

תאריך: 16/07/2012

שם תכשיר באנגלית: DEPO MEDROL SUSPENSION FOR INJECTION 40MG/ML

מספר רישום: 024.49.21841.00 שם בעל הרישום: פיזור פרמצבטיקה ישראל בע"מ

השינויים בעלון מסומנים על רקע צהוב

בעלון לרופא

פרטים על השינויים המבוקשים		
טקסט חדש	טקסט נוכחי	פרק בעלון
<p>...</p> <p>Methylprednisolone is a potent anti-inflammatory steroid. It has greater anti-inflammatory potency than prednisolone and less tendency than prednisolone to induce sodium and water retention.</p> <p>Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. The plasma protein binding of methylprednisolone in humans is approximately 77%.</p> <p>In humans, methylprednisolone is metabolized in the liver to inactive metabolites; the major ones are 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4. (For a list of drug interactions based on CYP3A4-mediated metabolism, see section 15. Interactions). 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.</p> <p>The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours. Its apparent volume of distribution is approximately 1.4 L/kg, and its total clearance is approximately 5 to 6 mL/min/kg.</p> <p>Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for the ATP-binding cassette (ABC) transport protein p-glycoprotein, influencing tissue distribution and interactions with other medicines.</p> <p>No dosing adjustments are necessary in renal failure. Methylprednisolone is hemodialyzable.</p>	<p>Methylprednisolone is hemodialyzable. Metabolism of methylprednisolone 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.</p>	<p><u>5. Properties</u> 5.1 <u>Pharmacodynamics</u></p> <p><u>5. Properties</u> <u>5.2 Pharmacokinetics</u></p>

טקסט חדש	טקסט נוכחי	פרק בעלון
<p>For the treatment of conditions responsive to steroid injection therapy.</p> <p>A. FOR (INTRAMUSCULAR ADMINISTRATION)</p> <p>Methylprednisolone acetate (DEPO-MEDROL) 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 (SOLU-MEDROL) is indicated.</p> <p>When oral therapy is not feasible and the strength, dosage form, and route of administration of the drug reasonably lend this preparation to the treatment of the condition, the intramuscular use of DEPO-MEDROL is indicated as follows:</p> <p>...</p> <p>3. Dermatologic diseases</p> <p>...</p> <p>- Severe psoriasis</p> <p>4. Allergic states</p> <p>Bronchial asthma</p> <p>...</p> <p>9. Endocrine disorders</p> <p>...</p> <p>Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice, mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used)</p> <p>...</p> <p>10. Ophthalmic diseases</p> <p>Severe acute and chronic allergic and inflammatory processes involving the eye, such as:</p> <p>- Herpes zoster ophthalmicus</p> <p>- Drug hypersensitivity reactions</p> <p>- Iritis, iridocyclitis</p> <p>- Anterior segment inflammation</p> <p>- Chorioretinitis</p> <p>- Allergic conjunctivitis</p> <p>- Diffuse posterior uveitis</p> <p>- Allergic corneal marginal ulcers</p> <p>- Optic neuritis</p> <p>- Keratitis</p> <p>11. Edematous states</p> <p>To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus</p> <p>D. FOR INTRARECTAL INSTALLATION</p> <p>Ulcerative colitis</p> <p>Intrarectal Administration</p> <p>DEPO-MEDROL in doses of 40 to 120 mg administered as retention enemas or by continuous drip three to seven times weekly for periods of two or more weeks, have been shown to be a useful adjunct in the treatment of some patients with ulcerative colitis. Many patients can be controlled with 40 mg of methylprednisolone acetate administered in from 30-300 ml of water depending upon the degree of involvement of the inflamed colonic mucosa. Other accepted therapeutic measures should, of course, be</p>	<p>Glucocorticoids should only be considered as symptomatic treatment, unless in case of some endocrine disorders, where they are used as a substitution treatment.</p> <p>A. FOR (INTRAMUSCULAR ADMINISTRATION)</p> <p>Methylprednisolone acetate (DEPO-MEDROL™) 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 (SOLU-MEDROL™) is indicated.</p> <p>When oral therapy is not feasible and this preparation lend to the treatment of the condition, the intramuscular use of DEPO-MEDROL™ is indicated as follows:</p> <p>...</p> <p>4. Allergic states</p> <p>chronic asthmatic respiratory disorders</p> <p>...</p> <p>9. Endocrine disorders</p> <p>...</p> <p>Acute adrenocortical insufficiency</p>	<p>6. Indications</p> <p>7. Dosage and administration</p>

instituted.

Depo Medrol is contraindicated :

- in patients who have systemic fungal infections
- in patients with known hypersensitivity to methylprednisolone or any component of the formulation
- for use by the intrathecal route of administration
- for use by the intravenous route of administration

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

Respiratory, thoracic and Mediastinal disorders:
Hiccups.

...

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

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Immunosuppressant Effects/Increased Susceptibility to Infections

Corticosteroids may increase susceptibility to infection, 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 corticosteroids are used. Infections with any pathogen, including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids.

Do not use intra-synovially, intrabursally or intratendinous administration for local effect in the presence of acute infection.

The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended. A systematic review of short-course high-dose corticosteroids did not support their use. However, meta-analyses and a review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

Depo Medrol is contraindicated for intrathecal administration.

- Systemic fungal infections
- Known hypersensitivity to components

9. Contra Indications

11. Adverse reactions

12. Special warnings and precautions for use

The use of corticosteroids 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 corticosteroids 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.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Immune System Effects

Allergic reactions may occur. Because rare instances of skin reactions and anaphylactic/anaphylactoid reactions have occurred in patients receiving corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

Endocrine Effects

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.

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 glucocorticoid therapy. This effect may be minimized by use of alternate-day therapy.

In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Drug-induced secondary adrenocortical insufficiency may therefore be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

A steroid "withdrawal syndrome," seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.

Because glucocorticoids can produce or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease.

There is an enhanced effect of corticosteroids on patients with hypothyroidism.

Metabolism and Nutrition

Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus.

Psychiatric Effects

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Potentially severe psychiatric adverse reactions may occur with systemic steroids. 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.

Psychological effects have been reported upon withdrawal of corticosteroids; the frequency is unknown. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms develop in the patient, especially if depressed mood or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.

Nervous System Effects

Corticosteroids should be used with caution in patients with seizure disorders.

Corticosteroids should be used with caution in patients with myasthenia gravis (Also see myopathy statement in Musculoskeletal Effects section below).

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect (see section 7.

Dosage and administration)

Ocular Effects

Prolonged use of corticosteroids may produce posterior 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, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Corticosteroids should be used cautiously in

patients with ocular herpes simplex for fear of corneal perforation.

Cardiac Effects

Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed.

Systemic corticosteroids should be used with caution, and only if strictly necessary, in cases of congestive heart failure.

Vascular Effects

Corticosteroids should be used with caution in patients with hypertension.

Gastrointestinal Effects

There is no universal agreement on whether corticosteroids per se are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or hemorrhage may occur without significant pain.

Corticosteroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection. Caution must also be used in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, when steroids are used as direct or adjunctive therapy.

Hepatobiliary Effects

High doses of corticosteroids may produce acute pancreatitis.

Musculoskeletal Effects

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

Osteoporosis is a common but infrequently recognized adverse effect associated with a long-term use of large doses of glucocorticoid.

Renal and Urinary Disorders

Corticosteroids should be used with caution in patients with renal insufficiency.

Investigations

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

Other Warnings and Precautions

Caution is recommended with prolonged corticosteroid treatment in the elderly due to a potential increased risk for osteoporosis, as well as increased risk for fluid retention with possible resultant hypertension. Since complications of treatment with glucocorticoids are dependent on the amount 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 as to whether daily or intermittent therapy should be used.

Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids.

Use in Children

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. 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.

Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure.

High doses of corticosteroids may produce pancreatitis in children.

Fertility

No evidence exists showing that corticosteroids are carcinogenic, mutagenic or impair fertility.

Pregnancy

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One retrospective study found an increased incidence of low birth weights in infants born of mothers receiving corticosteroids.

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.

Although neonatal adrenal insufficiency appears to be rare in infants who were exposed in utero to corticosteroids, those exposed to substantial doses of corticosteroids must be carefully observed and evaluated for signs of adrenal insufficiency.

Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.

Pregnancy

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 chronic treatment with corticosteroids has to be stopped during pregnancy (as with other chronic treatments), this should occur gradually (see also section 7. DOSAGE AND ADMINISTRATION).In some cases (e.g. substitution treatment of adrenocortical insufficiency) however, it may be necessary to continue treatment or even to increase dosage. Corticosteroids readily cross the placenta. New-born infants born of mothers who have

14. Fertility, pregnancy and lactation

In case of labor and delivery no effects are known.

Lactation

Corticosteroids are excreted in breast milk.

Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. Since adequate reproductive studies have not been performed in humans with glucocorticoids, these drugs should be administered to nursing mothers only if the benefits of therapy are judged to outweigh the potential risks to the infant.

Adequate human reproductive studies have not been done with corticosteroids. The use of this drug in pregnancy, nursing mothers, or women of childbearing potential requires that the benefits of the drug be weighed against the potential risk to the mother and embryo or fetus.

UNDESIRE INTERACTIONS

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 6 β -hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme (**Table 2**).

CYP3A4 INHIBITORS – Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance and increase the plasma concentration of CYP3A4 substrate medications, such as methylprednisolone. In the presence of a CYP3A4 inhibitor, the dose of methylprednisolone may need to be titrated to avoid steroid toxicity (**Table 2**).

CYP3A4 INDUCERS – Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrates for CYP3A4. Coadministration may require an increase in methylprednisolone dosage to achieve the desired result (**Table 2**).

CYP3A4 SUBSTRATES – In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be inhibited or induced, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration (**Table 2**).

NON-CYP3A4-MEDIATED EFFECTS – Other interactions and effects that occur with methylprednisolone are described in Table 2 below

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.

Lactation

Corticosteroids are excreted in breast milk.

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 may be required in order to avoid an overdose,

- 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 glucocorticoids, especially on high doses because of possible hazards of neurological complications and lack of antibody response.

- Glucocorticoids may increase the requirements for insulin or oral hypoglycemic agents in diabetics. Combination of glucocorticosteroids with thiazid-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.

15. Interactions

There is no clinical syndrome of acute overdosage with methylprednisolone acetate.

Reports of acute toxicity and/or death following overdosage of corticosteroids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic. Methylprednisolone is dialyzable.

Store at controlled room temperature **below** 25°C.

Do not freeze.

The expiry date (month/year) is mentioned on the package after "EXP.:"
(EXP. = expiry date).

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.

19. Storage

Store at controlled room temperature (20°-25°C). The expiry date (month/year) is mentioned on the package after "EXP.:" (EXP. = expiry date).

18. Overdose

19. Storage

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