Depo-pred 40

Methylprednisolone Acetate BP 40 mg

Composition
Depo-pred Sterile aqueous suspension 40 mg per ml.
Each ml Contains:
Methylprednisolone Acetate BP 40 mg (Polyethylene glycol 335O - Sodium chloride - Myristyl-gamma-picolinium chloride 0.2 mg - Water for injection).

Forms, ways of administration and packages
FORM: Sterile aqueous suspension for single use.
WAYS OF ADMINISTRATION
- Intramuscular
- Intra-articular, periarticular, intrabursal or soft tissues
- Intralesional
- Intrarectal instillation

Depo-pred is contra-indicated for I.V administration. **Depo-pred** is not recommended for intrathecal, epidural, intranasal, intra-ocular or any other unapproved route of administration (see ADVERSE REACTIONS reported from non recommended routes of administration).
PACKAGES
Depo-pred 40 mg Injection : Each box contains 3 vial of Methylprednisolone Acetate 40 mg per ml/vial.

Properties
Depo-pred is a sterile aqueous suspension of the synthetic glucocorticoid Methylprednisolone Acetate. It has a strong and prolonged anti-inflammatory, immunosuppressive and anti-allergic activity. **Depo-pred** can be administered I.M. for a prolonged systemic activity as well as in situ for a local treatment. The prolonged activity of **Depo-pred** is explained by the slow release of the active substance.
Pharmacodynamics
Methylprednisolone Acetate has the general properties of the glucocorticoid Methylprednisolone but is less soluble and less readily metabolized, which explains its prolonged activity.
Glucocorticoids diffuse across cell membranes and complex with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA (chromatin) and stimulate transcription of mRNA and subsequent protein synthesis of various enzymes thought to be ultimately responsible for the numerous effects after systemic use. Glucocorticoids not only have an important influence on inflammatory and immune processes but also affect the carbohydrate, protein and fat metabolism.
They also act on the cardiovascular system, the skeletal muscles and the central nervous system.
- Effect on the inflammatory and immune process:
The anti-inflammatory, immunosuppressive and anti-allergic properties of glucocorticoids are responsible for most of the therapeutic applications. These properties lead to the following results:
- reduction of the immunoactive cells near the inflammation focus;
- reduced vasodilation;
- stabilization of the lysosomal membranes;
- inhibition of phagocytosis;
- reduced production of prostaglandins and related substances.

A dose of 4.4 mg Methylprednisolone Acetate (4 mg Methylprednisolone) has the same glucocorticosteroid (anti-inflammatory) effect as 20 mg hydrocortisone. Methylprednisolone has only a minimal mineralocorticoid effect (200 mg Methylprednisolone are equivalent to 1 mg desoxycorticosterone).
- Effect on carbohydrate and protein metabolism:
Glucocorticoids have a protein catabolic action. The liberated amino acids are converted into glucose and glycogen in the liver by means of the gluconeogenesis process. Glucose absorption in peripheral tissues decreases, which can lead to hyperglycemia and glucosuremia, especially in patients who are prone to diabetes.
- Effect on fat metabolism:
Glucocorticoids have a lipolytic action. This lipolytic activity mainly affects the limbs. They also have a lipogenetic effect which is most evident on chest, neck and head. All this leads to a redistribution of the fat deposits. Maximum pharmacologic activity of glucocorticoids lays behind peak blood levels, suggesting that most effects of the drugs result from modification of enzyme activity rather than from direct actions by the drug.

Pharmacokinetics
Methylprednisolone Acetate is hydrolized to its active form by serum cholinesterases. In man, Methyiprednisolone forms a weak dissociable bond with albumin and transcortin. Approximately 40 to 90% of the drug is bound.
The intracellular activity of glucocorticoids results in a clear difference between plasma half-life and pharmacological half-life. Pharmacological activity persists after measurable plasma levels have disappeared. The duration of anti-inflammatory activity of glucocorticoids approximately equals the duration of hypothalamic-pituitary-adrenal (HPA) axis suppression.
I.M. injections of 40 mg/ml give after approximately 7.3 ± 1 hour (Tmax) Methylprednisolone serum peaks of 1,48 ± 0.86 ig/100 ml(Cmax). The half-life is in this case 69.3 hours. After a single I.M, injection of 40 to 80 mg methylprednisolone acetate, duration of HPA axis suppression ranged from 4 to 8 days.
An intra-articular injection of 40 mg in both knees (total dose: 80 mg) gives after 4 to 8 hours Methylprednisolone peaks of approximately 21.5 ìg/100 ml. After intra-articular administration Methylprednisolone Acetate difuses from the joint into systemic circulation over approximately 7 days, as demonstrated by the duration of the HPA axis suppression and by the serum methylprednisolone values. Metabolism of Methyiprednisolone occurs via hepatic routes qualitatively similar to that of cortisol. The major metabolites are 20 beta-hydroxy-methylprednisolone and 20 beta-hydroxy-6 alpha- methylprednisone. The metabolites are mainly excreted in the urine as glucuronides, sulfates and unconjugated compounds. These conjugation reactions occur principally in the liver and to some extent in the kidney.

Indications
Glucocorticoids should only be considered as symptomatic treatment, unless in case of some endocrine disorders, where they are used as a substitution treatment.

A. FOR (INTRAMUSCULAR ADMINISTRATION
Methylprednisolone Acetate (**Depo-pred**) is not suitable for the treatment of acute life threatening conditions. If a rapid hormonal effect of maximum intensity is required, the I.V administration of highly soluble methylprednisolone sodium succinate is indicated.
When oral therapy is not feasible and this preparation lend to the treatment of the condition, the intramuscular use of **Depo-pred** is indicated as follows:
ANTI-INFLAMMATORY TREATMENT
1. Rheumatic disorders
As adjuvant for short-term administration (to tide the patient over an acute episode or exacerbation) in:
- psoriatic arthritis
- ankylosing spondylitis.
For the following indications, preference should be given to in situ administration if possible:
- post-traumatic osteoarthritis
- synovitis of osteoarthritis
- rheumatoid arthritis, including juvenile rheumatoid arthritis
(selected cases may require low-dose maintenance therapy)
- acute and subacute bursitis
- epicondylitis
- acute nonspecific tenosynovitis
- acute gouty arthritis.
2. Collagen diseases
During an exacerbation or as maintenance therapy in selected cases of:
- systemic lupus erythematosus
- systemic dermatomyositis (polymyositis)
- acute rheumatic carditis.
3. Dermatologic diseases
- pemphigus
- severe erythema multiforme (Stevens-Johnson syndrome)
- exfoliative dermatitis
- mycosis fungoides
- bulious dermatitis herpetiformis (sulfone is the drug of first choice and systemic administration of glucocorticoids is an adjuvant).
4. Allergic states
Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:
- chronic asthmatic respiratory disorders
- contact dermatitis
- atopic dermatitis
- serum sickness
- seasonal or perennial allergic rhinitis
- drug hypersensitivity reactions
- urticarial transfusion reactions
- acute noninfectious laryngeal edema (epinephrine is the drug of first choice).
5. Gastrointestinal diseases
To tide the patient over a critical period of the disease in:
- ulcerative colitis (systemic therapy)
- Crohn disease (systemic therapy),
6. Respiratory diseases
- symptomatic pulmonary sarcoidosis
- berylliosis
- fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy (Loeffler's syndrome not manageable by other means).
- aspiration pneumonitis

TREATMENT OF HEMATOLOGICAL AND ONCOLOGICAL DISORDERS
1. Hematologic disorders
- acquired (autoimmune) hemolytic anemia
- secondary thrombocytopenia in adults
- erythroblastopenia (RBC anemia)
- congenital (erythroid) hypoplastic anemia.
2. Oncological diseases
For palliative management of:
- leukemias and lymphomas
- acute leukemia of childhood.

ENDOCRINE DISORDERS
- primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice. Synthetic analogues may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance.)
- acute adrenocortical insufficiency
- congenital adrenal hyperplasia
- hypercalcemia associated with cancer
- nonsuppurative thyroiditis

MISCELLANEOUS
- tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
- trichinosis with neurologic or myocardial involvement
- nervous system: acute exacerbations of multiple sclerosis.

B. FOR INTRASYNOVIAL, PERIARTICULAR, INTRABURSAL OR SOFT TISSUE ADMINISTRATION (see also SPECIAL PRECAUTIONS)
Depo-pred is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
- synovitis of osteoarthritis
- rheumatoid arthritis
- acute and subacute bursitis
- acute gouty arthritis
- epicondylitis
- acute nonspecific tenosynovitis
- post-traumatic osteoarthritis.

C. FOR INTRALESIONAL ADMINISTRATION
Depo-pred is indicated for intralesional use in the following conditions:
- keloids
- localized hypertropic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare and lichen simplex chronicus (neurodermatitis)
- discoid lupus erythematosus
- alopecia areata.

Depo-pred may also be useful in cystic tumors or an aponeurosis or tendon (ganglia).

Dosage and administration
A. I.M. ADMINISTRATION FOR SYSTEMIC EFFECT
The intramuscular dosage will vary with the condition being treated. When a prolonged effect is desired, the weekly dose may be calculated by multiplying the daily oral dose by 7 and given as a singular intramuscular injection. Dosage must be individualized according to the severity of the disease and response of the patient. In general, the duration of the treatment should be kept as short as possible. Medical surveillance is necessary. For infants and children, the recommended dosage will have to be reduced, but dosage should be governed by the severity of the condition rather than by strict adherence to the ratio indicated by age or body weight. Hormone therapy is adjunct to and not a replacement for conventional therapy. Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. Severe medical surveillance is recommended when a chronic treatment is discontinued. The severity, prognosis and expected duration of the disease and the reaction of the patient to medication are primary factors in determining dosage. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight and a chest x-ray should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia. In patients with the adrenogenital syndrome, a single intramuscular injection of 40 mg every two weeks may be adequate. For maintenance of patients with rheumatoid arthritis, the weekly intramuscular dose will vary from 40 to 120 mg. The usual dosage for patients with dermatologic lesions benefited by systemic corticoid therapy is 40 to 120 mg of Methylprednisolone Acetate administered intramuscularly at weekly intervals for one to four weeks. In acute severe dermatitis due to poison ivy, relief may result within 8 to 12 hours following intramuscular administration of a single dose of 80 to 120 mg. In chronic contact dermatitis repeated injections at 5 to 10 day intervals may be necessary. In seborrheic dermatitis, a weekly dose of 80 mg may be adequate to control the condition. Following intramuscular administration of 80 to 120 mg to asthmatic patients. Relief may result within 6 to 48 hours and persist for several days to two weeks. Similarly in patients with allergic rhinitis (hay fever) an intramuscular dose of 80 to 120 mg may be followed by relief of coryzal symptoms within six hours persisting for several days to three weeks. If signs of stress are associated with the condition being treated, the dosage of the suspension should be increased. If a rapid hormonal effect of maximum intensity is required, the intravenous administration of highly soluble methylprednisolone sodium succinate is indicated.

B. IN SITU ADMINISTRATION FOR LOCAL EFFECT
Therapy with **Depo-pred** does not obviate the need for the conventional measures usually employed. Although this method of treatment will ameliorate symptoms, it is in no sense a cure and the hormone has no effect on the cause of the inflammation.
1. Rheumatoid and osteoarthritis
The dose for intra-articular administration depends upon the size of the joint and varies with the severity of the condition in the individual patient. In chronic cases, several injections can vary from one to five per week, depending on the degree of relief obtained from the initial injection. The doses in the following table are given as a general guide:

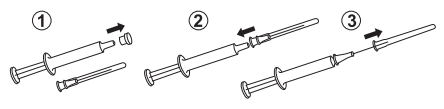
Size of joint	Examples	Range of dosage
Large	Knees Ankles Shoulders	20 to 80 mg
Medium	Elbows Wrists	10 to 40 mg
Small	Metacarnophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4 to 10 mg

Procedure: It is recommended that the anatomy of the joint involved be reviewed before attempting intra-articular injection. In order to obtain the full anti-inflammatory effect it is important that the injection be made into the synovial space. Employing the same sterile technique as for a lumbar puncture, a sterile 20 to 24 gauge needle (on a dry syringe) is quickly inserted into the synovial cavity. Procaine infiltration is elective. The aspiration of only a few drops of joint fluid proves the joint space has been entered by the needle. The injection site for each joint is determined by that location where the synovial cavity is most superficial and most free of large vessels and nerves. With the needle in place, the aspirating syringe is removed and replaced by a second syringe containing the desired amount of **Depo-pred**. The plunger is then pulled outward slightly to aspirate synovial fluid and to make sure the needle is still in the synovial space. After injection, the joint is moved gently a few times to aid mixing of the synovial fluid and the suspension. The site is covered with a small sterile dressing. Suitable sites for intra-articular injection are the knee, ankle, wrist, elbow. shoulder, phalangeal and hip joints. Since difficulty is occasionally encountered in entering the hip joint, precautions should be taken to avoid any large blood vessels in the area. Joints not suitable for injection are those that are anatomically inaccessible such as the spinal joints and those like the sacroiliac joints that are devoid of synovial space. Treatment failures are most frequently the result of failure to enter the joint space. Little or no benefit follows injection into surrounding tissue. If failures occur when injections into the synovial spaces are certain, as determined by aspiration of fluid, repeated injections are usually futile. Local therapy does not alter the underlying disease process, and whenever possible comprehensive therapy including physiotherapy and orthopedic correction should be employed.
2. Bursitis: The area around the injection site is prepared in a sterile way and a wheal at the site made with 1% procaine hydrochloride solution. 20 to 24 gauge needle attached to a dry syringe is inserted into the bursa and the fluid aspirated. The needle is left in place and the aspirating syringe changed for a small syringe containing the desired dose. After injection, the needle is withdrawn and a small dressing applied.
3. Miscellaneous: Ganglion, tendinitis, epicondylitis. In the treatment of conditions such as tendinitis or tenosynovitis, care should be taken to inject the suspension into the tendon sheath rather than into the substance of the tendon. The tendon may be readily palpated when placed on a stretch. When treating conditions such as epicondylitis, the area of greatest tenderness should be outlined carefully and the suspension infiltrated into the area. For ganglia of the tendon sheaths, the suspension is injected directly into the cyst. In manv cases, a single injection causes a marked decrease in the size of the cystic tumor and may effect disappearance. The usual sterile precautions should be observed, of course, with each injection (application of a suitable antiseptic to the skin). The dose in the treatment of the various conditions of the tendinous or bursal structures listed above varies with the condition being treated and ranges from 4 to 30 mg. In recurrent or chronic conditions, repeated injections may be necessary.
4. Injections for local effect in dermatologic conditions: Following cleansing with an appropriate antiseptic such as 70% alcohol, 20 to 60 mg of the suspension is injected into the lesion. It may be necessary to distribute doses ranging from 20 to 40 mg by repeated local injections in the case of large lesions. Care should be taken to avoid injection of sufficient material to cause blanching since this may be followed by a small slough. One to four injections are usually employed, the intervals between injections varying with the type of lesion being treated and the duration of improvement produced by the initial injection.

C. FOR INTRALESIONAL ADMINISTRATION
Depo-pred is indicated for intralesional use in the following conditions:
- keloids
- localized hypertropic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare and lichen simplex chronicus (neurodermatitis)
- discoid lupus erythematosus
- alopecia areata.

Depo-pred may also be useful in cystic tumors or an aponeurosis or tendon (ganglia).

INSTRUCTIONS FOR USE
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. A strict sterile technique is needed in order to prevent iatrogen infections. This product is not suitable for I.V and intrathecal administration and may not be used as a multidose vial. Following administration of the desired dose, any remaining suspension should be discarded.
DIRECTIONS FOR USING THE SYRINGE
Shake thoroughly to obtain a uniform suspension.
1. Remove tip cap.
2. In a sterile way position needle.
3. Remove needle shield, The syringe is now ready for use.



After administration discard the syringe Do not reuse.

Contra-indications
Depo-pred is contraindicated for intrathecal administration.
- Systemic fungal infections
- Known hypersensitivity to components

RELATIVE CONTRA-INDICATIONS
Special risk groups
Children, diabetics, hypertensive patients and patients with psychiatric antecedents, certain infectious diseases such as tuberculosis or certain viral diseases such as herpes and zona associated with ocular symptoms should be under strict medical surveillance and should be treated during an as short as possible period (see also sections SPECIAL PRECAUTIONS and ADVERSE REACTIONS).

Adverse reactions
Systemic adverse reactions may be observed. Although rarely occurring in very short term therapy, they should always be carefully traced. This is part of the follow-up of any corticotherapy, and does not specifically pertain to any particular product. These possible adverse reactions of glucocorticoids like Methylprednisolone are:
INTRAMUSCULAR
- Fluid and electrolyte disturbances : In comparison with cortisone or hydrocortisone, mineralocorticoid effects are less likely to occur with synthetic derivatives as Methylprednisolone Acetate, Sodium retention, Fluid retention, Congestive heart failure in susceptible patients, Potassium loss, Hypokalemic alkalosis, Hypertension
- Musculoskeletal : Muscle weakness, Steroid myopathy, Osteoporosis, Vertebral compression fractures, Aseptic necrosis, Pathologic fracture
- Gastrointestinal : Peptic ulceration with possible perforation and hemorrhage, Gastric hemorrhage, Pancreatitis, Esophagitis, Perforation of the bowel, a temporary and moderate increase in the SGOT, SGPT values and the alkaline phosphatase can occur; but it is not associated with any clinical syndrome.
- Dermatologic : Impaired wound healing, Thin fragile skin, Petechiae and ecchymoses
- Neurological : Increased intracranial pressure, Pseudotumor cerebri, Seizures, Psychic derangements may appear when glucocorticoids are used ranging from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic manifestations, Vertigo
- Endocrine : Menstrual irregularities, Development of Cushingoid state, Suppression of growth in children, Suppression of pituitary-adrenal axis, Decreased carbohydrate tolerance, Manifestations of latent diabetes mellitus, Increased requirements for insulin or oral hypoglycemic agents in diabetics
- Ophthalmic : Prolonged use of glucocorticoids 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. Glucocorticoids should be used cautiously in patients with ocular herpes simplex for fear of cornea perforation. Increased intra-ocular pressure, Exophthalmos
- Metabolic : Negative nitrogen balance due to protein catabolism
- Immune system : Masking of infections, Latent infections becoming active, Opportunistic infections, Hypersensitivity reactions including anaphylaxis may suppress reactions to skin tests

IN SITU ADMINISTRATION
Because of the resorption from the place of administration into the systemic circulation, sufficient attention is recommended for the above-mentioned systemic adverse reactions. In addition, in situ administration can cause dermal and subdermal atrophy while crystals of corticosteroids in the dermis suppress inflammatory reactions, their presence may cause disintegration of the cellular elements and physiochemical changes in the ground substance of the connective tissue. The resultant infrequently occurring dermal and/or subdermal changes may form depressions in the skin at the injection site. The degree to which this reaction occurs will vary with the amount of corticosteroids injected. Regeneration is usually complete within a few months or after all crystals of the corticosteroid have been absorbed
THE FOLLOWING ADDITIONAL REACTIONS ARE RELATED TO PARENTERAL CORTICOSTEROID THERAPY
Rare instances of blindness associated with intralesional therapy around the face and head, Anaphylactic or allergic reactions, Hyperpigmentation or hypopigmentation, Subcutaneous and cutaneous atrophy, Sterile abscess, Post-injection flare, following intra-synovial use, Charcot-like anthropathy, Injection site infections following non sterile technique
ADVERSE REACTIONS REPORTED WITH SOME NON RECOMMENDED ROUTES OF ADMINISTRATION
- Intrathecal/epidural : Arachnoiditis, meningitis, paraparesis/paraplegia, sensory disturbances, bowel/bladder dysfunction, headache, seizures
- Intranasal : Temporary or permanent visual impairment including blindness; allergic, reactions; rhinitis
- Ophthalmic : Temporary or permanent visual impairment including blindness, increased, intra-ocular pressure, ocular and peri-ocular inflammation including allergic reactions, infections, residue or slough at injection site
- Miscellaneous injection sites (scalp, tonsillar fauces, sphenopalatine ganglion): blindness

Special precautions
- SPECIAL RISK GROUPS
Patients belonging to the following special risk groups should be under strict medical surveillance and should be treated during an as short as possible period:
Children : Growth may be suppressed in children receiving long-term, daily-divided dose glucocorticoid therapy. The use of such a regimen should be restricted to those most serious indications.
Diabetics: Manifestations of latent diabetes mellitus or increased requirements for insulin or oral hypoglycemic agents. Hypertensive patients: aggravation of arterial hypertension. Patients with psychiatric antecedents: existing emotional instability or psychotic tendencies may be aggravated by glucocorticoids.
- Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermitent therapy should be used.
- Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight and a chest X-ray should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia.
- Medical surveillance is recommended in case of discontinuation of a chronic treatment. The possibility of a drug-induced secondary adrenocortical insufficiency can be minimized by a gradual reduction or discontinuation of the dosage. The adrenocortical function should be evaluated after discontinuation of a chronic treatment. The most important symptoms of adrenocortical insufficiency are asthenia, orthostatic hypotension and depression.
- In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Multiple small injections into the area of the lesion should be made whenever possible. The technique of intra-articular and intramuscular injection should include precautions against injection or leakage into the dermis. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.
- In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting glucocorticoids before, during and after the stressful situation is indicated.
- Glucocorticoids may mask some signs of infection, and new infections may appear during their use.
- There may be decreased resistance and inability to localize infection when glucocorticoids are used. Do not use intra-articularly, intrabursally or intratendinous administration in the presence of acute infection; I.M. administration can only be considered after institution of an appropriate antimicrobial treatment.
- The use of **Depo-pred** in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculosis regimen. If glucocorticoids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.
- Because rare instances of anaphylactic reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.
- Allergic skin reactions have been reported apparently related to the excipients. Rarely has skin testing demonstrated a reaction to Methylprednisolone Acetate.
- Glucocorticoids should be used with caution in non specific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection. Caution must also be used in diventiculitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis, when steroids are used as direct or adjunctive therapy.
- No evidence exists showing that glucocorticoids are carcinogenic, mutagenic or impair fertility.
- Corticotherapy has to be considered when interpreting a whole series of biological tests and parameters (e.g. skin tests, thyroid hormone levels).

INTRA-ARTICULAR USE
In case of intra-articular use and/or other local administration a strict sterile technique is needed to avoid iatrogen infections. Following intra-articular corticosteroid therapy, care should be taken to avoid overuse of joints in which symptomatic benefit has been obtained. Negligence in this matter may permit an increase in joint deterioration that will more than offset the beneficial effects of the steroid. Unstable joints should not be injected. Repeated intra-articular injection may in some cases result in instability of the joint. X-ray follow-up is suggested in selected cases to detect deterioration. If a local anesthetic is used prior to injection of Depo-pred®, the anesthetic package insert should be read carefully and
all the precautions observed.
THE FOLLOWING ADDITIONAL PRECAUTIONS APPLY FOR PARENTERAL GLUCOCORTICOIDS
- Intrasynovial injection of a corticosteroid 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 the diagnosis of sepsis is confirmed, local injections of glucocorticoids should be discontinued and appropriate antimicrobial therapy should be instituted.
- Local injection of a steroid into a previously infected joint is to be avoided.
- Glucocorticoids should not be injected into unstable joints. Sterile technique is necessary to prevent infections or contamination.
- Although controlled clinical trials have shown glucocorticoids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that glucocorticoids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of glucocorticoids are necessary to demonstrate a significant effect.

Incompatibilities
Because of possible physical incompatibilities **Depo-pred** should not be diluted or mixed with other solutions.

Pregnancy and lactation
Some animal studies have shown that corticosteroids when administered to the mother at high doses may cause fetal malformations. Since adequate human reproduction studies have not been done with glucocorticoids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential, requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus.
Glucocorticoids should be used during pregnancy only if clearly needed. If a chronic treatment with corticosteroids has to be stopped during pregnancy (as with other chronic treatments), this should occur gradually (see also DOSAGE AND ADMINISTRATION). In some cases (e.g. substitution treatment of adrenocortical insufficiency) however, it can be necessary to continue treatment or even to increase dosage. Corticosteroids readily cross the placenta. New-born infants born of mothers who have received substantial doses of glucocorticosteroids during pregnancy should be carefully observed and evaluated for signs of adrenal insufficiency. In case of labor and delivery no effects are known. Corticosteroids are excreted in breast milk.

Interactions
DESIRED INTERACTIONS
- By the treatment of fulminating or disseminated pulmonary tuberculosis and tuberculous meningitis with subarachnoid block or impending block, Methylprednisolone is used concurrently with appropriate antituberculous chemotherapy.
- By the treatment of neoplastic diseases like leukemia and lymphoma, Methylprednisolone is usually used in conjunction with an alkylating agent, an antimetabolite and a vinca alkaloid.

UNDESIRED INTERACTIONS
- Glucocorticoids may increase renal clearance of salicylates. This could lead to a decrease in salicylate serum levels and to salicylate toxicity when the administration of corticoids is stopped.
- Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of corticoids. An adaptation of the corticoid dose mav be required in order to avoid an overdosage.
- Concurrent administration of barbiturates, phenylbutazone, phenytoin or rifampicin may enhance the metabolism and reduce the effects of corticoids.
- Response to anticoagulants can both be reduced and increased by corticoids. Therefore coagulation should be monitored.
- While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on glucocorticolds, especially on high doses because of possible hazards of neurological complications and lack of antibody response.
- Glucocorticolds may increase the requirements for insulin or oral hypoglycemic agents in diabetics. Combination of glucocorticosteroids with thiazide-diuretics increases the risk of glucose intolerance.
- Concurrent use of ulcerogenic drugs (e.g. salicylates, N.S.A.I. drugs) may increase the risk of gastrointestinal ulceration.
- Acetylsalicylic acid should be used cautiously in conjunction with glucocorticoids in hypoprothrombinemia.
- Convulsions have been reported with concurrent use of Methylprednisolone and cyclosporin. Mutual inhibition of metabolism occurs with concurrent use of these two products. Therefore it is possible that convulsions and other adverse reactions associated with the individual use of these drugs may be more apt to occur.

Ability to drive and to operate machinery
Although visual disorders belong to the rare adverse reactions. Caution is recommended by patients driving cars and/or using machines.

Overdosage
There is no clinical syndrome of acute overdosage with Methylprednisolone Acetate.
Repeated frequent doses (daily or several times per week) over a protracted period may result in a Cushingoid state.

Storage
Store at controlled room temperature (below 30^{0}C).

Packaging
Depo-pred 40 mg Injection : Each box contains 3 vial of Methylprednisolone Acetate 40 mg per ml/vial.

Manufactured by :
ZISKA PHARMA
Ziska Pharmaceuticals Ltd.
Kaliakoir, Gazipur, Bangladesh