning stiffness and the divided dosage regimen are associated with greater suppression of the hypothalamo-pituitary-adrenal axis. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial dosage by small amounts at appropriate intervals to the lowest dosage which will maintain an adequate clinical response. Chronic dosage should preferably not exceed 500 micrograms dexamethasone daily. Close monitoring of the drug dosage is needed.

To avoid hypoadrenalism and/or a relapse of the underlying disease, it may be necessary to withdraw the drug gradually.

Whenever possible, the intravenous route should be used for the initial dose and for as many subsequent doses as are given while the patient is in shock (because of the irregular rate of absorption of any medicament administered by any other route in such patients). When the blood pressure responds, use the intramuscular route until oral therapy can be substituted. For the comfort of the patient, not more than 2 ml should be injected intramuscularly at any one site.

In emergencies, the usual dose of Dexamethasone solution for injection by intravenous or intramuscular injection is 3.3 mg – 16.6 mg (1.0 ml – 5.0 ml) - in shock use only the i.v. route. This dose may be repeated until adequate response is noted.

After initial improvement, single doses of 1.7 mg – 3.3 mg (0.5 ml – 1.0 ml), repeated as necessary, should be sufficient. The total daily dosage usually need not exceed 66.4 mg (20.0 ml), even in severe conditions.

When constant maximal effect is desired, dosage must be repeated at three-hour or four-hour intervals or maintained by slow intravenous drip.

Intravenous or intramuscular injections are advised in acute illness. When the acute stage has passed, oral steroid therapy should be substituted as soon as feasible.

For the treatment of COVID-19

Adult patients 6 mg (1.8ml) IV, once a day for up to 10 days.

Paediatric population

Paediatric patients (adolescents aged 12 years and older) are recommended to be given a 6mg dose (1.8ml) 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.

Shock (of hemorrhagic, traumatic, or surgical origin):

Usually 1.7 mg – 5.0 mg/kg (0.5 ml – 1.5 ml/kg) bodyweight as a single intravenous injection. This may be repeated in two to six hours if shock persists. Alternatively, this may be followed immediately by the same dose in an intravenous infusion. Therapy with Dexamethasone solution for injection is an adjunct to and not a replacement for conventional therapy.

Administration of these high doses should be continued only until the patient's condition has stabilized and usually no longer than 48-72 hours.

Cerebral oedema:

• *Management of recurrent or inoperable brain tumour:*

Maintenance therapy should be determined for each patient; 1.7 mg (0.5 ml) two or three times a day may be effective. The smallest dose necessary to control cerebral oedema should be used.

• *Cerebral oedema associated with primary or metastatic brain tumour, preoperative preparation of patients with increased intracranial pressure secondary to brain tumour:*

Initially 8.3 mg (2.5ml) intravenously, followed by 3.3 mg (1.0 ml) intramuscularly every six hours until symptoms of cerebral oedema subside. Response is usually noted within 12-24 hours; dosage may be reduced after two to four days and gradually discontinued over five to seven days.

High doses of Dexamethasone solution for injection are recommended for initiating short-term intensive therapy for acute life-threatening cerebral oedema. Following the high-loading dose schedule of the first day therapy, the dose is scaled down over the seven- to ten- day period of intensive therapy and subsequently reduced to zero over the next seven to ten days. When maintenance therapy is required, substitute oral dexamethasone as soon as possible.

Suggested high-dose schedule in cerebral oedema	
Adults	
Initial dose 41.5 mg dexamethasone (12.5 ml) i.v.	
1st day	6.6 mg dexamethasone (2.0 ml) i.v. every 2 hours
2nd day	6.6 mg dexamethasone (2.0 ml) i.v. every 2 hours
3rd day	6.6 mg dexamethasone (2.0 ml) i.v. every 2 hours
4th day	3.3 mg dexamethasone (1.0 ml) i.v. every 2 hours
5th-8th days	3.3 mg dexamethasone (1.0 ml) i.v. every 4 hours
Thereafter	decrease by daily reduction of 3.3 mg dexamethasone (1.0 ml)
Children (35 kg and over)	
Initial dose 20.8 mg dexamethasone (6.25 ml) i.v.	
1st day	3.3 mg dexamethasone (1.0 ml) i.v. every 2 hours
2nd day	3.3 mg dexamethasone (1.0 ml) i.v. every 2 hours
3rd day	3.3 mg dexamethasone (1.0 ml) i.v. every 2 hours
4th day	3.3 mg dexamethasone (1.0 ml) i.v. every 4 hours
5th-8th days	3.3 mg dexamethasone (1.0 ml) i.v. every 6 hours
Thereafter	decrease by daily reduction of 1.7 mg dexamethasone (0.5 ml)
Children (below 35 kg)	
Initial dose 16.6 mg dexamethasone (5.0 ml) i.v.	
1st day	3.3 mg dexamethasone (1.0 ml) i.v. every 3 hours
2nd day	3.3 mg dexamethasone (1.0 ml) i.v. every 3 hours
3rd day	3.3 mg dexamethasone (1.0 ml) i.v. every 6 hours
4th day	3.3 mg dexamethasone (1.0 ml) i.v. every 3 hours
5th-8th days	1.7 mg dexamethasone (0.5 ml) i.v. every 6 hours
Thereafter	decrease by daily reduction of 0.83 mg dexamethasone (0.25 ml)

Dual therapy to treat hypersensitivity reactions:

In acute self-limiting allergic disorders or acute exacerbations of chronic allergic disorders, the following schedule combining oral and parenteral therapy is suggested:

First day:	Dexamethasone solution for injection, 3.3 mg – 6.6 mg (1.0 ml – 2.0 ml) intramuscularly
Second day	Two 500 microgram dexamethasone tablets twice a day
Third day:	Two 500 microgram dexamethasone tablets twice a day
Fourth day:	One 500 microgram dexamethasone tablet twice a day
Fifth day:	One 500 microgram dexamethasone tablet twice a day
Sixth day:	One 500 microgram dexamethasone tablet once daily
Seventh day:	One 500 microgram dexamethasone tablet once daily
Eighth day:	Reassessment day

Subcutaneous administration

In palliative care, subcutaneous Dexamethasone solution for injection may be administered by injection or Continuous Subcutaneous Infusion (CSCI). Doses usually range between 4 mg to 16 mg over 24 hours, taking into consideration local clinical guidelines, and should be titrated according to the response.

Intraarticular, intrabursal or intralesional injection

In general, these injections are employed when only one or two joints or areas are affected.

Some of the usual single doses are:

SITE OF INJECTION	DEXAMETHASONE DOSE
Large joint (e.g., knee)	1.7 mg – 3.3 mg (0.5 ml – 1.0 ml)
Small joints (e.g., interphalangeal, temporomandibular)	0.66 mg – 0 .8 mg (0.2 ml – 0.25 ml)
Bursae	1.7 mg – 2 .5 mg (0.5 ml – 0.75 ml)
Tendon sheaths*	0.33 mg – 0.8 mg (0.1 ml – 0.25 ml)
Soft-tissue infiltration	1.7 mg – 5.0 mg (0.5 ml – 1.5 ml)
Ganglia	0.8 mg – 1.7 mg (0.25 ml – 0.5 ml)

*Injection should be made into the tendon sheath and not directly into the tendon.

Frequency of injection: once every three to five days to once every two to three weeks, depending on response.

Use in special population groups

Paediatric population

• *Neonates*

Any decision to use Dexamethasone 3.3mg/ml solution for injection in this population should be made on a case-by-case basis and following a careful assessment of the potential benefits and risks of treatment.

• *Infants and children younger than 5 years old*

Dexamethasone solution for injection contains propylene glycol (20 mg per ml). The product should therefore be used with **caution** in infants and children younger than 5 years old when high doses of dexamethasone are required.

Where possible, administration should be limited to a single dose on alternate days to lessen retardation of growth and minimize suppression of the hypothalamo-pituitary adrenal axis.

Use in patients with hepatic or renal impairment

Due to the presence of excipient propylene glycol, medical monitoring is required in patients with impaired hepatic or renal function when Dexamethasone solution for injection is administered at doses above 8.5 mg/kg/day (equivalent to 50 mg/kg/day propylene glycol) –.

Use in the elderly:

Treatment of elderly patients, particularly if long term, should be planned bearing in mind the more serious consequences of the common side effects of dexamethasones in old age, especially osteoporosis, diabetes, hypertension, Hypokalaemia, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life threatening reactions.

Method of administration

Dexamethasone solution for injection can be given without mixing or dilution. Alternatively, it can be added, without loss of potency, to sodium chloride, or dextrose, injection and given by intravenous infusion.

In palliative care, Dexamethasone 3.3mg/ml solution for injection can be diluted with sodium chloride injection 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.

CONTRAINDICATIONS

Systemic fungal infection; systemic infection unless specific anti-infective therapy is employed; hypersensitivity to the active ingredient or any other component of this medication. Administration of live virus vaccines.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with hematological 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.

Patients/and or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure, although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic dexamethasones in patients with existing or previous history of severe affective disorders in themselves or in their first-degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

Frequent intraarticular injections over a prolonged period may lead to joint destruction with bone necrosis. Intraarticular injection of dexamethasone may produce systemic adverse reactions including adrenal suppression.

Undesirable effects may be minimised by using the lowest effective dose for minimum period. Frequent patient review is required to appropriately titrate the dose against disease activity. When reduction in dosage is possible, the reduction should be gradual.

Systemic dexamethasones should not be stopped for patients who are already treated with systemic (oral) dexamethasones for other reasons (e.g., patients with chronic obstructive pulmonary disease) but not requiring supplemental oxygen.

Dexamethasones may exacerbate systemic fungal infections and, therefore, should not be used in the presence of such infections, unless they are needed to control drug reactions due to amphotericin. Moreover, there have been cases reported in which, concomitant use of amphotericin and hydrocortisone, was followed by cardiac enlargement and congestive failure.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, retention of salt and water and increased excretion of potassium, but these effects are less likely to occur with synthetic derivates, except when used in large doses. Dietary salt restrictions and potassium supplementation may be necessary. All dexamethasones increase calcium excretion.

The slower rate of absorption by intramuscular administration should be recognized.

In patients on dexamethasone therapy subjected to unusual stress (e.g., intercurrent illness, trauma or surgical procedures), dosage should be increased before, during and after the stressful situation. Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of dexamethasones and may be minimised by gradual dosage reduction, being tapered off over weeks and months, depending on the dose and duration of treatment, but may persist for up to a year after discontinuation of therapy. In any stressful situation during that period, therefore, dexamethasone therapy should be reinstated. If the patient is already receiving dexamethasones, the current dosage may have to be temporarily increased. Salt and/or a mineralocorticoid should be given concurrently, since mineralocorticoid secretion may be impaired.

Stopping dexamethasones after prolonged therapy may cause withdrawal symptoms, including fever, myalgia, arthralgia and malaise. This may occur in patients even without evidence of adrenal insufficiency.

In patients who have received more than physiological doses of systemic dexamethasones (approximately 1 mg dexamethasone) for greater than three weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic dexamethasones is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic dexamethasones but there is uncertainty about hypothalamic-pituitary adrenal (HPA) suppression, the dose of systemic dexamethasones *may* be reduced rapidly to physiological doses. Once a daily dose of 1 mg dexamethasone is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic dexamethasone treatment, which has continued up to three weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 6 mg daily of dexamethasone for three weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic dexamethasone therapy should be *considered* even after courses lasting three weeks or less:

• patients who have had repeated courses of systemic dexamethasones, particularly if taken for greater than three weeks,

• when a short course has been prescribed within one year of cessation of long-term therapy (months or years),

• patients who may have reasons for adrenocortical insufficiency other than exogenous dexamethasone therapy,

• patients receiving doses of systemic dexamethasone greater than 6 mg daily of dexamethasone,

• patients repeatedly taking doses in the evening.

Patients should carry 'steroid treatment' cards, which give clear guidance on the precautions to be taken to minimize risk and which provide details of prescriber, drug, dosage and the duration of treatment.

Because anaphylactoid reactions have occurred, rarely, in patients receiving parenteral dexamethasone therapy, appropriate precautions should be taken prior to administration, especially when the patient has a history of allergy to any drug.

Administration of live virus vaccines is contraindicated in individuals receiving immunosuppressive doses of dexamethasones. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of dexamethasones, the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving dexamethasones as replacement therapy, e.g., for Addison's disease.

Literature reports suggest an apparent association between use of dexamethasones and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with dexamethasones should be used with great caution in these patients.

The use of Dexamethasone solution for injection in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the dexamethasone is used for the management of the disease in conjunction with an appropriate antituberculosis regimen. If the dexamethasones are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation may occur. During prolonged dexamethasone therapy, these patients should receive prophylactic chemotherapy.

Dexamethasones may mask some signs of infection and new infections may appear during their use. Suppression of the inflammatory response and immune function increasing the susceptibility to infections and their severity. The clinical presentation may often be atypical and serious infections such as septicemia and tuberculosis may be masked and reach an advanced stage before being recognized. There may be decreased resistance and inability to localize infection.

A report shows that the use of dexamethasones in cerebral malaria is associated with a prolonged coma and an increased incidence of pneumonia and gastro-intestinal bleeding.

Chickenpox is of particular concern, since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they

should seek urgent medical attention. Passive immunization with varicella/zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic dexamethasones or who have used them within the previous three months; this should be given within ten days of exposure to chickenpox.

If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Dexamethasones should not be stopped and the dose may need to be increased.

Measles can have a more serious or even fatal course in immunosuppressed patients. In such children or adults particular care should be taken to avoid exposure to measles. If exposed, prophylaxis with intramuscular pooled immunoglobulin (IG) may be indicated. Exposed patients should be advised to seek medical advice without delay.

Dexamethasones may activate latent amoebiasis or strongyloidiasis or exacerbate active disease. Therefore, it is recommended that latent or active amoebiasis and strongyloidiasis be ruled out, before initiating dexamethasone therapy in any patient at risk of or with symptoms of either condition.

Prolonged use of dexamethasones may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Dexamethasones may increase or decrease motility and number of spermatozoa.

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 dexamethasone side-effects, in which case patients should be monitored for systemic dexamethasone side-effects.

Special precautions:

Particular care is required when considering the use of systemic dexamethasones in patients with the following conditions and frequent patient monitoring is necessary: renal insufficiency and liver failure, hypertension, diabetes or in those with a family history of diabetes, congestive heart failure, osteoporosis, previous steroid myopathy, glaucoma (or family history of glaucoma), myasthenia gravis, non-specific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, existing or previous history of severe affective disorders (especially previous steroid psychosis), and epilepsy. Signs of peritoneal irritation, following gastrointestinal perforation in patients receiving large doses of dexamethasones, may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisolism.

There is an enhanced effect of dexamethasones in patients with hypothyroidism and in those with cirrhosis.

Dexamethasones should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

Local steroid injection should be undertaken in an aseptic environment to reduce the particular risk of bacterial infection, injection of a steroid into an infected site should be avoided.

Appropriate examination of joint fluids is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Patients should understand the great importance of not over-using joints that are still diseased, despite symptomatic improvement.

Dexamethasones should not be injected into unstable joints.

Frequent intraarticular injections have been reported to cause development of Charcot-like arthropathies.

Paediatric population

Neonates:

Dexamethasone has been used to treat and prevent bronchopulmonary dysplasia (formerly known as chronic lung disease) in preterm neonates (unlicensed use). Clinical trials have shown no long-term benefit in reducing time to discharge, the incidence of chronic lung disease or mortality. Recent trials have suggested an association between the use of dexamethasone in preterm neonates and the development of cerebral palsy. Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours) of premature infants in this indication at starting doses of 0.25mg/kg twice daily. In view of these safety concerns, any decision to use Dexamethasone solution for injection in this population should be made on a case-by-case basis and following a careful assessment of the potential benefits and risks of treatment. Any benefit-risk assessment of the use of Dexamethasone solution for injection in this population should take into account the propylene glycol content of the product –.

Children:

Dexamethasones cause growth retardation in infancy, childhood and adolescence, which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. In order to minimize suppression of the hypothalamo-pituitary-adrenal axis and growth retardation, treatment should be limited, where possible, to a single dose on alternate days.

Growth and development of infants and children on prolonged dexamethasone therapy should be carefully monitored.

Dexamethasone solution for injection should be used with **caution** in infants and children younger than 5 years old when high doses are required –

Propylene glycol content

Dexamethasone solution for injection contains propylene glycol (20 mg per ml). The following population groups are particularly at risk of developing propylene glycol toxicity:

• *Neonates*

In neonates, a safety threshold of 1mg/kg/day has been set for excipient propylene glycol by the European Medicines Agency (corresponding to a 0.17 mg/kg/day dose of Dexamethasone solution for injection) Exceeding this threshold may induce serious adverse effects in this population when co-administered with any substrate for alcohol dehydrogenase such as ethanol. The potential for propylene glycol toxicity should therefore be considered as part of any benefit-risk assessment of the use of Dexamethasone solution for injection in this population – see *Paediatric population*, above. Any use of the product in this population would require close medical monitoring.

• *Infants and children younger than 5 years' old*

In infants and children younger than 5 years old, a safety threshold of 50 mg/kg/day has been set for excipient propylene glycol by the European Medicines Agency (corresponding to an 8.5 mg/kg/day dose of Dexamethasone solution for injection). When high doses of Dexamethasone solution for injection are required, the corresponding propylene glycol exposure may exceed the 50 mg/kg/day threshold in some patients from this population. The co-administration of propylene glycol at or above this safety threshold with any substrate for alcohol dehydrogenase (such as ethanol) may induce adverse effects in children younger than 5 years old. Dexamethasone solution for injection should therefore be used with **caution** in this population when the product is used in high doses.

• *Patients with hepatic or renal impairment*

Various adverse events attributable to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure, and liver dysfunction. Medical monitoring in this population is required when Dexamethasone solution for injection is administered at doses of 8.5 mg / kg / day (equivalent to 50 mg / kg / day propylene glycol) and above.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per each 1 ml and 2 ml ampoule, that is to say essentially 'sodium-free'.

DRUG INTERACTIONS

Aspirin should be used cautiously in conjunction with dexamethasones in hypoprothrombinemia.

The renal clearance of salicylates is increased by dexamethasones and therefore salicylate dosage should be reduced along with steroid withdrawal.

As phenytoin, barbiturates, ephedrine, rifabutin, carbamazepine, rifampicin and aminoglutethimide may enhance the metabolic clearance of dexamethasones, resulting in decreased blood levels and reduced physiological activity, the dosage may have to be adjusted. These interactions interfere with dexamethasone suppression tests which should be interpreted with caution during administration of these drugs.

False-negative results in the dexamethasone suppression test in patients being treated with indomethacin have been reported.

The efficacy of coumarin anticoagulants may be changed by concurrent dexamethasone treatment. The prothrombin time should be checked frequently in patients who are receiving dexamethasones and coumarin anticoagulants at the same time, in order to avoid spontaneous bleeding.

The desired effects of hypoglycemic agents (including insulin) are antagonized by dexamethasones.

When dexamethasones are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of Hypokalaemia.

Dexamethasones may affect the nitro blue tetrazolium test for bacterial infection and produce false-negative results.

Antiretroviral protease inhibitors (ritonavir, darunavir, indinavir, lopinavir, saquinavir and efavirenz) are metabolized by CYP3A. Medicinal products that induce CYP3A activity, such as dexamethasone, may increase the clearance of medicines metabolized by CYP3A, resulting in lowered plasma concentrations.

Certain antiretroviral protease inhibitors (ritonavir, indinavir) may also be inhibitors of CYP3A themselves and as a result may increase the plasma concentration of dexamethasone.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The ability of dexamethasones to cross the placenta varies between individual drugs, however, dexamethasone readily crosses the placenta.

Administration of dexamethasones 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 dexamethasones result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man.

However, when administered for prolonged periods or repeatedly during pregnancy, dexamethasones may increase the risk of intrauterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to dexamethasones but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, dexamethasones should only be prescribed when the benefits to the mother and child outweigh the risks. When dexamethasones are essential however, patients with normal pregnancies may be treated as though they were in non-gravid state.

Lactation

Dexamethasones may pass into breast milk, although no data are available for dexamethasone. Infants of mothers taking high doses of systemic dexamethasones for prolonged periods may have a degree of adrenal suppression.

EFFECTS ON ABILITY TO DRIVE

None reported

ADVERSE DRUG REACTIONS

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.

Fluid and electrolyte disturbances:

Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension, increased calcium excretion

Musculoskeletal:

Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis (especially in post-menopausal females), vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones, tendon rupture and post-injection flare (following intraarticular use')

Gastrointestinal:

Peptic ulcer with possible perforation and haemorrhage, perforation of the small and large bowel, particularly in patients with inflammatory bowel disease, pancreatitis, abdominal distension, ulcerative esophagitis, dyspepsia, esophageal candidiasis

Dermatological:

Impaired wound healing, thin fragile skin, petechiae and ecchymoses, erythema, striae, telangiectasia, acne, increased sweating, possible suppression of skin tests, burning or tingling especially in the perineal area (after intravenous injection), other cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic oedema and hypo- or hyper-pigmentation

Neurological:

Convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache, cerebral palsy in pre-term infants

Psychiatric:

A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of dexamethasones; the frequency is unknown.

Endocrine:

Menstrual irregularities, amenorrhea, development of Cushingoid state, suppression of growth in children and adolescents, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress as in trauma, surgery or illness), decreased carbohydrate tolerance, manifestation of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetes, hirsutism

Anti-inflammatory and immunosuppressive effects:

Increased susceptibility and severity of infections with suppression of clinical symptoms and signs; opportunistic infections, recurrence of dormant tuberculosis

Ophthalmic:

Posterior subcapsular cataracts, increased intraocular pressure, papilledema, corneal or scleral thinning, exacerbation of ophthalmic viral disease, glaucoma exophthalmos, rare instances of blindness associated with intralesional therapy around the face and head, retinopathy of prematurity, chorioretinopathy.

Metabolic:

Negative nitrogen balance due to protein catabolism, negative calcium balance

Cardiovascular:

Myocardial rupture following recent myocardial infarction (see 'Special warnings and precautions for use'), hypertrophic cardio-myopathy in low-birth-weight infants

Other:

Hypersensitivity, including anaphylaxis has been reported, leukocytosis, thrombo-embolism, weight gain, increased appetite, nausea, malaise, hiccups and sterile abscess.

Multiple myeloma patients treated with lenalidomide or thalidomide in combination with dexamethasone have an increased risk of thromboembolic events including deep vein thrombosis and pulmonary embolism.

Withdrawal symptoms and signs

Too rapid a reduction of dexamethasone dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death

In some instances, withdrawal symptoms may simulate a clinical relapse of the disease for which the patient has been undergoing treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 at pv@searlecompany.com

OVERDOSE

Reports of acute toxicity and/or deaths following overdosage with glucocorticoids are rare. 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 unusually susceptible to ill effects from dexamethasones. 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. The patient should be kept warm and quiet.

The biological half-life of dexamethasone in plasma is about 190 minutes.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids

ATC code: H02AB02

Dexamethasone possesses the actions and effects of other basic glucocorticoids and is among the most active members of its class.

Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. They cause profound and varied metabolic effects and in addition, they modify the body's immune responses to diverse stimuli. Naturally-occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used primarily for their potent anti-inflammatory effects in disorders of many organ systems.

Dexamethasone has predominant glucocorticoid activity with little propensity to promote renal retention of sodium and water. Therefore, it does not offer complete replacement therapy and must be supplemented with salt or desoxycorticosterone.

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 noninvasive 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)** *no./total no. of patients (%)*	**Rate or Risk Ratio (95% CI)***
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.

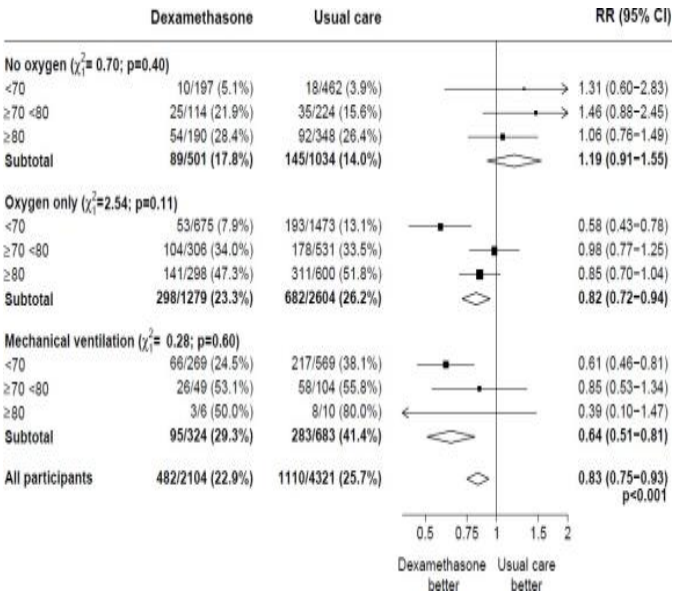
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

Safety

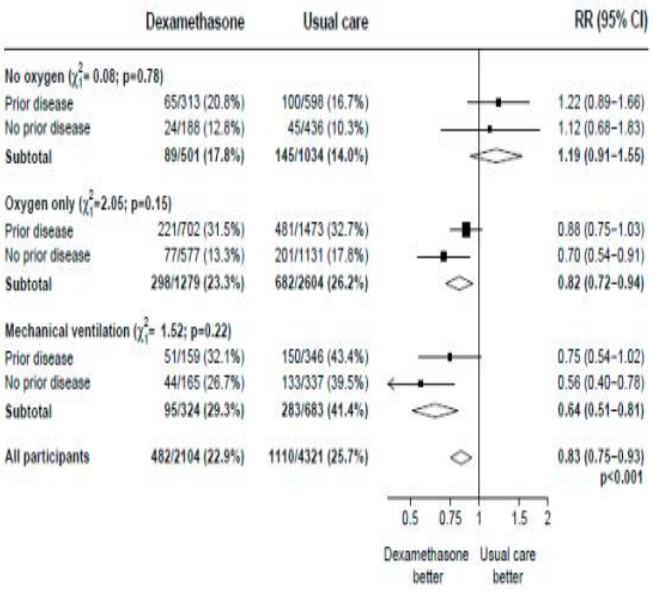
There were four serious adverse events (SAEs) related to study treatment: two SAEs of Hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved.

Subgroup analyses

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



Effects of allocation to DEXAMETHASONE on 28−day mortality, by respiratory support received at randomization 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)

Pharmacokinetic properties

The biological half-life of dexamethasone in plasma is about 190 minutes.

Binding of dexamethasone to plasma proteins is less than for most other dexamethasones and is estimated to be about 77%.

Up to 65% of a dose is excreted in the urine in 24 hours, the rate of excretion being increased following concomitant administration of phenytoin.

The more potent halogenated dexamethasones such as dexamethasone, appear to cross the placental barrier with minimal inactivation.

PRECLINICAL SAFETY DATA

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 of the heart. In primates, effects in the brain were seen after exposure. Moreover, intra-uterine growth can be delayed. All these effects were seen at high dosages.

PRESENTATION

Dexamethasone injection is supplied in 1ml (25x1ml pack)

INSTRUCTIONS

Dosage: As directed by the physician.

Protect from light & moisture, store below 30OC. Keep all medicines out of the reach of children.

To be sold on the prescription of registered medical practitioner only.

Do not use if markedly discolored

REGISTRATION NUMBER

Dexamethasone Injection: R.N. 020304

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Manufactured by:

Amros Pharmaceuticals

A/96, S.I.T.E., Super Highway Karachi - Pakistan.

The Searle Company Limited.

One IBL Centre, 2nd Floor, Plot # 1,

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