DBL™ DEXAMETHASONE SODIUM PHOSPHATE INJECTION
(Dexamethasone sodium phosphate) Solution for injection

1 NAME OF THE MEDICINE
Dexamethasone sodium phosphate injection 8 mg/2 mL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each millilitre of DBL Dexamethasone Sodium Phosphate Injection (8 mg/2 mL) solution contains dexamethasone sodium phosphate equivalent to 4 mg of dexamethasone phosphate. The 8 mg/2 mL vial contains sodium sulfite as an antioxidant.

Excipient(s) with known effect
Sodium sulfite

For the full list of excipients, see **6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM
DBL Dexamethasone Sodium Phosphate Solution for injection is a clear colourless solution, free from visible particulate matter.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Replacement therapy - adrenocortical insufficiency
Dexamethasone has predominantly glucocorticoid activity and therefore is not a complete replacement therapy in cases of adrenocortical insufficiency. Dexamethasone should be supplemented with salt and/or a mineralocorticoid, such as deoxycorticosterone. When so supplemented, dexamethasone is indicated in:

- Acute adrenocortical insufficiency – Addison's disease, bilateral adrenalectomy;
- Relative adrenocortical insufficiency - Prolonged administration of adrenocortical steroids can produce dormancy of the adrenal cortex. The reduced secretory capacity gives rise to a state of relative adrenocortical insufficiency which persists for a varying length of time after therapy is discontinued. Should a patient be subjected to sudden stress during this period of reduced secretion (for up to two years after therapy has ceased) the steroid output may not be adequate. Steroid therapy should therefore be reinstituted to help cope with stress such as that associated with surgery, trauma, burns, or severe infections where specific antibiotic therapy is available;
- Primary and secondary adrenocortical insufficiency.

Disease therapy
Dexamethasone is indicated for therapy of the following diseases:

Collagen diseases: Systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis, giant cell arteritis, adjunctive therapy for short-term administration during an acute episode or exacerbation, acute rheumatic carditis – during an exacerbation or as maintenance therapy.

Pulmonary disorders: Status asthmaticus, chronic asthma, sarcoidosis, respiratory insufficiency.

Blood disorders: Leukaemia, idiopathic thrombocytopaenic purpura in adults, acquired (autoimmune) haemolytic anaemia.

Rheumatic diseases: Rheumatoid arthritis, osteoarthritis, adjunctive therapy for short-term administration during an acute episode or exacerbation of rheumatoid arthritis or osteoarthritis.

Skin diseases: Psoriasis, erythema multiforme, pemphigus, neutrophilic dermatitis, localised neurodermatitis, exfoliative dermatitis, sarcoidosis of skin, severe seborrhoeic dermatitis, contact dermatitis.

Gastrointestinal disorders: Ulcerative colitis, regional enteritis.

Oedema: Cerebral oedema associated with primary or metastatic brain tumours, neurosurgery or stroke, oedema associated with acute non-infectious laryngospasm (or laryngitis).

Eye disorders: Allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, chorioretinitis, optic neuritis, anterior ischaemic optic neuropathy.

Neoplastic states: Cerebral neoplasms, hypercalcaemia associated with cancer, leukaemias and lymphomas in adults, acute leukaemia in children.

Endocrine disorders: Adrenal insufficiency.

Preoperative and postoperative support
Dexamethasone may be used in any surgical procedure when the adrenocortical reserve is doubtful. This includes the treatment of shock due to excessive blood loss during surgery.

Shock
Dexamethasone may be used as an adjunct in the treatment of shock. Dexamethasone should not be used as a substitute for normal shock therapy.

4.2 Dose and method of administration
Dosage
Dosage of dexamethasone sodium phosphate is usually expressed in terms of dexamethasone phosphate.

Dosage requirements are variable and must be individualised on the basis of the disease being treated and patient response.

Intravenous and intramuscular administration
Intravenous or intramuscular dosage usually ranges from 0.5 to 24 mg of dexamethasone phosphate daily. The duration of therapy is dependent on the clinical response of the patient and as soon as improvement is indicated, the dosage should be adjusted to the minimum required to maintain the desired clinical response. Withdrawal of the drug on completion of therapy should be gradual.

Parenteral dexamethasone is generally reserved for patients who are unable to take the drug orally, or for use in an emergency situation.

Shock (of haemorrhagic, traumatic or surgical origin)
The usual dose for the treatment of shock is 2 to 6 mg/kg bodyweight as a single intravenous injection. This may be repeated in 2 to 6 hours if shock persists.

An alternative regimen of 20 mg by intravenous injection initially, followed by continuous intravenous infusion of 3 mg/kg bodyweight per 24 hours, has been suggested. If required for intravenous infusion, dexamethasone phosphate may be diluted with glucose or sodium chloride injection.

High dose therapy should be continued only until the patient's condition has stabilised and usually for no longer than 48 to 72 hours.

To avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation of the mixture and if storage is necessary, store solution at 2 to 8°C. Infusion should be completed within 24 hours of preparation of the solution and any residue discarded.

WARNING: Further diluted solutions which are not clear, or which show evidence of particulate matter contamination, should be discarded.

Cerebral oedema
The treatment schedule and route of administration should reflect the severity and aetiology of the cerebral oedema. Treatment needs to be tailored to the individual response. An initial dose of 10 mg intravenously followed by 4 mg intramuscularly every 6 hours until the symptoms of oedema subside (usually after 12 to 24 hours). After 2 to 4 days the dosage should be reduced and gradually stopped over a period of 5 to 7 days. Patients with cerebral malignancy may require maintenance therapy with doses of 2 mg intramuscularly or intravenously 2 to 3 times daily.

High doses of dexamethasone may be used to initiate short-term intensive therapy for acute cerebral oedema. Following an initial high loading dose, the dose is scaled down over the 7 to 10 days period of intensive therapy, and subsequently reduced to zero over the next 7 to 10 days.

High Dose Schedule:

	Adults	**Children >35 kg**	**Children <35 kg**
Initial Dose	50 mg (mg) IV	25 mg (mg) IV	20 mg (mg) IV
1st day	8 mg IV every 2 hours	4 mg IV every 2 hours	4 mg IV every 3 hours
2nd day	8 mg IV every 2 hours	4 mg IV every 2 hours	4 mg IV every 3 hours
3rd day	8 mg IV every 2 hours	4 mg IV every 2 hours	4 mg IV every 3 hours
4th day	4 mg IV every 2 hours	4 mg IV every 4 hours	4 mg IV every 6 hours
5th-8th day	4 mg IV every 4 hours	4 mg IV every 6 hours	2 mg IV every 6 hours
After 8 days	Decrease by daily reduction of 4 mg	Decrease by daily reduction of 2 mg	Decrease by daily reduction of 1 mg

NOTE: The intravenous and intramuscular routes of administration of DBL Dexamethasone Sodium Phosphate Injection should only be used where acute illness or life-threatening situations exist. Oral therapy should be substituted as soon as possible.

Intra-synovial & soft tissue injections:
Dosage varies with the degree of inflammation and the size and location of the affected area. Injections may be repeated from once every 3 to 5 days (e.g., for bursae) to once every 2 to 3 weeks (for joints). Frequent intra-articular injection may result in damage to joint tissues.

Site of Injection	Dosage
Large Joints	2 mg to 4 mg
Small Joints	800 micrograms to 1 mg
Bursae	2 mg to 3 mg
Tendon Sheaths	400 micrograms to 1 mg
Soft Tissue Infiltration	2 mg to 6 mg
Ganglia	1 mg to 2 mg

Method of administration
DBL Dexamethasone Sodium Phosphate Injection may be administered intravenously or intramuscularly for systemic effect, or as an intra-synovial or soft tissue injection for local effect.

For single patient use. Use once only and discard any residue.

4.3 Contraindications
Administration of dexamethasone is contraindicated in the following cases:

- Systemic fungal infections, or other systemic infections unless specific anti-infective therapy is given (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**);
- Hypersensitivity to dexamethasone or other corticosteroids or to any component of the injection (including sulfites (8 mg/2 mL vial));
- Administration of live virus vaccines (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**);
- In patients with myasthenia gravis, peptic ulcer, osteoporosis or psychoses;
- Local injection in patients who have:
    - Bacteraemia;
    - Unstable joints;
    - Infection at the injection site e.g., septic arthritis resulting from gonorrhoea or tuberculosis.

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

Dexamethasone formulations containing sulfites should not be used for intrathecal therapy. This sulfite-containing formulation has an altered risk profile compared to other sulfite-free formulations; there is a potential risk of neurotoxicity when administered intrathecally.

The excipient sodium sulfite may rarely cause severe hypersensitivity reactions and bronchospasm.

The vial stopper contains dry natural rubber (a derivative of latex), which may cause severe allergic reactions.

Long term treatment should not be abruptly discontinued, as too rapid withdrawal may lead to drug induced secondary adrenocortical insufficiency. This may be minimised by gradual dosage reduction. This type of relative insufficiency may persist for months after therapy is discontinued. Therefore, in any situation of stress occurring in that period (such as anaesthesia, surgery or trauma), corticosteroid doses may need to be increased or the therapy reinstituted. Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome, including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules, loss of weight and malaise.

Dexamethasone should be used only with extreme caution and frequent monitoring is necessary in patients with:
- diabetes mellitus or in those with a family history of diabetes;
- infectious diseases;
- congestive heart failure or recent myocardial infarction;

- chronic renal failure;
- diverticulitis;
- hypertension;
- keratitis;
- epilepsy and/or seizure disorder, migraine;
- non-specific ulcerative colitis (if there is a probability of impending perforation, abscess or other pyogenic infection), fresh intestinal anastomoses, active or latent peptic ulcer;
- osteoporosis, myasthenia gravis or in elderly persons. Geriatric patients may be more likely to develop hypertension and osteoporosis as a result of corticosteroid therapy.

Corticosteroids may cause reactivation of latent amoebiasis. Prior to treatment, amoebiasis should be ruled out in any patient with unexplained diarrhoea or who has recently spent time in the tropics.

Corticosteroids should be used with caution in patients who have had a recent cardiac infarction, as there have been reports of an apparent association between the use of corticosteroids and left ventricular free wall rupture in these patients; in patients with a history of severe affective disorders particularly of steroid induced psychoses; patients with previous steroid myopathy, liver failure, renal insufficiency, glaucoma (or a family history of glaucoma); patients with thromboembolic disorders; patients with Duchenne's muscular dystrophy since transient rhabdomyolysis and myoglobinuria have been reported following strenuous physical activity; Cushing's disease; incomplete statural growth since glucocorticoids on prolonged administration may accelerate epiphyseal closure. Corticosteroids show an enhanced effect in patients with hypothyroidism or cirrhosis.

There is a lack of evidence to support the prolonged use of corticosteroids in septic shock. Although they may be of value in the early treatment, the overall survival may not be influenced.

Intra-articular injection of corticosteroids may produce systemic as well as local effects. Appropriate examination of any joint fluid present 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 sepsis is confirmed, appropriate antimicrobial therapy should be commenced.

Local injection of a steroid into an infected site is to be avoided. Corticosteroids should not be injected into unstable joints. Frequent intra-articular injection may result in damage to joint tissues. Patients should be advised strongly of the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active.

Intraarticular corticosteroids are associated with a substantially increased risk of an inflammatory response in the joint, particularly if a bacterial infection is introduced with the injection. Great care is required and all intraarticular corticosteroid injections should be undertaken in an aseptic environment.

Severe anaphylactoid reactions have occurred after administration of parenteral corticosteroids. Glottis oedema, urticaria and bronchospasm, have occasionally occurred, particularly in patients with history of allergy. Appropriate precautions should be taken prior to administration. If such an anaphylactoid reaction occurs, the following measures are recommended: immediate slow intravenous injection of adrenaline (epinephrine), intravenous administration of aminophylline, and artificial respiration if necessary.

Corticosteroids should not be used for the management of head injury or stroke because it is unlikely to be of any benefit and may even be harmful.

The results of a randomised, placebo-controlled study suggest an increase in mortality if methylprednisolone therapy starts more than two weeks after the onset of Acute Respiratory Distress Syndrome (ARDS). Therefore, treatment of ARDS with corticosteroids should be initiated within the first two weeks of onset of ARDS.

The slower rate of absorption after intramuscular injection should be noted.

Adrenocortical insufficiency
Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration and duration of therapy.

Symptoms of adrenal insufficiency include: malaise, muscle weakness, mental changes, muscle and joint pain, desquamation of the skin, dyspnoea, anorexia, nausea and vomiting, fever, hypoglycaemia, hypotension and dehydration.

During prolonged courses of corticosteroid therapy, sodium intake may need to be reduced and calcium and potassium supplements may be necessary. Monitoring of fluid intake and output and daily weight records may give an early warning of fluid retention.

Acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly, therefore withdrawal of corticosteroids should always be gradual. A degree of adrenal insufficiency may persist for 6 to 12 months; therefore, in any situation of stress occurring during that period steroid therapy may need to be reinstituted. Since mineralocorticoid secretion may be impaired, treatment with salt and/or a mineralocorticoid may also be needed.

Anti-inflammatory/immunosuppressive effects and infection
Suppression of the inflammatory response and immune function increases susceptibility to or mask the symptoms of infections, and their severity, and therefore should be used with caution in patients with systemic infections. Immunosuppression is most likely to occur in patients receiving longer term, high dose systemic corticosteroid treatment; however, patients receiving moderate doses for short periods, or low doses over a prolonged period, may also be at risk.

Corticosteroids should be administered with caution to patients with latent tuberculosis or tuberculin reactivity, as reactivation of the disease may occur. These patients should therefore undergo chemoprophylaxis during prolonged corticosteroid therapy.

Chickenpox, measles and other infections can have a more serious or even fatal effect in non-immune children or adults on corticosteroids.

The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised when corticosteroids are used. The immunosuppressive effects of glucocorticoids may result in activation of latent infection or exacerbation of intercurrent infections.

Chickenpox is of particular concern since this may be fatal in immunosuppressed patients. Patients 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 immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic dexamethasone or who have received it during the previous 3 months; this should be given within 10 days of exposure to

chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment.

Patients should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs; prophylaxis with intramuscular normal immunoglobin may be needed.

Appropriate antimicrobial therapy should accompany glucocorticoid therapy when necessary e.g., in tuberculosis and viral and fungal infections of the eye.

Live vaccines are contraindicated in individuals on high doses or immunosuppressive doses of corticosteroids and should be postponed until at least 3 months after stopping corticosteroid therapy (see **4.3 CONTRAINDICATIONS**). The antibody response to other vaccines may be diminished. If inactivated viral or bacterial vaccines are administered to patients receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunisation procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Musculoskeletal disorders
Acute myopathy has been reported with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blocking drugs (e.g., pancuronium bromide). This acute myopathy is generalised, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Cases of rhabdomyolysis have been reported with the use of corticosteroids. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

In the treatment of conditions such as tendinitis or tenosynovitis, care should be taken to inject into the space between the tendon sheath and the tendon as cases of ruptured tendon have been reported.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes. These may include cataract glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Prolonged use of corticosteroids may produce subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves.

Corticosteroids should only be initiated in patients with ocular herpes simplex with appropriate viral cover by ophthalmologists because of the risk of corneal scarring loss of vision and corneal perforation.

Psychiatric effects
Patients and/or carers should be warned that potentially severe psychiatric reactions may occur. Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients and/or carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected.

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

Psychic derangements range from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic manifestations.

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 interactions have been reported infrequently.

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.

Use in the elderly
Long-term use in the elderly should be planned bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age, especially osteoporosis, diabetes, hypertension, hypokalaemia, susceptibility to infection and thinning of the skin. Close medical supervision is required to avoid life threatening reactions.

Paediatric use
Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible and therefore long-term administration of pharmacological doses should be avoided. If prolonged therapy is necessary, treatment should be limited to the minimum suppression of the hypothalamic-pituitary adrenal axis and growth retardation, the growth and development of infants and children should be closely monitored. Treatment should be limited, where possible, to a single dose on alternate days.

Children are at special risk from raised intracranial pressure.

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

Effects on laboratory tests
Dexamethasone suppression tests may be affected by drugs which enhance the metabolic clearance of corticosteroids (see **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

False negative results in the dexamethasone suppression test have been reported in patients being treated with indomethacin or high doses of benzodiazepines or cyproheptadine.

Corticosteroids have been reported to alter the response to anticoagulant agents (see **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**). The prothrombin time should be checked frequently in patients receiving these combinations.

Corticosteroids may affect a wide range of diagnostic tests. They may affect brain and skeletal imaging using ^{99}Tc, by decreasing uptake of ^{99}Tc into cerebral tumours or bone respectively, and may decrease ^{123}I and ^{131}I uptake into the thyroid. Corticosteroids may alter the results of

the gonadorelin test for hypothalamic-pituitary-gonadal axis function, affect thyroid function test results, and suppress skin test reactions including tuberculin and histoplasmin skin tests, and patch tests for allergy. Corticosteroids may also affect the nitroblue tetrazolium test for bacterial infection and produce false negative results.

4.5 Interactions with other medicines and other forms of interactions

Medicines that induce hepatic enzyme cytochrome P-450 isozyme 3A4 such as barbiturates, phenylbutazone, phenobarbital (phenobarbitone), phenytoin or rifampicin, rifabutin, carbamazepine, primidone and aminoglutethimide may increase the metabolism and thus reduce the effects of corticosteroids. Ephedrine and aminoglutethimide may also increase dexamethasone metabolism.

Medicines that inhibit hepatic enzyme cytochrome P-450 isozyme 3A4 such as ketoconazole, cyclosporin or ritonavir may decrease glucocorticoid clearance. A reduction in corticosteroid dose may be needed to reduce the risk of adverse effects.

Antithyroid agents, oestrogens and other oral contraceptives may decrease hepatic metabolism and thus increase the effects of corticosteroids. The dose of corticosteroid may need to be adjusted if oestrogen therapy is commenced or stopped.

The effects of anticholinesterases are antagonised by corticosteroids in myasthenia gravis.

Corticosteroids may influence the effect of anticholinergics, neuromuscular blockers:

- Acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**, Musculoskeletal disorders).
- Antagonism of the neuromuscular blocking effects of pancuronium bromide and vecuronium bromide has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.

The effects of anticoagulant agents are usually decreased (but may be increased in some patients) if corticosteroids are administered concurrently. Close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Seizures have reportedly occurred in adult and paediatric patients receiving high dose corticosteroid therapy concurrently with cyclosporin.

Concurrent administration of dexamethasone with anticoagulants, heparin, streptokinase, urokinase, alcohol or non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin may increase the risk of gastrointestinal ulceration or haemorrhage. Salicylates should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinaemia. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Patients should be observed closely for adverse effects of either medicine.

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 effects.

Diuretics, hypoglycaemic agents (including insulin), and cardiac glycosides are antagonised by corticosteroids and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

Potassium loss may occur as a result of dexamethasone administration (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). Concurrent administration of corticosteroids with potassium depleting diuretics (such as thiazides, frusemide or ethacrynic acid), carbonic anhydrase inhibitors such as acetazolamide or amphotericin B may result in severe hypokalaemia. The activity of digitalis glycosides and nondepolarising neuromuscular blocking agents may be potentiated as a result of glucocorticoid induced hypokalaemia. The efficacy of potassium supplements and potassium sparing diuretics on serum potassium concentrations may be reduced by concurrent corticosteroid administration. Monitoring of serum potassium concentration is therefore recommended.

Glucocorticoids may increase blood glucose concentrations. Dosage adjustment of asparaginase and of anti-diabetic agents such as sulfonylureas and insulins may be necessary.

The growth promoting effect of somatropin may be inhibited.

There is an increased risk of hypokalaemia if high doses of corticosteroids are given with high doses of salbutamol, salmeterol, terbutaline or formoterol.

Concurrent use of antacids may decrease absorption of corticosteroids – efficacy may be decreased sufficiently to require dosage adjustments in patients receiving small doses of corticosteroids.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Corticosteroids may increase or decrease the motility and number of spermatozoa in some patients.

Use in pregnancy

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

In animal experiments, corticosteroids have been found to cause malformations of various kinds (cleft palate, skeletal malformations). These findings do not seem to be relevant to humans. Reduced placental and birth weight have been recorded in animals and humans after long-term treatment. Since the possibility of suppression of the adrenal cortex in the newborn baby after long term treatment must be considered, the needs of the mother must be carefully weighed against the risk to the foetus when prescribing corticosteroids. However, the short-term use of antepartum corticosteroids for the prevention of respiratory distress syndrome, when warranted, does not seem to pose a risk.

There is evidence of harmful effects on pregnancy in animals. Infants born to mothers who have received substantial doses of corticosteroids during the pregnancy should be carefully observed, for signs of adrenal insufficiency.

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

Use in lactation

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production or cause other unwanted effects in breastfed infants. Women taking corticosteroids should be advised not to breastfeed.

Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression. Suppression of growth or other adverse effects may occur.

4.7 Effects on ability to drive and use machines
The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of these medicines include dizziness, drowsiness, insomnia, convulsions and vertigo which could affect the ability to drive or use machines (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Serious neurologic adverse reactions with epidural administration
Serious neurologic events, sometimes resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

4.8 Adverse effects (undesirable effects)
The following adverse effects have been reported with dexamethasone therapy. Except for allergic reactions, the adverse effects listed have been associated with prolonged therapy and/or high doses.

Endocrine disorders: Adrenal suppression, development of Cushingoid state, secondary adrenocortical and pituitary unresponsiveness particularly in times of stress (e.g., trauma, surgery or illness).

Cardiovascular disorders: Thromboembolism, hypertension, polymorphonuclear leucocytosis, neuropathy, vasculitis, impaired myocardial contractility (prolonged treatment), congestive heart failure in susceptible patients, myocardial rupture following recent cardiac infarction, hypertrophic cardiomyopathy in low birth weight and prematurely born infants (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Musculoskeletal and connective tissue disorders: Proximal myopathy, rhabdomyolysis, osteoporosis, arthropathy, Charcot-like arthropathy following intra-articular injection, premature epiphyseal closure, muscular atrophy, muscle weakness, steroid myopathy, vertebral compression aseptic necrosis of femoral and humeral heads, avascular osteonecrosis, myalgia, growth suppression in infancy, childhood and adolescence. These may occur as a result of protein catabolism associated with prolonged glucocorticoid therapy.

Eye disorders: Glaucoma, papilloedema, posterior subcapsular cataracts, or increased intraocular pressure may lead to glaucoma or occasionally damage to the optic nerve, cataracts, exophthalmos, corneal or scleral thinning, retinopathy of prematurity, enhanced establishment of secondary fungal and viral eye infections, chorioretinopathy, blurred vision, blindness associated with intralesional therapy around the face and neck.

Reproductive system and breast disorders: A transient burning or tingling sensation mainly in the perineal area following intravenous injection of large doses of corticosteroid phosphates, menstrual irregularities and amenorrhoea.

Skin and subcutaneous tissue disorders: Hirsutism, skin atrophy-subcutaneous and cutaneous atrophy, allergic dermatitis, urticaria, erythema, thin fragile skin, telangiectasia, petechiae and ecchymoses, increased sweating, may suppress skin test reactions, angioneurotic oedema, acne, striae, sterile abscess, hyperpigmentation or hypopigmentation, candidiasis and panniculitis.

Blood and lymphatic system disorders: Diminished lymphoid tissue and leucocytosis.

Injury, poisoning, and procedural complications: Easy bruising, tendon rupture and pathological fracture of long bones.

Infections and infestations: Increased susceptibility to and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, candidiasis, recurrence of dormant tuberculosis. Glucocorticoids, especially in large doses, increase susceptibility to infection, and may mask the symptoms of infection (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Immune system disorders: Diminished immune response, decreased responsiveness to vaccination. Hypersensitivity including anaphylaxis has been reported.

Gastrointestinal disorders: Dyspepsia, nausea, peptic ulcer with possible perforation and haemorrhage, abdominal distension, abdominal pain, diarrhoea, acute pancreatitis, perforation of the small or large bowel particularly in patients with inflammatory bowel disease, abdominal distension, ulcerative oesophagitis, oesophageal candidiasis, nausea.

Nervous system disorders: Dizziness, headache, burning and tingling, convulsions, increased intracranial pressure with papilloedema, labile mood. Aggravation of epilepsy, behavioural disturbances, sleep disturbances, cognitive dysfunction, amnesia.

Ear and labyrinth disorders: Vertigo.

Psychiatric disorders: Affective disorders (such as irritable, euphoric, depression, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), irritability, anxiety, confusion, psychological dependence, mental disturbances, insomnia.

Fluid and electrolyte disturbances: Electrolyte imbalance (retention of sodium and water with oedema and hypertension), potassium loss, hypokalaemic alkalosis, hypocalcaemia, increased calcium and potassium excretion.

Metabolism and nutrition disorders: Nitrogen depletion, negative nitrogen and calcium balance due to protein catabolism, negative protein/nitrogen and calcium balance, decreased carbohydrate tolerance, increased requirements for insulin or oral hypoglycaemic agents in diabetes, development of diabetes mellitus, hyperglycaemia, weight gain, increased appetite.

General disorders and administration site conditions: Post-injection flare.

Other effects: Allergic reactions, fatigue, malaise, hiccups.

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.

Withdrawal
In patients who have received more than physiological doses of systemic corticosteroids (approximately 1 mg dexamethasone intravenously or intramuscularly) for greater than 3 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 corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty

about HPA suppression, the dose of systemic corticosteroid 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 corticosteroid treatment, which has continued up to 3 weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses up to 6 mg of dexamethasone for 3 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 corticosteroid therapy should be considered even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 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 corticosteroid therapy,
- Patients receiving doses of systemic corticosteroid greater than 6 mg daily of dexamethasone,
- Patients repeatedly taking doses in the evening.

Withdrawal symptoms and signs: Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

A 'withdrawal syndrome' may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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.

4.9 Overdose
Symptoms
It is difficult to define an excessive dose of a corticosteroid as the therapeutic dose will vary according to the indication and patient requirements. High dose corticosteroids given as recommended for pulse therapy are relatively free from hazardous effects.

Reports of acute toxicity and/or deaths following overdosage with glucocorticoids are rare. Exaggeration of corticosteroid related adverse effects may occur including hypertension, oedema, peptic ulceration, hyperglycaemia and altered mental state. Anaphylactic or hypersensitivity reactions may occur.

Treatment
No antidote is available. Treatment of overdosage is symptomatic. The dosage should be reduced or the drug withdrawn. Anaphylactic and hypersensitivity reactions may be treated with adrenaline (epinephrine), positive pressure artificial respiration, and aminophylline. The patient should be kept warm and quiet.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Mechanism of action
Dexamethasone is a synthetic adrenocorticosteroid with glucocorticoid activity. It is one of the most active glucocorticoids, being about 25 to 30 times as potent as hydrocortisone. Unlike hydrocortisone, dexamethasone has little if any mineralocorticoid activity.

Dexamethasone has anti-inflammatory and immunosuppressant activity. Glucocorticoids prevent the development of the inflammatory response, i.e., redness, swelling, tenderness. They also inhibit capillary dilation and phagocytosis and appear to prevent the hypersensitivity responses which occur after antigen-antibody reactions.

The principal metabolic actions of dexamethasone are on gluconeogenesis, glycogen deposition and protein and calcium metabolism. Dexamethasone also influences the mobilisation, oxidation, synthesis and storage of fats.

Dexamethasone suppresses the release of adrenocorticotrophic hormone (ACTH) from the pituitary, resulting in inhibition of endogenous corticotrophin secretion.

Except for its use in the treatment of adrenal insufficiency, dexamethasone does not cure disease. Rather, the anti-inflammatory and immunosuppressant actions of dexamethasone suppress the symptoms associated with the disease.

Clinical trials
No data available.

5.2 Pharmacokinetic properties
Absorption
Dexamethasone phosphate (as sodium) is absorbed rapidly following intramuscular or intravenous injection. Intramuscular injections of dexamethasone phosphate give maximum plasma concentrations of dexamethasone at 1 hour. The biological half-life of dexamethasone is about 190 minutes.

Distribution
In the circulation, small amounts of dexamethasone are bound to plasma proteins.

Metabolism
Synthetic corticosteroids such as dexamethasone are less extensively protein bound and more slowly metabolised than hydrocortisone. Dexamethasone penetrates into tissue fluids and cerebrospinal fluids. Metabolism occurs in most tissues, but primarily in the liver.

Excretion
The inactive metabolites are excreted in the urine, mainly as glucuronides and sulfates, but also as unconjugated metabolites. Small amounts of unchanged drug are also excreted in the urine. Up to 65% of a dose of dexamethasone is excreted in the urine within 24 hours.

5.3 Preclinical safety data
Genotoxicity
No data available.

Carcinogenicity
No data available.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium citrate dihydrate
Disodium edetate
Hydrochloric acid
Sodium hydroxide
Sodium sulfite*
Water for injections

*Sodium sulfite is used as an antioxidant.

6.2 Incompatibilities
Dexamethasone sodium phosphate is physically incompatible with daunorubicin, doxorubicin and vancomycin and should not be admixed with solutions containing these drugs. Dexamethasone sodium phosphate is also incompatible with doxapram HCl and glycopyrrolate in syringe.

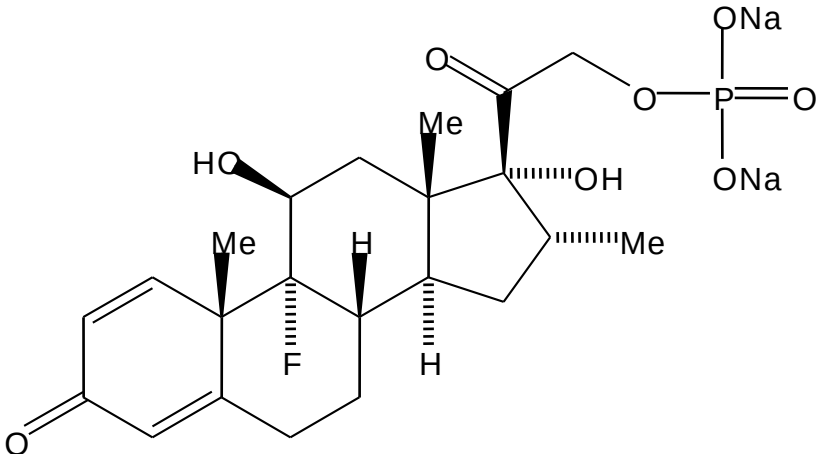
6.3 Shelf life
Please refer to outer carton for expiry date.

6.4 Special precautions for storage
Store below 25°C. Protect from light.

6.5 Nature and contents of container
DBL Dexamethasone Sodium Phosphate Injection (8 mg/2 mL) is available as a Type I coloured glass vial containing 2 mL solution in cartons of 5 vials.

6.6 Special precautions for disposal
Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties
Chemical structure
Dexamethasone sodium phosphate is a white or slightly yellow, very hygroscopic, crystalline powder. It is odourless or has a slight odour of alcohol. Dexamethasone sodium phosphate is soluble 1 in 2 of water, slightly soluble in alcohol, practically insoluble in chloroform and ether, and very slightly soluble in dioxane.



Chemical formula: $C_{22}H_{28}FNa_2O_8P$

Molecular weight: 516.4

CAS number
2392-39-4

Pfizer Corporation Hong Kong Limited