SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM:

DEPO-MEDROL™ 40 mg Injection

DEPO-MEDROL™ 80 mg Injection

COMPOSITION:

DEPO-MEDROL 40 mg:

Each ml of the preparation contains

Methylprednisolone acetate.....40 mg

Myristyl-gamma-picolinium chloride (preservative) 0,233 % m/v

DEPO-MEDROL 80 mg:

Each ml of the preparation contains

Methylprednisolone acetate.....80 mg

Myristyl-gamma-picolinium chloride (preservative) 0,233 % m/v

PHARMACOLOGICAL CLASSIFICATION:

A 3.1 Antirheumatics (Anti-inflammatory agents)

PHARMACOLOGICAL ACTION:

Methylprednisolone, an anti-inflammatory steroid synthesized and developed in the Research Laboratories of Pharmacia, is the 6-methyl derivative of prednisolone.

Estimates of the relative potencies of methylprednisolone and prednisolone range from 1,13 to 2,1 with an average of 1,5. In general, the required daily dose can be estimated to be two-thirds (or 0,7) the required daily dose of prednisolone. While the effect of

parenterally administered DEPO-MEDROL is prolonged, it has the same metabolic and anti-inflammatory actions as orally administered methylprednisolone.

Since this steroid lacks significant mineralo-corticoid activity in usual therapeutic doses, it is not likely to afford adequate support in states of acute adrenocortical insufficiency. For treatment of the latter, the parent adrenocortical steroids, hydrocortisone or cortisone should be used.

INDICATIONS:

Administration for Local Effect:

Rheumatoid and Osteoarthritis: Following intra-articular administration, relief from pain may be experienced within 12 to 24 hours. The duration of relief varies, but averages 3 to 4 weeks with a range of one to five or more weeks. Injections have been well tolerated.

The intra-articular injection of DEPO-MEDROL is recommended as an adjuvant to general therapeutic measures to effect suppression of inflammation in one or a few peripheral rheumatoid or osteoarthritic joints when:

(1) the disease is limited to one or a few peripheral joints;

(2) the disease is widespread with one or a few peripheral joints actively inflamed;

(3) systemic therapy with other corticoids or corticotropin controls all but a few of the more actively involved joints;

(4) systemic therapy with cortisone, hydrocortisone, or corticotropin is contraindicated;

(5) joints show early, but actively progressing deformity (to enhance the effect of physiotherapy and corrective procedures); and

(6) surgical or other orthopaedic corrective measures are to be or have been done.

The action of intrasynovial injections appears to be well localized since significant metabolic effects characteristic of systemic administration of adrenal steroids have not been observed. In a few instances mild and transient improvement of joints other than those injected have been reported. No other systemic effects have been noted. However, it is possible that mild systemic effects may occur following intrasynovial administration. This possibility is greater the larger the number of joints injected and the higher the total dose employed.

Bursitis: Intrabursal injections of corticoid suspensions have been found of value in the treatment of various types of bursitis including subdeltoid, prepatellar, and olecranon bursitis. In general the use of corticoids for this purpose has been found to give better results in acute than in chronic subdeltoid bursitis. In acute subdeltoid bursitis, pain has been alleviated with return of full range of motion within a few hours after one injection. In most cases, additional injections have not been required. In chronic subdeltoid bursitis, partial relief of pain with return of normal range of shoulder motion may be obtained in many cases. In post-traumatic prepatellar bursitis (housemaid's knee) and olecranon bursitis, improvement has usually occurred within 24 hours, with a return to normal within a week.

Miscellaneous: Ganglion, Tendinitis, Epicondylitis: Injections of DEPO-MEDROL have been found beneficial in a number of conditions including tendinitis, tenosynovitis, epicondylitis, and ganglia of the tendon sheaths.

Injections for Local Effect in Dermatologic Conditions: Injections of corticoid suspensions for local effect are being employed in the treatment of various lesions of the skin. In many instances, such therapy is followed by improvement or involution of the lesion. In recurrent and/or chronic conditions, repeated injections may be required. The dermatologic lesions which may benefit by injections of DEPO-MEDROL include

localized neurodermatitis, hypertrophic lichen planus, nummular eczema, necrobiosis lipoidica diabeticorum, alopecia areata, discoid lupus erythematosus, and insect bites. Intrakeloidal injections have resulted in softening and regression of the lesion. In general, better results are obtained in young and/or soft lesions than in chronic and/or firm lesions.

Instillation for Local Effect in Patients with Ulcerative Colitis: Retention enemas or continuous drip have been shown to be a useful adjunct in the treatment of some patients with ulcerative colitis.

Administration for Systemic Effect:

When methylprednisolone therapy is indicated, oral administration is preferred ordinarily because of its obvious convenience. Intramuscular therapy with the suspension provides an alternate route of administration when oral use is contraindicated, such as in patients with acute gastro-enteritis or in pre- or post-operative patients.

Following intramuscular administration, absorption occurs slowly from the site of injection and prolonged systemic effect results. This therapy may also be employed in conditions such as the adrenogenital syndrome in which a prolonged effect is desired. While intramuscular administration of recommended doses has resulted in effective suppression of adrenal cortical function for approximately two weeks in patients with the adrenogenital syndrome, the average duration of systemic effect in patients with rheumatoid arthritis appears to be approximately one week.

This suspension may also be employed in those dermatologic conditions known to be benefited by systematic therapy with corticoids. Thus, DEPO-MEDROL has been employed with good effect in patients with acute or chronic contact dermatitis, including poison ivy dermatitis and seborrhoeic dermatitis. Intramuscular administration has been

employed effectively in asthmatic patients and in patients with perennial allergic-rhinitis. However, systemic corticoid therapy should be limited to those conditions which do not respond to other therapeutic measures.

CONTRAINDICATIONS:

Known hypersensitivity to the components.

Intravenous and intrathecal administration.

Intra-articular, intrabursal, intratendinous or other injections for local effect are contraindicated in the presence of acute infectious conditions. Exacerbation of pain, further loss of joint motion, with fever and malaise following intra-articular injection may indicate that the arthritis has become septic. Appropriate antibacterial therapy should be instituted immediately.

Systemic therapy is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia and varicella. Corticosteroids are contraindicated in systemic fungal infections.

Usage in pregnancy

Although there is inadequate evidence of safety in human pregnancy, therapy with corticoids does not appear to be contraindicated during pregnancy. This medicine should however only be used in pregnancy if clearly indicated. Caution is recommended particularly during the first trimester. Corticosteroids readily cross the placenta. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency, and appropriate measures instituted. There are no known effects of corticosteroids on labour and delivery.

Corticosteroids are excreted in breast milk.

WARNINGS AND SPECIAL PRECAUTIONS:

These preparations should not be administered intravenously or intrathecally.

Too rapid administration could cause hypotension.

While on corticosteroid therapy, patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and lack of antibody response.

This product is not suitable for multidose use. Following administration of the desired dose, any remaining suspension should be discarded.

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

Caution must also be used in the presence of nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection. The presence of diverticulitis, fresh intestinal anastomoses, diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, myasthenia gravis and active tuberculosis necessitates carefully controlled use of methylprednisolone.

Because of its inhibitory effect on fibroplasia, methylprednisolone acetate may mask the signs of infection and enhance dissemination of the infecting organism. Hence, all patients receiving DEPO-MEDROL should be monitored for evidence of intercurrent infection. Should infection occur, it must be brought under control by

the use of appropriate anti-bacterial measures, or administration of methylprednisolone acetate should be discontinued.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

Routine laboratory tests, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body mass, 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.

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Since concurrent administration of these agents results in a mutual inhibition of metabolism, it is possible that convulsions and other adverse events associated with the individual use of either medicine may be more apt to occur.

Precautions applicable to parenteral corticosteroids

Following intra-articular corticosteroid therapy, care should be taken to avoid overuse of joints in which symptomatic benefit has been obtained. Negligence in this matter may permit an increase in joint deterioration that will more than offset the beneficial effects of the steroid.

Unstable joints should not be injected. Repeated intra-articular injection may in some cases result in instability of the joint. X-ray follow-up is suggested in selected cases to detect deterioration.

If a local anaesthetic is used prior to injection of DEPO-MEDROL, the anaesthetic package insert must be studied and all the precautions observed.

Intra-synovial injection of a corticosteroid may produce systemic as well as local effects.

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

Sterile technique is necessary to prevent infections or contamination.

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

A risk benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

DOSAGE AND DIRECTIONS FOR USE:

The severity, prognosis and expected duration of the disease and the reaction of the patient to medication are primary factors in determining dosage. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Dosage must be decreased or discontinued gradually after administration of more than a few days.

DEPO-MEDROL should not be administered by any route other than those listed under Indications. Administration by other than indicated routes has been associated with reports of serious medical events including: arachnoiditis, meningitis, paraparesis/paraplegia, sensory disturbances, bowel/bladder dysfunction, seizures,

visual impairment including blindness, ocular and periocular inflammation, and residue or slough at injection site.

It is critical that, during administration of DEPO-MEDROL, appropriate technique be used and care taken to ensure proper placement of the drug. **The technique of intra-synovial and intramuscular injection should include precautions against leakage into the dermis.** Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

DEPO-MEDROL should not be diluted or mixed with other solutions.

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.

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

SIZE OF JOINT	EXAMPLES	RANGE OF DOSAGE
Large	Knee Ankle Shoulder	20 to 80 mg
Medium	Elbow Wrist	10 to 40 mg
Small	Metacarpophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4 to 10 mg

Procedure: It is recommended that the anatomy of the joint involved be reviewed before attempting intra-articular injection. In order to obtain the full anti-inflammatory effect it is important that the injection be made into the synovial space. Employing the same sterile technique as for a lumbar puncture, a sterile 20 to 24 gauge needle (on a dry syringe) is quickly inserted into the synovial cavity. Procaine infiltration is optional. 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 not infrequently 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 space. Little or no benefit follows injection into surrounding tissues. 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 orthopaedic correction, should be employed.

Bursitis: The area around the injection site is prepared in a sterile way and a wheal at the site made with 1 per cent 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 aspiration syringe changed for a small syringe containing the desired dose. After injection, the needle is withdrawn and a small dressing applied.

Miscellaneous: In the treatment of conditions such as **tendinitis or tenosynovitis,** care should be taken, following application of a suitable antiseptic to the overlying skin, 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 cyst tumour and may effect disappearance. The usual sterile precautions should be observed, of course, with each injection.
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.

Dermatological 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. **In order to minimize the incidence of atrophy of the dermis, care must be exercised not to exceed recommended doses in intradermal injections. Multiple small injections into the area of the lesion should be made whenever possible.**

Instillation for Local Effect in Patients with Ulcerative Colitis: 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 administered in from 30 ml to 300 ml of water depending upon the degree of involvement of the inflamed colonic mucosa. Other accepted therapeutic measures should, of course, be instituted.

Administration for Systemic Effect: Intramuscular injections of DEPO-MEDROL, must be made deeply into the gluteal muscles. The usual techniques of aspirating prior to

injection should be employed to avoid intravascular administration. Do not administer doses recommended for intramuscular injection superficially or subcutaneously.

The intramuscular dosage will vary with the condition being treated. When employed as a temporary substitute for oral therapy, a single injection during each 24 hour period of a dose of the suspension equal to the total daily oral dose of Medrol (methylprednisolone) is usually sufficient. When a prolonged effect is desired, the weekly dose may be calculated by multiplying the daily oral dose by 7 and given as a single intramuscular injection.

In patients with the **adrenogenital syndrome,** a single intramuscular injection of 40 mg every 2 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 DEPO-MEDROL 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 and 10 day intervals may be necessary. In **seborrhoeic dermatitis,** a weekly dose of 80 mg may be adequate to control the condition.

Following intramuscular administration of 80 to 120 mg to **asthmatic** patients, relief may result within 6 to 48 hours and persist for several days to two weeks. Similarly in patients with **allergic rhinitis (hay fever)** an intramuscular dose of 80 to 120 mg may be followed by relief of coryzal symptoms within 6 hours persisting for several days to three weeks.

If a rapid hormonal effect of maximum intensity is required, the intravenous administration of highly soluble methylprednisolone sodium succinate is indicated.

SIDE EFFECTS:

Fluid and electrolyte disturbances

Sodium retention, fluid retention, potassium loss, electrolyte imbalance. Congestive heart failure may occur in susceptible patients, as well as hypertension.

Musculoskeletal

Steroid myopathy, muscle weakness, osteoporosis, pathological fractures, aseptic necrosis.

Gastro-intestinal

Peptic ulceration with possible perforation and haemorrhage, pancreatitis, oesophagitis, perforation of the bowel.

Dermatologic

Impaired wound healing, petechiae and ecchymosis, thin fragile skin, purpura, allergic reactions, facial erythema, thinning of hair and scalp.

Metabolic

Negative nitrogen balance due to protein catabolism. Hypokalaemic alkalosis.

Neurological

Increased intracranial pressure, pseudotumor cerebri, psychic derangements, seizures, insomnia, nervousness, vertigo, sweating.

Endocrine

Menstrual irregularities, development of Cushingoid state, suppression of pituitary-adrenal axis, suppression of growth in children.

Decreased carbohydrate tolerance

Manifestation of latent diabetes mellitus; increased requirements for insulin or oral hypoglycaemic agents in diabetics.

Ophthalmic

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, exophthalmos, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Immune system

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance, and inability to localize infection, opportunistic infections and hypersensitivity reactions including anaphylaxis. Reactions to skin tests may be suppressed.

Psychiatric 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.

Paediatric use:

Growth may be suppressed in children receiving long-term, daily divided dose glucocorticoid therapy. The use of such regimen should be restricted to those most serious indications.

The following additional reactions are related to parenteral corticosteroid therapy:

Rare instances of blindness associated with intralesional therapy around the face and head.

Anaphylactic reaction or allergic reactions, hyperpigmentation or hypopigmentation, subcutaneous and cutaneous atrophy, post-injection flare following intra-synovial use, Charcot-like arthropathy, injection site infections following non-sterile technique, sterile abscess.

While crystals of adrenal steroids in the dermis suppress inflammatory reactions, their presence may cause disintegration of the cellular elements and physicochemical changes in the ground substance of the connective tissue. The resultant infrequently occurring atrophic changes in the dermis may form shallow 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF TREATMENT:

Treatment should be symptomatic and supportive.

IDENTIFICATION:

Milky suspension.

PRESENTATION:

DEPO-MEDROL 40 mg - 1 ml, 2 ml and 5 ml vials.

DEPO-MEDROL 80 mg - 1 ml vial.

STORAGE INSTRUCTIONS:

Store at or below room temperature (15 °C - 30 °C).

Keep out of reach of children.

REGISTRATION/REFERENCE NUMBERS:

DEPO-MEDROL 40 mg: C726 (Act 101/1965)

DEPO-MEDROL 80 mg: C/3.1/198

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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Manufacturer

Pfizer Manufacturing Belgium NV, Puurs, Belgium

BOTSWANA: S2

DEPO-MEDROL 40 mg: B9311995

DEPO-MEDROL 80 mg: B9312000

NAMIBIA: NS2

DEPO-MEDROL 40 mg: 13/3.1/0120

DEPO-MEDROL 80 mg: 90/3.1/001307

ZAMBIA: POM

DEPO-MEDROL 40 mg: 120/022

ZIMBABWE: PP

DEPO-MEDROL 40 mg (1 ml vial): 77/3.4/848

DEPO-MEDROL 40 mg (2 ml vial): 2019/3.4/5895

DEPO-MEDROL 80 mg: C/3.1/198