PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Taro-Methylprednisolone Injection

Methylprednisolone Acetate Injectable Suspension

Suspension, 40 mg / mL and 80 mg / mL, for intramuscular, intra-synovial, intralesional and intra-articular use

USP

Glucocorticoid

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RECENT MAJOR LABEL CHANGES

4.1 Dosing Considerations	05/2024
7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism	05/2024

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PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

Taro-Methylprednisolone Injection (methylprednisolone acetate injectable suspension) is indicated for:

A. FOR INTRAMUSCULAR ADMINISTRATION

When oral therapy is not feasible and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, the intramuscular use of Taro-Methylprednisolone Injection (methylprednisolone acetate) is indicated as follows:

1. Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice, synthetic analogs 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). Congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

2. Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: 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 non-specific tenosynovitis, acute gouty arthritis, psoriatic arthritis, ankylosing spondylitis.

3. Collagen Diseases

During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis), acute rheumatic carditis.

4. Dermatologic Diseases

Pemphigus, severe erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, bullous dermatitis herpetiformis, severe seborrheic dermatitis, severe psoriasis, mycosis fungoides.

5. 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 non-infectious laryngeal oedema (epinephrine is the drug of first choice).

6. **Ophthalmic Diseases**

   Severe acute and chronic allergic and inflammatory processes involving the eye, such as: herpes zoster ophthalmicus, iritis, iridocyclitis, chorioretinitis, diffuse posterior uveitis, optic neuritis, drug hypersensitivity reactions, anterior segment inflammation, allergic conjunctivitis, allergic corneal marginal ulcers, keratitis.

7. **Gastrointestinal Diseases**

   To tide the patient over a critical period of the disease in: ulcerative colitis (systemic therapy), regional enteritis (systemic therapy).

8. **Respiratory Diseases**

   Symptomatic sarcoidosis, berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, Loeffler's syndrome not manageable by other means, aspiration pneumonitis.

9. **Hematologic Disorders**

   Acquired (autoimmune) hemolytic anemia, secondary thrombocytopenia in adults, erythroblastopenia (RBC anemia), congenital (erythroid) hypoplastic anemia.

10. **Neoplastic Diseases**

    For palliative management of: leukemias and lymphomas in adults, acute leukemia of childhood.

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 INTRA-SYNOVIAL OR SOFT TISSUE ADMINISTRATION** (including periarticular and intrabursal) SEE 7 WARNINGS AND PRECAUTIONS

Taro-Methylprednisolone Injection 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

Taro-Methylprednisolone Injection is indicated for intralesional use in the following conditions: keloids, localized hypertrophic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare, and Lichen Simplex chronicus (neurodermatitis), discoid lupus erythematosus, necrobiosis lipoidica diabeticorum, alopecia areata.

Taro-Methylprednisolone Injection may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of methylprednisolone acetate injectable suspension in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 3 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Neurologic and 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 4.1 Dosing Considerations).

2 CONTRAINDICATIONS

Taro-Methylprednisolone Injection is contraindicated:

- in patients with known hypersensitivity to any components of the product (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- in patients with systemic fungal infections
- in idiopathic thrombocytopenic purpura when administered intramuscularly
- in patients administered with live or live, attenuated vaccines while receiving immunosuppressive doses of corticosteroids.
- in herpes simplex of the eye, except when used for short-term or emergency therapy as in acute sensitivity reactions
- in patients with vaccinia and varicella, except when used for short-term or emergency therapy as in acute sensitivity reactions
- epidural, intrathecal and intravascular administration
- for intra-articular injection in unstable joints

- in premature infants: Taro-Methylprednisolone Injection with myristyl gamma picolinium chloride may be used.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Taro-Methylprednisolone Injection is available in one formulation containing myristyl gamma picolinium chloride (MGPC).

Taro-Methylprednisolone Injection with MGPC is supplied in single-use 1 mL vials and is not suitable for multidose use. Following administration of the desired dose, any remaining suspension should be discarded.

Because of possible physical incompatibilities, Taro-Methylprednisolone Injection should not be diluted or mixed with other solutions. Parenteral suspensions should be inspected visually for foreign particulate matter and discolouration prior to administration whenever drug product and container permit.

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-synovial 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.

Caution must be used in renal insufficiency, hypertension, osteoporosis and myasthenia gravis, when steroids are used as direct or adjunctive therapy.

Dosage adjustments may be required based on the following:
- during remission
- exacerbation of the disease process
- the patient's individual response to therapy
- upon exposure of the patient to emotional or physical stress such as serious infection, surgery or injury. Taro-Methylprednisolone Injection dosage may need to be increased during and after the stressful situation.

Geriatrics:

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, increased risk for osteoporosis and fluid retention (with possible resultant hypertension) and of concomitant disease or other drug therapy.

4.2 Recommended Dose and Dosage Adjustment

A. ADMINISTRATION FOR LOCAL EFFECT

Although administration of Taro-Methylprednisolone Injection may ameliorate symptoms, it is not a cure and the hormone has no effect on the cause of the inflammation. Hormone therapy should be used as an adjunct to conventional therapy.

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, 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	Knees Ankles Shoulders	20 to 80 mg
Medium	Elbows Wrists	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 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 Taro-Methylprednisolone Injection. 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 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 treatment failures occur even when injections into the synovial spaces have been confirmed by aspiration of fluid, repeated injections are usually futile.

Following intra-articular steroid 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 (see 2 CONTRAINDICATIONS). Repeated intra-articular injection may in some cases result in instability of the joint. X-ray follow-up is suggested in selected cases to detect deterioration.

If a local anesthetic is used prior to the injection of Taro-Methylprednisolone Injection, the anesthetic package insert should be read carefully and all the precautions observed.

2. **Bursitis**

The area around the injection site is prepared in a sterile way and a wheal at the site made with 1 percent 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.

Sterile precautions should be observed 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.

4. **Injections for Local Effect in Dermatologic Conditions**

Following cleansing with an appropriate antiseptic such as 70% alcohol, 20 to 60 mg of Taro-Methylprednisolone Injection 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.

B. 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 single intramuscular injection.

Dosage must be individualized according to the severity of the disease and response of the patient. 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.

Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. 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 G.I. X-rays are desirable in patients with an ulcer history or significant dyspepsia.

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.

Condition	**Dose**	**Comments**
adrenogenital syndrome	a single intramuscular injection of 40 mg every two weeks may be adequate.	
rheumatoid arthritis	weekly intramuscular dose will vary from 40 to 120 mg for maintenance patients	
dermatologic lesions benefited by systemic corticoid therapy	40 to 120 mg intramuscularly at weekly intervals for one to four weeks	
acute severe dermatitis due to poison ivy	intramuscular administration of a single dose of 80 to 120 mg	relief may result within 8 to 12 hours
chronic contact dermatitis	repeated injections (40 to 120 mg intramuscularly) at 5 to 10 day intervals may be necessary	
seborrheic dermatitis	weekly dose of 80 mg	may be adequate to control the condition

Condition	Dose	Comments
asthmatic patients	intramuscular administration of 80 to 120 mg	relief may result within 6 to 48 hours and persist for several days to two weeks

5 OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of corticosteroid may be reduced only temporarily**.**

Methylprednisolone is dialyzable.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular, intra-synovial, intralesional, and intra-articular	40 mg/mL 80 mg/mL injectable suspension	Myristyl gamma picolinium chloride, polyethylene glycol 3350 and sodium chloride.

Taro-Methylprednisolone Injection containing myristyl gamma picolinium chloride (MGPC) is available in the following formats:

40 mg/mL, supplied in 1 mL vials and packaged in cartons of 10.
80 mg/mL, supplied in 1 mL vials and packaged in cartons of 5.

Each mL of this preparation contains:

Methylprednisolone acetate	40 mg	80 mg
Polyethylene Glycol 3350	29 mg	28 mg
Myristyl gamma picolinium chloride	0.19 mg	0.19 mg
Sodium Chloride added to adjust tonicity	9 mg	9 mg

When necessary, pH of Taro-Methylprednisolone Injection was adjusted with Sodium Hydroxide and/or Hydrochloric Acid. The pH of the finished product remains within the USP specified range i.e. 3.0 to 7.0.

7 WARNINGS AND PRECAUTIONS

General

Taro-Methylprednisolone Injection should not be administered by any route other than those listed under 1 INDICATIONS. It is critical that, during administration of Taro-Methylprednisolone Injection, appropriate technique be used and care taken to assure proper route of administration.

Administration by routes other than the ones listed under 1 INDICATIONS has been associated with serious medical events.

Sterile technique is necessary to prevent infections or contamination.

Intra-synovial and intra-articular injected corticosteroids may be systemically absorbed and produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process. A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

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

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

Carcinogenesis and Mutagenesis

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

Animal studies found corticosteroids to have possible tumorigenic and mutagenic potential (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenesis and Genotoxicity).

Cardiovascular

Literature reports suggest an apparent association between the use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

As sodium retention with resultant oedema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution, and only if strictly necessary, in patients with congestive heart failure. Corticosteroids should also be used with caution in hypertension, or renal insufficiency (see also 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

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

modification and additional cardiac monitoring if needed.

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.

Endocrine and Metabolism
Corticosteroid administration may result in hypothalamic-pituitary-adrenal (HPA) axis suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency depends on the dose, frequency, time of administration and duration of glucocorticoid therapy. This type of relative insufficiency may persist for months after discontinuation of therapy, therefore, in any situation of stress occurring during that period, corticosteroid therapy may need to be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid may need to be administered concurrently. If glucocorticoids are withdrawn abruptly, acute adrenal insufficiency leading to a fatal outcome may occur.

Because glucocorticoid therapy can lead to or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease.

Average and large doses of cortisone or hydrocortisone 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. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.

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

There is an enhanced effect of corticosteroids in patients with hypothyroidism. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids, including methylprednisolone. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

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

Gastrointestinal
Corticosteroids should be used with caution in non-specific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection and in diverticulitis, fresh intestinal anastomoses, and active or latent peptic ulcer, when steroids are used as direct or adjunctive therapy, since they may increase the risk of a perforation. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

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 such as Aspirin (acetylsalicylic acid), the risk of developing gastrointestinal ulcers is increased.

Hematologic
Aspirin (acetylsalicylic acid) should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. See 9 DRUG INTERACTIONS.

Hepatic/Biliary/Pancreatic
There is an enhanced effect of corticosteroids in patients with cirrhosis.

High doses of corticosteroids may produce acute pancreatitis.

Hepatobiliary disorders have been reported which may be reversible after discontinuation of therapy. Therefore appropriate monitoring is required.

Immune
Corticosteroids may suppress the immune system and may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

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

Recent studies suggest that corticosteroids should not be used in septic shock (an unapproved indication), and suggest that increased mortality may occur in some subgroups at higher risk (e.g., elevated serum creatinine greater than 2.0 mg/dL or secondary infections).

Fungal Infections
Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections. There have been cases reported in which concomitant use of

amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see 2 CONTRAINDICATIONS; 9 DRUG INTERACTIONS).

Special pathogens
Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis, Taxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Stronglyoides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe entercolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition.

Tuberculosis
The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with 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.

Vaccinations
Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see 2 CONTRAINDICATIONS). Killed or inactivated vaccines may be administered; however the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

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 in high doses, because of possible hazards of neurological complications and lack of antibody response.

Viral Infections
Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases,

particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Monitoring and Laboratory Tests
Corticosteroids may suppress reactions to skin tests.

Monitoring for signs and symptoms of drug-induced secondary adrenocortical insufficiency may be necessary for up to one year following cessation of long-term or high-dose corticosteroid therapy.

Musculoskeletal
An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis, see 7 WARNINGS AND PRECAUTIONS, Neurologic), 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 quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to increased risk of osteoporosis (e.g., postmenopausal women) before initiating corticosteroid therapy.

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

Neurologic
Results from one multicenter, randomized, placebo controlled study with IV methylprednisolone hemisuccinate, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma. Therefore systemic corticosteroids, including Taro-Methylprednisolone Injection, are not indicated for, and therefore should not be used to treat traumatic brain injury.

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

Corticosteroids should be used with caution in patients with myasthenia gravis.

There have been reports of epidural lipomatosis in patients taking corticosteroids (including reports in children).

Ophthalmologic
Use of corticosteroids may produce posterior sub-capsular 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. As intraocular pressure may become elevated in some individuals, if steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored. The use of systemic corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

Corticosteroid therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.

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

Potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary.

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

Renal
Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone.

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

Reproductive Health: Female and Male Potential
Steroids may increase or decrease motility and number of spermatozoa in some patients.

Sensitivity/Resistance
Allergic reactions may occur. Because rare instances of skin reactions and

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

Skin
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 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.

7.1 Special Populations

7.1.1 Pregnant Women

Pregnant Women:
Corticosteroids readily cross the placenta. Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to human dose. Administration of corticosteroids to pregnant animals can cause fetal malformations (cleft palate, skeletal malformations) and intra-uterine growth retardation (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

One retrospective study found an increased incidence of low birth weights in infants born to mothers receiving corticosteroids. Cataracts have been observed in infants born to mothers undergoing long-term treatment with corticosteroids during pregnancy.

Since adequate human reproductive studies have not been done with methylprednisolone acetate, this medicinal product should be used during pregnancy at the lowest possible dose, only if clearly needed, where the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Infants born to mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency. There are no known effects of corticosteroids on labour and delivery.

7.1.2 Breast-feeding

Nursing Women:
Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants.

Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a

careful benefit-risk assessment should be conducted and a decision should be made whether to discontinue nursing, or discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

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. Pediatric patients may experience a decrease in their growth velocity at low systemic doses and in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression. Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis.

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

High doses of corticosteroids may produce pancreatitis in children.

7.1.4 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Treatment of elderly patients with corticoids should be cautious because of the existence of concomitant conditions in elderly patients such as decreased hepatic, renal and cardiac function and the presence of diabetes or osteoporosis (see **4.1 Dosing Considerations**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse reactions have been reported with methylprednisolone acetate injectable suspension or other corticosteroids (Frequency Not Known)

Allergic reactions: Angioedema.

Blood and lymphatic system disorders: Leukocytosis

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, cardiac failure congestive (in susceptible patients), fat embolism, flushing, hypertension, hypotension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction, pulmonary oedema, syncope, tachycardia, thromboembolism, thrombophlebitis, thrombosis, vasculitis.

Dermatologic: Acne, allergic dermatitis, dry scaly skin, ecchymoses and petechiae, oedema peripheral, erythema, skin hyperpigmentation, skin hypopigmentation, impaired healing, rash, abscess sterile, skin striae, suppressed reactions to skin tests, skin atrophy, thinning scalp hair, urticaria, angioedema, pruritus, hyperhidrosis, injection site reaction, and injection site infection. Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy.

Endocrine: Carbohydrate tolerance decreased, Cushingoid, moon face, weight gain, abnormal fat deposits, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin (or oral hypoglycemic agents in diabetes), glucose tolerance impaired, menstruation irregular, Hypothalamic pituitary adrenal axis suppression, growth retardation, steroid withdrawal syndrome, urine calcium increased, blood urea increased.

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.

Fluid and electrolyte disturbances: Sodium retention, fluid retention, congestive heart failure in susceptible patients, blood potassium decreased, alkalosis hypokalemic, hypertension.

Gastrointestinal: Abdominal distension, abdominal pain, functional gastrointestinal disorder/bladder dysfunction, nausea, pancreatitis, peptic ulcer (with possible subsequent peptic ulcer perforation and peptic ulcer haemorrhage), intestinal perforation (particularly in patients with inflammatory bowel disease), oesophagitis ulcerative, oesophagitis, diarrhoea, dyspepsia, gastric haemorrhage, peritonitis (peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis).

Hepatic: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased. Hepatomegaly has also been observed.

Immune System*:* Infection, decreased resistance to infection, opportunistic infections, drug hypersensitivity, anaphylactoid reaction, anaphylactic reaction, suppression of reactions to skin tests**.**

Metabolic*:* Nitrogen balance negative (due to protein catabolism), dyslipidaemia, lipomatosis, increased appetite (which may result in weight gain), metabolic acidosis.

Musculoskeletal: Osteonecrosis, calcinosis (following intra-articular or intralesional use),

Charcot-like arthropathy, muscle atrophy, muscular weakness, malaise, osteoporosis, pathological fracture, postinjection flare (following intra-articular use, periarticular and tendon sheath injections), myopathy, tendon rupture (particularly of the Achilles tendon), spinal compression fracture, arthralgia, myalgia.

Neurologic/Psychiatric: Convulsion, headache, intracranial pressure increased (with papilloedema [idiopathic intracranial hypertension], usually following discontinuation of treatment), vertigo, neuritis, neuropathy, paresthesia, amnesia, cognitive disorder, dizziness, epidural lipomatosis, emotional instability, insomnia, mood swings, personality change, affective disorder (including affect lability, depressed mood, euphoric mood, psychological dependence, suicidal ideation), psychotic disorder (including mania, delusion, hallucination, schizophrenia [aggravation of]), confusional state, mental disorder, anxiety, abnormal behaviour, irritability.

Ophthalmic: Cataract, increased intraocular pressure, glaucoma, exophthalmos, central serous chorioretinopathy.

Reproductive System: Increased or decreased motility and number of spermatozoa

Other: hiccups, fatigue, pulmonary embolism.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 6β-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. Coadministration 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 coadministration.

NON-CYP3A4-MEDIATED EFFECTS – Other interactions that may occur with methylprednisolone are described in the Table below.

9.3 Drug-Behavioural Interactions

Dizziness, vertigo, visual disturbances and fatigue are possible side effects associated with corticosteroid use. If affected, patients should not drive or operate machinery.

9.4 Drug-Drug Interactions

Drug Class or Type - DRUG or SUBSTANCE	**Interaction or Effect**
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
Antibiotic - RIFAMPIN	CYP3A4 INDUCER
Anticoagulants (oral)	The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects. Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.
Anticonvulsant - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. (See 7 WARNINGS AND PRECAUTIONS - Musculoskeletal, for additional information.) 2) 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.

Drug Class or Type - DRUG or SUBSTANCE	Interaction or Effect
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis. Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)
Antifungal - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATE)
Antitubercular drugs	Serum concentrations of isoniazid may be decreased.
Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
Aromatase inhibitor - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment. Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.
Cholestyramine	Cholestyramine may increase the clearance of oral corticosteroids.
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHINDRONE	CYP3A4 INHIBITOR (and SUBSTRATE) Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.
Digitalis glycosides	Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Drug Class or Type - DRUG or SUBSTANCE	Interaction or Effect
Immunosuppressant - CYCLOSPORINE	CYP3A4 INHIBITOR (and SUBSTRATE) 1) Mutual inhibition of metabolism occurs with concurrent use of cyclosporine and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon coadministration. 2) Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. 3) Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with concurrent use. Mutual inhibition of metabolism occurs with concurrent use of cyclosporine and methylprednisolone, therefore it is possible that adverse events associated with the individual use of either drug may be more apt to occur.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATE
Ketoconazole	Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.
Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITOR (and SUBSTRATE) Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see 9.2 Drug Interactions Overview, CYP3A4 INHIBITORS).
Macrolide Antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see 9.2 Drug Interactions Overview, CYP3A4 INHIBITORS).

Drug Class or Type - DRUG or SUBSTANCE	Interaction or Effect
NSAIDs (nonsteroidal anti-inflammatory drugs) - high-dose ASPIRIN (acetylsalicylic acid	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 2) 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. 3) Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with concurrent use of corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.
Potassium-depleting agents	When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., diuretics Amphotericin B injection), patients should be observed closely for development of hypokalemia. There is also an increased risk of hypokalaemia with concurrent use of corticosteroids with amphotericin B, xanthenes, or beta2 agonists. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.
Vaccines	Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or attenuated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see 7 WARNINGS AND PRECAUTIONS: Immune, Vaccinations).

9.5 Drug-Food Interactions
Grapefruit juice is a CYP3A4 inhibitor. See 9.4 DRUG INTERACTIONS, CYP3A4 INHIBITORS above.

9.6 Drug-Herb Interactions
Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions
Corticosteroids may suppress reactions to skin tests.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Corticosteroids bind to intracellular glucocorticoid receptors. The corticoid receptor complex mediates changes in gene expression that lead to multiple downstream effects over hours to days. Corticosteroid action results in inhibiting pro-inflammatory signals and promoting anti-inflammatory signals. Glucocorticoids inhibit neutrophil apoptosis and demargination; they inhibit phospholipase A2, which decreases the formation of arachidonic acid derivatives; they inhibit other inflammatory transcription factors, and they promote anti-inflammatory genes like interleukin-10. Lower doses of corticosteroids provide an anti-inflammatory effect, while higher doses are immunosuppressive. High doses of glucocorticoids for an extended period bind to mineralocorticoid receptors, raising sodium levels and decreasing potassium levels.

10.2 Pharmacodynamics

Taro-Methylprednisolone Injection is a sterile aqueous suspension of the synthetic glucocorticoid methylprednisolone acetate. It has a strong and prolonged anti-inflammatory, immunosuppressive and anti-allergic activity. Taro-Methylprednisolone Injection can be administered I.M. for a prolonged systemic activity as well as In Situ for a local treatment. The prolonged activity of Taro-Methylprednisolone Injection is explained by the slow release of the active substance.

10.3 Pharmacokinetics

Absorption: One in-house study of eight volunteers determined the pharmacokinetics of a single 40 mg intramuscular dose of methylprednisolone acetate injectable suspension. The average of the individual peak plasma concentrations was 14.8 ± 8.6 ng/mL, the average of the individual peak times (T_{max}) was 7.25 ± 1.04 hours, and the average area under the curve (AUC) was 1354.2 ± 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 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4. (For a list of drug interactions based on CYP3A4- mediated metabolism, see 9 DRUG INTERACTIONS).

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 modulated by P-gp.

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.

11 STORAGE, STABILITY AND DISPOSAL

Store between 20ºC to 25ºC, excursions permitted between 15ºC-30ºC. Protect from freezing.

Keep in a safe place out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

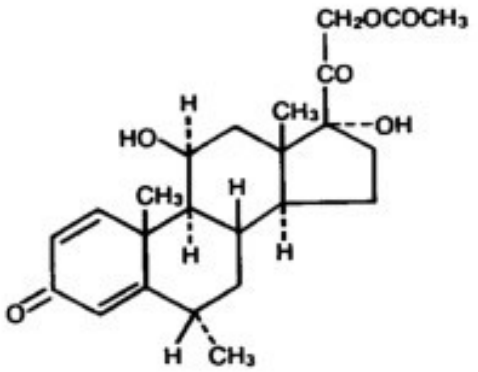
Drug Substance

Proper name: methylprednisolone acetate

Chemical name: (1) Pregna-1,4-diene-3,20-dione,21-(acetyloxy)-11-17-di-hydroxy-6-methyl-, (6α,11β)- ; (2)11β,17,21-Trihydroxy-6 α -methylpregna-1,4-diene-3,20-dione 21-acetate.

Molecular formula and molecular mass: $C_{24}H_{32}O_6$ and 416.51 g/mol

Structural formula:



Physicochemical properties: Methylprednisolone acetate is the 6-methyl derivative of prednisolone. It is a white or almost white crystalline powder which melts at about 213°C. It is soluble in dioxane, sparingly soluble in acetone, in alcohol, in chloroform, and in methanol, and slightly soluble in ether. It is practically insoluble in water. The partition coefficient is c log P = 2.792.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

A two-way, two-treatment, two-period, two-sequence, double-blinded, single-dose, crossover comparative bioavailability study of Taro-Methylprednisolone Injection (methylprednisolone acetate) 80 mg/mL injectable suspension (Taro Pharmaceuticals Inc.) versus DEPO-MEDROL® (methylprednisolone acetate) 80 mg/mL injectable suspension (Pfizer Canada Inc.) was conducted in 64 healthy, adult, male and female subjects with intramuscular administration in the gluteal muscles under fasting conditions. Comparative bioavailability data from 42 subjects that were included in the statistical analysis are presented in the following table:

Summary Table of the Comparative Bioavailability Data

Methylprednisolone (1 mL x 80 mg/mL methylprednisolone acetate) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng.h/mL)	2863.79 2917.42 (29.70)	2942.16 2922.08 (22.24)	97.3	91.4 - 103.6
AUC_I (ng.h/mL)	3274.76 3375.70 (23.87)	3278.36 3253.29 (20.72)	99.9	96.0 – 104.0
C_{max} (ng/mL)	4.96 5.39 (49.18)	5.29 5.77 (57.66)	93.7	81.0 - 108.5
T_{max}[3] (h)	14.00 (5.00 – 1440.98)	11.50 (2.00 – 1200.97)		
$T_{1/2}$[4] (h)	558.70 (47.58)	436.76 (55.52)		

[1] Taro-Methylprednisolone Injection (methylprednisolone acetate) 80 mg/mL injectable suspension (Taro Pharmaceuticals Inc.)
[2] DEPO-MEDROL® (methylprednisolone acetate) 80 mg/mL injectable suspension (Pfizer Canada Inc.)
[3] Expressed as median (range) only
[4] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Conventional studies of safety, pharmacology and repeated-dose toxicity using intravenous, intraperitoneal, subcutaneous, intramuscular, and oral routes of administration were done in mice, rats, rabbits and dogs using methylprednisolone sodium succinate. The toxicities seen in the repeated-dose studies are those expected to occur with continued exposure to exogenous adrenocortical steroids.

Carcinogenicity:
Methylprednisolone has not been 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^2 basis.

Genotoxicity:
Methylprednisolone has not been evaluated for genotoxicity.

However, methylprednisolone sulfonate, which is structurally similar to methylprednisolone sodium succinate, was not mutagenic with or without metabolic activation in Salmonella typhimurium, or in a mammalian cell gene mutation assay using Chinese hamster ovary cells. Methylprednisolone suleptanate did not induce unscheduled DNA synthesis in primary rat hepatocytes. Moreover, a review of published data indicates that prednisolone farnesylate (PNF), which is structurally similar to methylprednisolone, was not mutagenic with or without metabolic activation in Salmonella typhimurium and Escherichia coli strains. In a Chinese hamster fibroblast cell line, PNF produced a slight increase in the incidence of structural chromosomal aberrations with metabolic activation at the highest concentration tested.

Reproductive and Developmental Toxicology
Corticosteroids have been shown to reduce fertility when administered to rats. Male rats were administered corticosterone at doses of 0, 10, and 25 mg/kg/day by subcutaneous injection once daily for 6 weeks and mated with untreated females. The high dose was reduced to 20 mg/kg/day after Day 15. Decreased copulatory plugs were observed, which may have been secondary to decreased accessory organ weight. The numbers of implantations and live fetuses were reduced in untreated females mated with males treated at the administered doses of 10 and 25 mg/kg/day.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal reproduction studies, glucocorticoids such as methylprednisolone have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo-fetal lethality (e.g., increase in resorptions), and intra-uterine growth retardation.

17 SUPPORTING PRODUCT MONOGRAPHS

1. DEPO-MEDROL (Methylprednisolone Acetate Injectable Suspension; 20 mg / mL, 40 mg / mL and 80 mg / mL with Benzyl Alcohol injectable suspension and 40 mg / mL and 80 mg/ mL with MGPC injectable suspension), submission control 280641, Product Monograph, Pfizer Canada ULC. (MAR 15, 2024).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Taro-Methylprednisolone Injection
Methylprednisolone Acetate Injectable Suspension

Read this carefully before you start taking **Taro-Methylprednisolone Injection** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Taro-Methylprednisolone Injection**.

What is Taro-Methylprednisolone Injection used for?
Taro-Methylprednisolone Injection is used in the treatment of various conditions such as allergy or inflammation.

How does Taro-Methylprednisolone Injection work?
Taro-Methylprednisolone Injection contains a corticosteroid hormone. It decreases the body's immune response to certain diseases and reduces inflammation.

What are the ingredients in Taro-Methylprednisolone Injection?
Medicinal ingredients: Methylprednisolone acetate

Non-medicinal ingredients single-use: myristyl gamma picolinium chloride, polyethylene glycol 3350, and sodium chloride.

Taro-Methylprednisolone Injection comes in the following dosage forms:
Taro-Methylprednisolone Injection is available in one formulation containing myristyl gamma picolinium chloride (MGPC):
- 40 mg/mL dose, supplied in 1 mL vials and packaged in cartons of 10.
- 80 mg/mL dose, supplied in 1 mL vials and packaged in cartons of 5.

Do not use Taro-Methylprednisolone Injection if:

- you have allergies to methylprednisolone acetate or any other steroid medicine or any of the other ingredients in Taro-Methylprednisolone Injection
- you have any fungal infection
- you have a blood condition called idiopathic thrombocytopenic purpura if Taro-Methylprednisolone Injection is given to you through injection into your muscle. This condition is when you have a low blood platelet count.
- you received certain types of vaccines that are live or live- attenuated
- you have viral diseases including cowpox (vaccinia), chicken pox (varicella), and herpes simplex of the eye
- you have unstable joints, when Taro-Methylprednisolone Injection is injected into the joint.

Taro-Methylprednisolone Injection should not be injected into your veins or your spine.

Taro-Methylprednisolone Injection with myristyl gamma picolinium chloride (MGPC) may be given to premature infants.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Taro-Methylprednisolone Injection. Talk about any health conditions or problems you may have, including if you:

- have an infection (such as herpes simplex, chicken pox, tuberculosis, threadworm). **If you or your child is exposed to measles or chickenpox during treatment with Taro-Methylprednisolone Injection, contact your healthcare professional immediately. Serious or fatal side effects can occur if you or your child have not already had these infections;**
- have recently had or are about to have any vaccine;
- have recently had heart problems such as a heart attack (myocardial infarction), heart failure or heart disease;
- have bleeding or blood clotting problems (thromboembolic disorders);
- have brittle bone (osteoporosis);
- have high blood pressure;
- have water retention (oedema);
- have seizures (fits) or other nervous system problems;
- have thyroid problems;
- have muscle pain or weakness (such as myasthenia gravis);
- have skin cancer (Kaposi's sarcoma) or a tumor of the adrenal glands (pheochromocytoma);
- have certain eye diseases such as glaucoma, cataracts; herpes infection;
- have kidney disease;
- have liver disease such as cirrhosis;
- have certain mental or mood conditions (such as depression)
- have stomach or gut problems (such as ulcers or, ulcerative colitis);
- have low potassium or calcium;
- have Cushing's disease (caused by an excess of cortisol hormone)
- have weak immune response. Tell your healthcare professional if you suspect an infection has occurred, as corticosteroids (such as Taro-Methylprednisolone Injection) can make infections more likely and may mask their signs;
- have diabetes or high blood sugar;
- have a condition known as systemic sclerosis. This is a condition in which your body makes too much of a protein called collagen.

Other warnings you should know about:
Multidose use of Taro-Methylprednisolone Injection is not recommended for intra-synovial injection (injection to the joint).

Serious Side Effects: Taro-Methylprednisolone Injection can cause serious side effects, including:

- skin cancer (Kaposi's sarcoma): Kaposi's sarcoma has been reported with corticosteroid

therapy, such as Taro-Methylprednisolone Injection. Stopping treatment of Taro-Methylprednisolone Injection may result in signs of this cancer going away.
- tumor of the adrenal glands (pheochromocytoma). This tumor has been reported with corticosteroid therapy, such as Taro-Methylprednisolone Injection. Pheochromocytoma may cause death.
- fat deposition on or outside the lining of the spine (epidural lipomatosis). Taking corticosteroids in high doses for a long period of time can cause epidural lipomatosis.

Surgery
Before you have any operation, tell your health care professional (for example, your doctor, dentist or anesthetist) that you are taking Taro-Methylprednisolone Injection.

Pregnancy and breastfeeding
- If you are pregnant, or still able to get pregnant and/or breast-feed, there are specific risks you must discuss with your healthcare professional. Taking Taro-Methylprednisolone Injection may:
  - slow the growth and cause low birth weight of the baby.
  - cause cataracts in babies. This risk is associated with mothers who take corticosteroids for a long period of time during pregnancy.
- You should also tell your healthcare professional if you are breast feeding or planning to breastfeed as small amounts of corticosteroid medicines (such as Taro-Methylprednisolone Injection) may get into breast milk.

Male fertility:
Taking Taro-Methylprednisolone Injection may affect male fertility.

Stopping treatment:
Talk to your healthcare professional before stopping Taro-Methylprednisolone Injection.

If you suddenly stop taking Taro-Methylprednisolone Injection, you may experience:
- Serious adrenal insufficiency. This is when the body does not make enough of the cortisol hormone. This may cause death.
- “Withdrawal syndrome”. This includes symptoms such as anorexia, nausea, vomiting, lack of energy, headache, fever, joint pain, peeling of skin, muscle pain, weight loss, and/or low blood pressure.

Skin:
- Tell your healthcare professional you are taking Taro-Methylprednisolone Injection since it can affect the results of skin tests.

Children (less than 18 years of age):
- Children may have their growth slowed with use of Taro-Methylprednisolone Injection.
- Your healthcare professional will give the child the lowest dose to reduce the risk of slowing growth.
- Your healthcare professional will carry out tests on the child if they are taking Taro-

Methylprednisolone Injection for a long period of time. Taking methylprednisolone will increase the risk of developing a growing pressure in the skull (high intracranial pressure).
- Your healthcare professional may need to monitor the heart if methylprednisolone is given to a prematurely born baby.

Driving and Using Machines: Taro-Methylprednisolone Injection may cause dizziness, vertigo, vision problems and fatigue. If you experience these side effects you should not drive or operate machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Taro-Methylprednisolone Injection:

Medicines used to:
- treat glaucoma and epilepsy such as acetazolamide
- prevent or treat nausea and vomiting such as aprepitant or fosaprepitant
- treat cancer such as aminoglutethimide or cyclophosphamide
- "thin" the blood or prevent blood clotting (anticoagulants) such as acenocoumarol, phenindione and warfarin
- treat myasthenia gravis (a muscle condition) such as distigmine and neostigmine
- treat bacterial and fungal infections (antibiotics and antifungals) such as ketoconazole, itraconazole, amphotericin B, erythromycin, clarithromycin, troleandomycin, rifampin, rifampicin and rifabutin)
- treat inflammation such as aspirin and non-steroidal anti-inflammatory medicines (also called NSAIDs like ibuprofen
- treat epilepsy such as barbiturates, carbamezipine, phenobarbital, phenytoin and primidone
- treat heartburn and acid indigestion such as cimetidine
- help prevent organ rejection such as cyclosporine or tacrolimus
- treat heart problems or high blood pressure such as calcium channel blockers, digoxin and diltiazem
- reduce extra fluid in the body (water pills or diuretics)
- for hormone replacement therapy or hormonal oral contraceptives (such as ethinyl estradiol and norethindrone)
- treat HIV infections such as indinavir or ritonavir
- in surgery to block signals between nerves and muscles (neuromuscular blocking agents) such as pancuronium or vercuronium
- vaccines – Tell your doctor or nurse if you have recently had, or are about to have any vaccination
- treat diabetes
- treat tuberculosis (such as isoniazid)
- treat high cholesterol such as cholestyramine
- treat breast or ovarian cancer such as aromatase inhibitors
- suppress or reduce the strength of the body's immune system such as immunosuppressants

Do not drink grapefruit juice while taking Taro-Methylprednisolone Injection.

How to take Taro-Methylprednisolone Injection:
Taro-Methylprednisolone Injection is to be given to you as an injection to the joint (intra-articular or intra-synovial injection), or into a muscle (intramuscular injection) by your healthcare professional.

The dose of Taro-Methylprednisolone Injection you get will depend on your condition and how severe it is.

When your condition has improved, your dose will be lowered gradually.

Treatment with Taro-Methylprednisolone Injection should not be stopped suddenly.

Overdose:

If you think you, or a person you are caring for, have taken too much Taro-Methylprednisolone Injection, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Taro-Methylprednisolone Injection?
These are not all the possible side effects you may have when taking Taro-Methylprednisolone Injection. If you experience any side effects not listed here, tell your healthcare professional.

Infections:
Taro-Methylprednisolone Injection may:
- hide symptoms of infections
- reactivate dormant infections
- induce infections due to lowered body resistance

Allergic Reactions:
- anaphylaxis (a severe, life-threatening allergic reaction)
- bronchospasm (narrowing of the airway)

Heart Problems:
- heart failure
- heart attack
- arrhythmia (irregular heartbeat)
- high and low blood pressure
- blood clots
- thrombophlebitis (vein inflammation)
- cardiac arrest
- pediatric hypertrophic cardiomyopathy (thickening of heart muscle)
- facial blushing

Skin Problems:

- thin fragile skin
- impaired wound healing
- swelling
- ecchymosis (spots caused by ruptured blood vessels)
- petechiae (reddish spot containing blood that appears in skin)
- stretch marks
- dry, scaly skin
- rash
- redness
- itching
- acne
- increased sweating
- injection site reaction
- lightening or darkening of an area of skin
- abscess
- suppressed reaction to skin tests
- thinning hair

Endocrine and Metabolism Problems:

- development of Cushingoid state (abnormal bodily condition caused by excess corticosteroids)
- moon face (enlargement of chin and forehead)
- weight gain
- abnormal fat deposits
- suppression of hypothalamic pituitary-adrenal axis (a condition that could lead to disabling the body's responses to physiological stress such as severe infections or trauma)
- suppression of growth in children
- abnormal hair growth
- new symptoms of diabetes
- lowered carbohydrate (sugar) tolerance
- buildup of acid in the body (metabolic acidosis)
- sodium and fluid retention

Gastrointestinal Problems:

- stomach ulcer
- stomach bleeding
- inflammation of the pancreas and esophagus
- perforation of the bowel
- nausea
- vomiting or altered sense of taste (with rapid administration of large doses)
- abdominal pain
- bloating
- diarrhea
- indigestion

- bowl/bladder dysfunction
- increased appetite
- peritonitis

Blood Problems:
- Above normal white blood cell count
- Above normal cholesterol or triglycerides
- Abnormal blood tests (ex. liver enzymes and urea)

Liver Problems:
- enlarged liver

Musculoskeletal Problems:
- loss of muscle mass
- muscle weakness
- muscle pain
- malaise (feeling of general discomfort or uneasiness)
- osteoporosis
- pathological fractures
- vertebral compression fractures
- tendon rupture, (particularly of the Achilles tendon)
- Charcot joint disease (neuropathic arthropathy)
- pain and inflammation of the tissues surrounding the injection site
- joint pain
- Osteonecrosis (death of bone tissue)

Nervous System Problems :
- seizures
- headache
- vertigo
- pain and tenderness
- impaired sensation, strength, and reflexes
- sensation of tingling, tickling, prickling, or burning of a person's skin
- amnesia
- dizziness
- inflammation of nerves (neuritis)
- nerve damage
- abnormal amount of fat deposit around the spine (epidural lipomatosis)

Eye Problems:
- cataracts
- increased eye pressure
- glaucoma
- bulging of the eye (protrusion of the eyeball)
- blindness

- retinal detachment

Psychiatric Problems:
- depression
- emotional instability
- euphoria (intense feelings of well-being, elation, happiness, excitement and joy)
- insomnia
- mood swings
- personality changes
- thoughts of suicide
- delusion
- hallucination
- confusion
- schizophrenia
- anxiety

Sexual Function/Reproduction Problems:
- irregular periods
- increased or decreased motility and number of sperm

Other Problems:
- hiccups, fatigue, irritability, swelling
- Tumor lysis syndrome (TLS): This is the sudden, rapid death of cancer cells due to treatment. TLS can cause life-threatening kidney failure and heart problems

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Stomach ulcers (burst or bleeding ulcers): symptoms of which are stomach pain, black or bloodstained stools and/or vomiting blood			√
Flare up of a previous Tuberculosis: symptoms of which could be coughing blood or pain in the chest			√
Serious allergic reaction: symptoms of which include rash, itching/swelling (especially of the face/tongue/throat), severe dizziness and trouble breathing			√
Signs of infection: persistent fever/ cough/sore throat, painful urination, eye pain/discharge		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
High blood pressure: headaches or generally feeling unwell		√	
Fast, pounding or irregular heartbeat		√	
Swelling		√	
Cramps and spasms		√	
Vision changes		√	
Increased thirst or urination		√	
Mental problems: feeling high (mania), mood swings, depression, suicidal thinking, agitation, anxiety, trouble sleeping, confusion, losing your memory		√	
Tendon pain			√
Bone and joint pain			√
Easy bruising and bleeding			√
Pain, redness or swelling at the injection site	√		
Thinning skin	√		
Poor wound healing	√		
Unusual hair growth	√		
Unusual skin growth: nodules or blotches that may be red, purple, brown, or black and may be raised		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15°C-30°C. Protect from freezing. Keep out of reach and sight of children.

If you want more information about Taro-Methylprednisolone Injection:

- Talk to your healthcare professional

Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.taro.ca, or by calling 1-800-268-1975.

This leaflet was prepared by Taro Pharmaceuticals Inc.

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