הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך 2.5.2016

שם התכשיר באנגלית ומספר הרישום Depo-Medrol 40 mg/ml (024 49 21841 00)

שם בעל הרישום Pfizer PFE Pharmaceuticals Israel Ltd.

טופס זה מיועד לפרוט ההחמרות בלבד!

ההחמרות המבוקשות		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
Depo-medrol is contra-indicated where there is known hypersensitivity to components and in systemic infection unless specific anti-infective therapy is employed.	Depo Medrol is contraindicated : - in patients who have systemic fungal infections - in patients with known hypersensitivity to methylprednisolone or any component of the formulation	**Contraindications**
1. Undesirable effects may be minimised by using the lowest effective dose for the minimum period. Frequent patient review is required to appropriately titrate the dose against disease activity (see Posology and method of administration). 4. Due to the absence of a true tendon sheath, the Achilles tendon should not be injected with Depo-Medrol. 6. Intralesional doses should not be placed too superficially, particularly in easily visible sites in patients with deeply pigmented skins, since there have been rare reports of subcutaneous atrophy and depigmentation. 7. Systemic absorption of methylprednisolone occurs following intra articular injection of Depo-Medrol. Systemic as well as local effects can therefore be expected. 8. Intra-articular corticosteroids are associated with a substantially increased risk of inflammatory response in the joint, particularly bacterial infection introduced with the injection. Charcot-like arthropathies have been reported particularly after repeated injections. Appropriate examination of any joint fluid present is necessary to exclude any bacterial infection, prior to injection. 9. Following a single dose of Depo-Medrol, plasma cortisol levels are reduced and there is evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression. This suppression lasts for a variable period of up to 4 weeks. The usual dynamic tests of HPA axis function can be used to diagnose evidence of		**Special warnings and precautions for use**

impaired activity (e.g. Synacthen test). 10. Adrenal cortical atrophy develops during prolonged therapy and may persist for months after stopping treatment. In patients who have received more than physiological doses of systemic corticosteroids (approximately 6 mg methylprednisolone) 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 6 mg methylprednisolone 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 considered that the disease is unlikely to relapse. Abrupt withdrawal of doses up to 32 mg daily of methylprednisolone 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 32 mg daily of methylprednisolone. • Patients repeatedly taking doses in the evening. 13. Corticosteroids may mask some signs of infection, and new infections may appear during their use. Suppression of the	Glucocorticoids may mask some signs of infection, and new infections may appear during	

inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial infections and their severity. The clinical presentation may often be atypical and may reach an advanced stage before being recognised. 14. Chickenpox is of serious concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunization with varicella/zoster immunoglobin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within 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. Corticosteroids should not be stopped and the dose may need to be increased. 15. Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished. 17. Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see Undesirable effects). *Special precautions:* Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary. 1. Osteoporosis (post-menopausal females are particularly at risk). 3. Existing or previous history of severe affective disorders (especially previous steroid psychosis). 4. Diabetes mellitus (or a family history of diabetes). 5. History of tuberculosis. 6. Glaucoma (or a family history of glaucoma). 7. Previous corticosteroid-induced myopathy. 8. Liver failure or cirrhosis.	their use.	

10. Epilepsy. 13. Predisposition to thrombophlebitis. 15. Ulcerative colitis 20. Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 Interaction with Other Medicaments and Other Forms of Interaction that can increase the risk of side effects), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently. Use in Children: Corticosteroids cause growth retardation in infancy, childhood and adolescence which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. Use in the elderly: The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.	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. 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.	

2. Drugs that induce hepatic enzymes, such as rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone, and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced. 4. Steroids may reduce the effects of anticholinesterases in myasthenia gravis. The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids, and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced. 5. The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding. 6. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Salicylates and non-steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids in hypothrombinaemia. 7. Steroids have been reported to interact with neuromuscular blocking agents such as pancuronium with partial reversal of the neuromuscular block.	. Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.	**Interaction with other medicaments and other forms of interaction**
<u>Pregnancy</u> The ability of corticosteroids to cross the placenta varies between individual drugs, however, methylprednisolone does cross the placenta. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate in man, however, when administered for long periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory , occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be	<u>Pregnancy</u> 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	**Pregnancy and lactation**

prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential, however, patients with normal pregnancies may be treated as though they were in the non-gravid state.	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. 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. In case of labor and delivery no effects are known.	
Lactation Corticosteroids are excreted in small amounts in breast milk, however, doses of up to 40 mg daily of methylprednisolone are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses than this may have a degree of adrenal suppression, but the benefits of breastfeeding are likely to outweigh any theoretical risk.	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.	

The incidence of predictable undesirable side-effects associated with the use of corticosteroids, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and duration of treatment (see Special warnings and special PARENTERAL CORTICOSTEROID THERAPY - Anaphylactic reaction or allergic reactions, hypopigmentation or hyperpigmentation, subcutaneous and cutaneous atrophy, sterile abscess, post injection flare (following intra-articular use), Charcot-like arthropathy, rare instances of blindness associated with intralesional therapy around the face and head. GASTRO-INTESTINAL - Dyspepsia, peptic ulceration with perforation and haemorrhage, abdominal distension, oesophageal ulceration, oesophageal candidiasis, acute pancreatitis, perforation of bowel. ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE EFFECTS – Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, may suppress reactions to skin tests, recurrence of dormant tuberculosis (see Special warnings and special precautions for use). MUSCULOSKELETAL - Proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, aseptic necrosis, muscle weakness. FLUID AND ELECTROLYTE DISTURBANCE Sodium and water retention, potassium loss, hypertension, hypokalaemic alkalosis, congestive heart failure in susceptible patients. DERMATOLOGICAL - Impaired healing, petechiae and ecchymosis, thin fragile skin, skin atrophy, bruising, striae, telangiectasia, acne. ENDOCRINE/METABOLIC - Suppression of the hypothalamo-pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea. Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, negative nitrogen and calcium balance. Increased appetite. NEUROPSYCHIATRIC - A wide range of psychiatric reactions including affective		**Undesirable effects**

disorders (such as irritable, euphoric, depressed and labile mood psychological dependence and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported for all corticosteroids. . Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions was estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown. Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri) has been reported, usually after treatment withdrawal of methylprednisolone. OPHTHALMIC - Increased intra-ocular pressure, glaucoma, papilloedema, cataracts with possible damage to the optic nerve, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease, exophthalmos. GENERAL - Leucocytosis, hypersensitivity including anaphylaxis, thrombo-embolism, nausea, vertigo. WITHDRAWAL SYMPTOMS - Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. However, this is more applicable to corticosteroids with an indication where continuous therapy is given (see Special warnings and special precautions for use). A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight. <u>CERTAIN SIDE-EFFECTS REPORTED WITH SOME NON-RECOMMENDED ROUTES OF ADMINISTRATION.</u> Intrathecal (contra-indicated route of administration): Usual systemic corticoid adverse reactions, headache, meningismus, meningitis, paraplegia, spinal fluid abnormalities, nausea, vomiting, sweating, arachnoiditis, convulsions. Extradural: Wound dehiscence, loss of sphincter control. Intranasal: Permanent/temporary blindness, rhinitis.		

Ophthalmic: (Subconjunctival) - Redness and itching, abscess, slough at injection site, residue at injection site, increased intra-ocular pressure, decreased vision - blindness, infection. Miscellaneous injection sites - Scalp, tonsillar fauces, sphenopalatine ganglion: blindness. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il		
There is no clinical syndrome of acute overdosage with Depo-Medrol. Following overdosage the possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time. In such event the patient may require to be supported during any further traumatic episode.	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.	**Overdose**