

## DEPO-MEDROL® 40 MG/ML

### SUMMARY OF PRODUCT CHARACTERISTICS

#### 1. NAME OF THE MEDICINAL PRODUCT

DEPO- MEDROL® 40 MG/ml Suspension for Injection.

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylprednisolone acetate 40 mg/ml.

For the full list of excipients, see section 6.1.

#### 3. PHARMACEUTICAL FORM

Suspension for Injection.

White, sterile, aqueous suspension .

#### 4. CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

For the treatment of conditions responsive to steroid injection therapy.

##### A. For intramuscular administration

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.

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:

##### Anti-inflammatory treatment

##### 1. Rheumatic disorders

As adjunctive therapy 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. Dermatological diseases

Pemphigus  
Bullous dermatitis herpetiformis (sulfone is the drug of first choice and systemic administration of glucocorticoids is an adjuvant)  
Severe erythema multiforme (Stevens-Johnson syndrome)  
Exfoliative dermatitis  
Mycosis fungoides  
Severe psoriasis

4. Allergic states

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:  
Bronchial asthma  
Contact dermatitis  
Atopic dermatitis  
Serum sickness  
Drug hypersensitivity reactions  
Urticarial transfusion reactions  
Acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

5. Gastro-intestinal 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

7. Hematologic disorders

Acquired (autoimmune) hemolytic anemia  
Secondary thrombocytopenia in adults  
Erythroblastopenia (RBC anemia)  
Congenital (erythroid) hypoplastic anemia

8. Oncological diseases

For palliative management of:  
Leukemias and lymphomas  
Acute leukemia of childhood

9. 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 (hydrocortisone or cortisone is the drug of choice, mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used). In infancy mineralocorticoid supplementation is of particular importance.

Congenital adrenal hyperplasia

Hypercalcemia associated with cancer

Nonsuppurative thyroiditis

10. Ophthalmic diseases dermatological diseases

Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

Herpes zoster ophthalmicus

Drug hypersensitivity reactions

Iritis, iridocyclitis

Anterior segment inflammation

Chorioretinitis

Allergic conjunctivitis

Diffuse posterior uveitis

Allergic corneal marginal ulcers

Optic neuritis

Keratitis

11. Edematous states

To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

12. Miscellaneous

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Trichinosis with neurologic or myocardial involvement

**B. FOR INTRASYNOVIAL, PERIARTICULAR, INTRABURSAL OR SOFT TISSUE ADMINISTRATION** (see Special warnings and precautions for use)

Depo-Medrol 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-Medrol is indicated for intralesional use in the following conditions:

Keloids, Localized hypertrophic, infiltrated, inflammatory lesions of:

Lichen planus, psoriatic plaques

Necrobiosis lipodica diabetorum

Granuloma annulare  
 Lichen Simplex chronicus (neurodermatitis)  
 Discoid lupus erythematosus  
 Alopecia areata

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

#### **D. FOR INTRARECTAL INSTALLATION**

Ulcerative colitis

### **4.2 Posology and Method of Administration**

Depo-Medrol may be used by any of the following routes:

- Intramuscular
- Intra-articular, periarticular, intrabursal or soft tissues
- Intralesional
- Intrarectal instillation

Depo-Medrol is contra-indicated for I.V administration.

Depo-Medrol is contra-indicated for intrathecal route of **administration**

Depo-Medrol is not recommended for epidural, intranasal, intra-ocular or any other unapproved route of administration (see Undesirable effects reported from non recommended routes of 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. Strict 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 the 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.

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-Medrol 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, repeated injections, if needed, may be given at intervals of one to five or more weeks, depending on the degree of relief obtained from the initial injection. The doses in the following table are given as a general guide:

**Table 1. General guide for dosage**

| Size of Joint | Example                                                                         | Range of Dosage |
|---------------|---------------------------------------------------------------------------------|-----------------|
| Large         | Knees<br>Ankles<br>Shoulders                                                    | 20-80 mg        |
| Medium        | Elbows<br>Wrists                                                                | 10-40 mg        |
| Small         | Metacarpophalangeal<br>Interphalangeal<br>Sternoclavicular<br>Acromioclavicular | 4-10 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-Medrol. 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. A 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 many 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. INTRARECTAL ADMINISTRATION

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 instituted.

## 4.3 Contraindications

DepoMedrol is contraindicated:

- in patients with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- in patients who have systemic infection unless specific anti-infective therapy is employed
- for use by the intrathecal route (due to its potential for neurotoxicity, see section 4.8)
- for use by the intravenous route

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

#### 4.4 Special warnings and precautions for use

##### *Warnings and Precautions:*

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 section 4.2).

Depo-Medrol vials are intended for single dose use only. Any multidose use of the product may lead to contamination.

Severe medical events have been reported in association with the intrathecal/epidural routes of administration (see section 4.8). Appropriate measures must be taken to avoid intravascular injection.

Due to the absence of a true tendon sheath, the Achilles tendon should not be injected with Depo-Medrol.

While crystals of adrenal steroids 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 adrenal steroid injected. Regeneration is usually complete within a few months or after all crystals of the adrenal steroid have been absorbed.

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.

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.

Systemic absorption of methylprednisolone occurs following intra-articular injection of Depo-Medrol. Systemic as well as local effects can therefore be expected.

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.

##### *The following precautions apply for parenteral corticosteroids:*

Following intra-articular injection, the occurrence of a marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of

septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided.

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.

Corticosteroids should not be injected into unstable joints.

Sterile technique is necessary to prevent infections or contamination.

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

### **Immunosuppressant Effects/Increased Susceptibility to Infections**

Corticosteroids may increase susceptibility to infection, may mask some signs of infection, exacerbate existing infections, increase the risk of reactivation or exacerbation of latent infections and new infections may appear during their use. Suppression of the 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. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

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

Monitor for the development of infection and consider withdrawal of corticosteroids or dosage reduction as needed.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids.

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 immunoglobulin (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.

Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

The use of Depo- Medrol 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 an appropriate antituberculous 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.

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, especially in patients with vasopressor-dependent septic shock.

### **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 drug allergy.

### **Endocrine Effects**

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. Salt and/or a mineralocorticoid are only needed if mineralocorticoid secretion is impaired.

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.

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 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.

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.

Thyrotoxic Periodic Paralysis (TPP) can occur in patients with hyperthyroidism and with methylprednisolone-induced hypokalaemia.

TPP must be suspected in patients treated with methylprednisolone presenting signs or symptoms of muscle weakness, especially in patients with hyperthyroidism.

If TPP is suspected, levels of blood potassium must be immediately monitored and adequately managed to ensure the restoration of normal levels of blood potassium.

### **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**

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 section 4.5), 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.

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

### **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).

There have been reports of epidural lipomatosis in patients taking corticosteroids, typically with long-term use at high doses.

### **Ocular Effects**

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 which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids. Central serous chorioretinopathy, may lead to retinal detachment.

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, because of possible corneal perforation.

**Cardiac Effects**

Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidaemia 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.

Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

**Gastrointestinal Effects**

High doses of corticosteroids may produce acute pancreatitis.

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 haemorrhage may occur without significant pain. Glucocorticoid therapy may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

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**

Drug induced liver injury including acute hepatitis or liver enzyme increase can result from cyclical pulsed IV methylprednisolone (usually at initial dose  $\geq 1$  g / day). Rare cases of hepatotoxicity have been reported. The time to onset can be several weeks or longer. In the majority of case reports resolution of the adverse events has been observed after treatment was discontinued. Therefore, appropriate monitoring is required.

Corticosteroids should be used with caution in patients with liver failure or cirrhosis.

**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 (e.g., myasthenia gravis), or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevations of creatine kinase may occur. Cases of rhabdomyolysis have been reported. 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**

Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

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.

Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see section 4.8).

### **Injury, Poisoning and Procedural Complications**

Systemic corticosteroids are not indicated for, and therefore should not be used to treat, traumatic brain injury, a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate treatment has not been established.

### **Other**

Corticosteroids should be used with caution in patients with a predisposition to thrombophlebitis.

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 side-effects (see section 4.5).

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

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.

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with malignancies, including haematological malignancies and solid tumours, following the use of systemic corticosteroids alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with tumours that have a high proliferative rate, high tumour burden and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precautions should be taken.

Depo-Medrol contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

***Paediatric population***

Corticosteroids cause growth retardation in infancy, childhood and adolescence which may be irreversible. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Treatment should be limited to the minimum dosage for the shortest possible time. 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.

**4.5 Interaction with other medicinal products and other forms of interaction**

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 $\beta$ -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.

**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.

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

**CYP3A4 SUBSTRATES** – In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, 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 co-administration.

1. Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin (CYP3A4 inhibitor and substrate). Since concurrent administration of these agents results in a mutual inhibition of metabolism (which may increase the plasma concentrations of either or both drugs), it is possible that convulsions and other adverse effects associated with the individual use of either drug may be more apt to occur.
2. Drugs that induce hepatic enzymes, such as rifampicin (antibiotic CYP3A4 inducer), rifabutin, carbamazepine (anticonvulsant CYP3A4 inducer and substrate), phenobarbitone and phenytoin (anticonvulsants CYP3A4 inducers), primidone, and aminoglutethimide (aromatase inhibitor) enhance the metabolism of corticosteroids and its therapeutic effects may be reduced. Aminoglutethimide- induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.

The acetylation rate and clearance of isoniazid (CYP3A4 inhibitor), an antibacterial drug, can be increased by methylprednisolone.

3. Antibiotics/Antimycotics - Drugs such as erythromycin (macrolide antibacterial CYP3A4 inhibitor and substrate), itraconazole and ketoconazole (antifungal CYP3A4 inhibitors and substrates) may inhibit the metabolism of corticosteroids and thus decrease their clearance.  
Troleandomycin (CYP3A4 inhibitor), as well as clarithromycin, erythromycin, itraconazole and ketoconazole (CYP3A4 inhibitors and substrates) increase the effects and the side effects of methylprednisolone.
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. An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. (see section 4.4).  
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.
5. Anticoagulants (oral) (Vitamin K Antagonists) -The effect of methylprednisolone on vitamin K antagonists (e.g., warfarin, acenocoumarol, fluindione) is variable. The efficacy of these anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding and to maintain the desired anticoagulant effects.  
There are also reports of diminished effects of anticoagulants when given concurrently with corticosteroids.
6. There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs.  
Methylprednisolone may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity. Salicylates and non-steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids in hypothermia.
7. Antidiabetics- Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
8. Antiemetics - Aprepitant and fosaprepitant (CYP3A4 inhibitors and substrates)
9. Antivirals - HIV protease inhibitors:  
1) Indinavir, ritonavir and pharmacokinetic enhancers (cobicistat) (CYP3A4 inhibitors and substrates) may increase plasma concentrations of corticosteroids.  
2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
10. Calcium channel blocker - Diltiazem (CYP3A4 inhibitor and substrate).
11. Contraceptives (oral) - Ethinylestradiol/norethindrone (CYP3A4 inhibitors and substrate).
12. Other immunosuppressants like cyclophosphamide and tacrolimus are substrates of CYP3A4.

13. Potassium-depleting agents -When corticosteroids are administered concomitantly with potassium-depleting agents (e.g. diuretics), patients should be observed closely for development of hypokalaemia. There is also an increased risk of hypokalaemia with concurrent use of corticosteroids with amphotericin B, xanthenes, or beta2 agonists.
14. Grapefruit juice – CYP3A4 inhibitor.

#### **4.6 Fertility, pregnancy and lactation**

##### Fertility

Corticosteroids have been shown to impair fertility in animal studies (see section 5.3).

##### Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs, however, methylprednisolone does cross the placenta. One retrospective study found an increased incidence of low birth weights in infants born of mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses.

.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. 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. As with all drugs, corticosteroids should only be 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. However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women.

Since adequate human reproductive studies have not been done with methylprednisolone acetate, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

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

##### Breast-feeding

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 breast-feeding are likely to outweigh any theoretical risk.

Corticosteroids distributed into breast milk may interfere with endogenous glucocorticoid production in nursing infants. This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

#### **4.7 Effects on ability to drive and use machines**

The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as dizziness, vertigo, visual disturbances, and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

#### 4.8 Undesirable effects

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 section 4.4).

| <b>MedDRA<br/>System Organ Class</b>               | <b>Frequency</b>        | <b>Undesirable Effects</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b><i>Infections and infestations</i></b>          | <b><i>Not Known</i></b> | Infection (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs); Opportunistic infection; Injection site infection; Peritonitis; Recurrence of dormant tuberculosis                                                                                                                                                                                                                                                                                       |
| <b><i>Blood and lymphatic system disorders</i></b> | <b><i>Not Known</i></b> | <i>Leukocytosis</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b><i>Immune system disorders</i></b>              | <b><i>Not Known</i></b> | Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b><i>Endocrine disorders</i></b>                  | <b><i>Not Known</i></b> | Cushingoid; Hypothalamic pituitary adrenal axis suppression;; 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 section 4.4). A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight. |
| <b><i>Metabolism and nutrition disorders</i></b>   | <b><i>Not Known</i></b> | Metabolic acidosis; Glucose tolerance impaired; Sodium retention; Fluid retention; Increased requirements for insulin (or oral hypoglycemic agents in diabetics)*; Alkalosis hypokalaemic; Dyslipidaemia, Increased appetite (which may result in Weight increased); Lipomatosis                                                                                                                                                                                                                                    |
| <b><i>Psychiatric disorders</i></b>                | <b><i>Not Known</i></b> | Affective disorder (including Depressed mood, Euphoric mood, Affect lability, Drug dependence, Suicidal ideation). The following events were most common in children: Mood swings; Abnormal behaviour; Insomnia; Psychotic disorder (including Mania, Delusion, Hallucination, and Schizophrenia [aggravation of]); Confusional state; Mental disorder; Anxiety; Personality change; Mood swings; Abnormal behaviour; Insomnia; Irritability (children and adults)                                                  |

| <b>MedDRA<br/>System Organ Class</b>                        | <b>Frequency</b> | <b>Undesirable Effects</b>                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Nervous system disorders</i>                             | <i>Not Known</i> | Intracranial pressure increased (with Papilloedema [Benign intracranial hypertension]); Seizure; Amnesia; Cognitive disorder; Dizziness; Headache;                                                                                                                                                                                                  |
| <i>Eye disorders</i>                                        | <i>Not Known</i> | Cataract; Glaucoma; Exophthalmos; Vision blurred (see also section 4.4); Chorioretinopathy; rare instances of blindness associated with intralesional therapy around the face and head *; Increased intra-ocular pressure, with possible damage to the optic nerve; Corneal or scleral thinning; Exacerbation of ophthalmic viral or fungal disease |
| <i>Ear and labyrinth disorders</i>                          | <i>Not Known</i> | Vertigo                                                                                                                                                                                                                                                                                                                                             |
| <i>Cardiac disorders</i>                                    | <i>Not Known</i> | Cardiac failure congestive (in susceptible patients)                                                                                                                                                                                                                                                                                                |
| <i>Vascular disorders</i>                                   | <i>Not Known</i> | Hypertension; Hypotension; Embolism arterial, Thrombotic events, Flushing                                                                                                                                                                                                                                                                           |
| <i>Respiratory, thoracic and mediastinal disorders</i>      | <i>Not Known</i> | Pulmonary embolism, Hiccups                                                                                                                                                                                                                                                                                                                         |
| <i>Gastrointestinal disorders</i>                           | <i>Not Known</i> | Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer haemorrhage); Gastric haemorrhage; Intestinal perforation; Pancreatitis; Oesophagitis ulcerative; Oesophagitis; Abdominal pain; Abdominal distension; Diarrhoea; Dyspepsia; Nausea                                                                                            |
| <i>Hepatobiliary disorders</i>                              | <i>Not known</i> | Hepatitis, Increase of liver enzymes                                                                                                                                                                                                                                                                                                                |
| <i>Skin and subcutaneous tissue disorders</i>               | <i>Not Known</i> | Angioedema; Hirsutism; Petechiae; Ecchymosis; Skin atrophy; Erythema; Hyperhidrosis; Skin striae; Skin hyperpigmentation; Rash; Pruritus; Urticaria; Acne; Skin hypopigmentation;                                                                                                                                                                   |
| <i>Musculoskeletal and connective tissue disorders</i>      | <i>Not Known</i> | Growth retardation; Osteoporosis; Muscular weakness; Osteonecrosis; Pathological fracture; Muscle atrophy; Myopathy; Rhabdomyolysis; Neuropathic arthropathy; Arthralgia; Myalgia; Post injection pain flare (following intra-articular, periarticular, and tendon sheath injections)*                                                              |
| <i>Reproductive system and breast disorders</i>             | <i>Not Known</i> | Menstruation irregular                                                                                                                                                                                                                                                                                                                              |
| <i>General disorders and administration site conditions</i> | <i>Not Known</i> | Abscess sterile; Impaired healing; Oedema peripheral; Fatigue; Malaise; Injection site reaction;                                                                                                                                                                                                                                                    |

| <b>MedDRA<br/>System Organ Class</b>                         | <b>Frequency</b>        | <b>Undesirable Effects</b>                                                                                                                                                                                                                                            |
|--------------------------------------------------------------|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b><i>Investigations</i></b>                                 | <b><i>Not Known</i></b> | Blood potassium decreased; Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood alkaline phosphatase increased; Carbohydrate tolerance decreased; Urine calcium increased; suppression of reactions to skin tests *; Blood urea increased; |
| <b><i>Injury, poisoning and procedural complications</i></b> | <b><i>Not Known</i></b> | Tendon rupture (particularly of the Achilles tendon); Spinal compression fracture. Systemic corticosteroids are not indicated for, and therefore should not be used to treat, traumatic brain injury.                                                                 |

† Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Not known (frequency cannot be estimated from the available data)

\* Not a MedDRA PT

#Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4).

#### CERTAIN SIDE EFFECTS REPORTED WITH SOME CONTRAINDICATED AND NON-RECOMMENDED ROUTES OF ADMINISTRATION.

*Intrathecal/Epidural:* Usual systemic corticoid adverse reactions, headache, meningismus, meningitis, paraparesis/paraplegia, spinal fluid abnormalities, nausea, vomiting, sweating, arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, seizure, sensory disturbance.

*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 <https://sideeffects.health.gov.il/>

#### **4.9 Overdose**

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.

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 dialysable.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Glucocorticoids, ATC code: H02AB04

Methylprednisolone acetate is a synthetic glucocorticoid. It has greater anti-inflammatory potency than prednisolone and less tendency than prednisolone to induce sodium and water retention. An aqueous suspension may be injected directly into joints and soft tissues in the treatment of rheumatoid arthritis, osteoarthritis, bursitis and similar inflammatory conditions. For prolonged systemic effect it may be administered intramuscularly.

### **5.2 Pharmacokinetic properties**

#### Absorption:

One in-house study of eight volunteers determined the pharmacokinetics of a single 40 mg intramuscular dose of Depo-Medrol. The average of the individual peak plasma concentrations was  $14.8 \pm 8.6$  ng/ml, the average of the individual peak times was  $7.25 \pm 1.04$  hours, and the average area under the curve (AUC) was  $1354.2 \pm 424.1$  ng/ml x hrs (Day 1-21).

#### Distribution:

Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. Its apparent volume of distribution is approximately 1.4 l/kg. The plasma protein binding of methylprednisolone in humans is approximately 77%.

#### Metabolism:

In humans, methylprednisolone is metabolized in the liver to inactive metabolites; the major ones are 20 $\alpha$ -hydroxymethylprednisolone and 20 $\beta$ -hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4. (For a list of drug interactions based on CYP3A4-mediated metabolism, see section 4.5).

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.

#### Elimination:

The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours. Total clearance is approximately 5 to 6 ml/min/kg.

No dosing adjustments are necessary in renal failure. Methylprednisolone is haemodialysable.

Methylprednisolone acetate is less soluble than methylprednisolone.

### **5.3 Preclinical safety data**

Based on conventional studies of safety pharmacology and repeated dose toxicity, no unexpected hazards were identified. The toxicities seen in the repeated-dose studies were those expected to occur with continued exposure to exogenous adrenocortical steroids.

Mutagenesis:

Methylprednisolone has not been formally evaluated for genotoxicity. Studies using structurally related analogues of methylprednisolone showed no evidence of a potential for genetic and chromosome mutations in limited studies in bacteria and mammalian cells.

Carcinogenesis:

Methylprednisolone has not been formally evaluated in rodent carcinogenicity studies. Variable results have been obtained with other glucocorticoids tested for carcinogenicity in mice and rats. However, published data indicate that several related glucocorticoids including budesonide, prednisolone, and triamcinolone acetonide can increase the incidence of hepatocellular adenomas and carcinomas after oral administration in drinking water to male rats. These tumorigenic effects occurred at doses which were less than the typical clinical doses on a mg/m<sup>2</sup> basis. The clinical relevance of these findings is unknown.

Reproductive toxicity:

Methylprednisolone has not been evaluated in animal fertility studies. Corticosteroids have been shown to reduce fertility when administered to rats. Adverse effects on fertility in male rats administered corticosterone were observed and were reversible. Decreased weights and microscopic changes in prostate and seminal vesicles were observed. The numbers of implantations and live foetuses were reduced and these effects were not present following mating at the end of the recovery period..

An increased frequency of cleft palate was observed among the offspring of mice treated during pregnancy with methylprednisolone in doses similar to those typically used for oral therapy in humans.

An increased frequency of cardiovascular defects and decreased body weight were observed among the offspring of pregnant rats treated with methylprednisolone in a dose that was similar to that used for oral therapy in humans but was toxic to the mothers. In contrast, no teratogenic effect was noted in rats with doses <1-18 times those typically used for oral therapy in humans in another study. High frequencies of foetal death and a variety of central nervous system and skeletal anomalies were reported in the offspring of pregnant rabbits treated with methylprednisolone in doses less than those used in humans. The relevance of these findings to the risk of malformations in human infants born to mothers treated with methylprednisolone in pregnancy is unknown. Safety margins for the reported teratogenic effects are unknown.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Macrogol 3350  
Sodium chloride  
Myristyl-gamma-picolinium chloride  
Sodium hydroxide (for pH regulation)  
Hydrochloric acid (for pH regulation)  
Water for injection.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf-life**

The expiry date of the product is indicated on the packaging materials.

**6.4 Special precautions for storage**

Store below 25°C.  
Do not freeze.

**6.5 Nature and contents of container**

Type I glass vial with a butyl rubber stopper. Each vial contains 1 ml, 2ml, or 5 ml of Depo-Medrol 40 mg/ml. Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

Depo-Medrol should not be mixed with any other fluid. Discard any remaining suspension after use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. LICENCE HOLDER:**

Pfizer PFE pharmaceuticals Israel, 9 Shenkar St., Herzliya Pituach 46725.

**8. LICENCE NUMBER:**

024-49-21841

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