HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RAYOS safely and effectively. See full prescribing information for RAYOS.

RAYOS (prednisone) delayed-release tablets 1 mg, 2 mg, 5 mg
Initial U.S. Approval: [1955]

---------- INDICATIONS AND USAGE----------

RAYOS is a corticosteroid indicated

- as an anti-inflammatory or immunosuppressive agent for certain allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, renal, respiratory, rheumatologic, specific infectious diseases or conditions and organ transplantation (1)
- for the treatment of certain endocrine conditions (1)
- for palliation of certain neoplastic conditions (1)

----------DOSAGE AND ADMINISTRATION----------

Individualize dosing based on disease severity and patient response. The timing of administration should take into account the delayed-release pharmacokinetics and the disease or condition being treated (2, 12.1):

- Initial dose: RAYOS 5 mg administered once per day. Patients currently on immediate-release prednisone, prednisolone, or methylprednisolone should be switched to RAYOS at an equivalent dose based on relative potency. (2.1, 2.4)
- Maintenance dose: Use lowest dosage that will maintain an adequate clinical response. (2.1)
- Discontinuation: Withdraw gradually if discontinuing long-term or high-dose therapy. (2.1)
- RAYOS should be taken daily with food. (2.3, 12.3)
- RAYOS should be swallowed whole and not broken, divided, or chewed. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------

- Delayed-release tablets: 1 mg, 2 mg, and 5 mg prednisone (3)

---------- CONTRAINDICATIONS ----------

- Known hypersensitivity to prednisone or any excipients in the formulation (4, 6)

---------- WARNINGS AND PRECAUTIONS----------

- Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia: Monitor patients for these conditions with chronic use. Taper doses gradually for withdrawal after chronic use. (5.1)
- Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection. Signs and symptoms of infection may be masked. (5.2)
- Elevated blood pressure, salt and water retention, and hypokalemia: Monitor blood pressure and sodium, potassium serum levels (5.3)
- GI perforation: increased risk in patients with certain GI disorders. Signs and symptoms may be masked. (5.4)
- Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis. Existing conditions may be aggravated. (5.5)
- Decreases in bone density: Monitor bone density in patients receiving long term corticosteroid therapy. (5.6)
- Ophthalmic effects: May include cataracts, infections, and glaucoma. Monitor intraocular pressure if corticosteroid therapy is continued for more than 6 weeks (5.7)
- Live or live attenuated vaccines: Do not administer to patients receiving immunosuppressive doses of corticosteroids. (5.8)
- Negative effects on growth and development: Monitor pediatric patients on long-term corticosteroid therapy. (5.9)
- Use in pregnancy: Fetal harm can occur with first trimester use. Apprise women of potential harm to fetus. (5.10, 8.1)

---------- ADVERSE REACTIONS ----------

Common adverse reactions for corticosteroids include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Horizon Pharma USA, Inc. at 1-866-479-6742 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Anticoagulant agents: May enhance or diminish anticoagulant effects. (7.4)
- Antidiabetic agents: May increase blood glucose concentrations. Dose adjustments of antidiabetic agents may be required. (7.5)
- CYP 3A4 inducers and inhibitors: May, respectively, increase or decrease clearance of corticosteroids, necessitating dose adjustment. (7.7, 7.8)
- Cyclosporine: Increase in activity of both, cyclosporine and corticosteroid when administered concurrently. Convulsions have been reported with concurrent use. (7.10)
- NSAIDs including aspirin and salicylates: Increased risk of gastrointestinal side effects. (7.13)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [July 2016]

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RAYOS is indicated in the treatment of the following diseases or conditions:

1.1 Allergic Conditions

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in adults and pediatric populations with:

- Atopic dermatitis
- Drug hypersensitivity reactions
- Seasonal or perennial allergic rhinitis
- Serum sickness

1.2 Dermatologic Diseases

- Bullous dermatitis herpetiformis
- Contact dermatitis
- Exfoliative erythroderma
- Mycosis fungoides
- Pemphigus
- Severe erythema multiforme (Stevens-Johnson syndrome)

1.3 Endocrine Conditions

- Congenital adrenal hyperplasia
- Hypercalcemia of malignancy
- Nonsuppurative thyroiditis
- Primary or secondary adrenocortical insufficiency: hydrocortisone or cortisone is the first choice: synthetic analogs may be used in conjunction with mineralocorticoids where applicable

1.4 Gastrointestinal Diseases

During acute episodes in:

- Crohn's Disease
- Ulcerative colitis

1.5 Hematologic Diseases

- Acquired (autoimmune) hemolytic anemia
- Diamond-Blackfan anemia
- Idiopathic thrombocytopenic purpura in adults
- Pure red cell aplasia
- Secondary thrombocytopenia in adults

1.6 Neoplastic Conditions

For the treatment of:

- Acute leukemia
- Aggressive lymphomas

1.7 Nervous System Conditions

- Acute exacerbations of multiple sclerosis
- Cerebral edema associated with primary or metastatic brain tumor, craniotomy or head injury

1.8 Ophthalmic Conditions

- Sympathetic ophthalmia
- Uveitis and ocular inflammatory conditions unresponsive to topical steroids

1.9 Conditions Related to Organ Transplantation

- Acute or chronic solid organ rejection

1.10 Pulmonary Diseases

- Acute exacerbations of chronic obstructive pulmonary disease (COPD)
- Allergic bronchopulmonary aspergillosis
- Aspiration pneumonitis
- Asthma
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate chemotherapy
- Hypersensitivity pneumonitis
- Idiopathic bronchiolitis obliterans with organizing pneumonia
- Idiopathic eosinophilic pneumonias
- Idiopathic pulmonary fibrosis
- Pneumocystis carinii pneumonia (PCP) associated with hypoxemia occurring in an HIV(+) individual who is also under treatment with appropriate anti-PCP antibiotics.
- Symptomatic sarcoidosis

1.11 Renal Conditions

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

1.12 Rheumatologic Conditions

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

- Acute gouty arthritis

During an exacerbation or as maintenance therapy in selected cases of:

- Ankylosing spondylitis
- Dermatomyositis/polymyositis
- Polymyalgia rheumatica
- Psoriatic arthritis
- Relapsing polychondritis
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low dose maintenance therapy)
- Sjogren's syndrome
- Systemic lupus erythematosus
- Vasculitis

1.13 Specific Infectious Diseases

- Trichinosis with neurologic or myocardial involvement.
- Tuberculous meningitis with subarachnoid block or impending block used concurrently with appropriate antituberculous chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Dosage of RAYOS should be individualized according to the severity of the disease and the response of the patient. For pediatric patients, the recommended dosage should be governed by the same considerations rather than strict adherence to the ratio indicated by age or body weight.

The maximal activity of the adrenal cortex is between 2 am and 8 am and is minimal between 4 pm and midnight. Exogenous corticosteroids suppress adrenocorticoid activity the least when given at the time of maximal activity. RAYOS is a delayed-release formulation of prednisone which releases the active substance beginning approximately 4 hours after intake [*see Clinical Pharmacokinetics(12.3)*]. The timing of RAYOS administration should take into account the delayed-release pharmacokinetics and the disease or condition being treated.

The initial dosage of RAYOS may vary from 5 to 60 mg per day depending on the specific disease entity being treated. Patients currently on immediate release prednisone, prednisolone, or methylprednisolone should be switched to RAYOS at an equivalent dose based on relative potency (2.4).

In situations of less severity, lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period there is a lack of satisfactory clinical response, RAYOS should be discontinued and the patient transferred to other appropriate therapy. It should be emphasized that dosage requirements are variable and must be individualized on the basis of the disease under treatment and the response of the patient.

After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of RAYOS for a period of time consistent with the patient's condition. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

2.2 Recommended Monitoring

Blood pressure, body weight, routine laboratory studies (including 2-hour postprandial blood glucose and serum potassium), and chest X-ray should be obtained at regular intervals during prolonged therapy with RAYOS. Upper GI X-rays are desirable in patients with known or suspected peptic ulcer disease.

2.3 Method of Administration

RAYOS is for oral administration.

RAYOS should be taken daily with food. *[see Clinical Pharmacokinetics (12.3)]*

RAYOS tablets should not be broken, divided, or chewed because the delayed release of prednisone is dependent on an intact coating. (11)

2.4 Corticosteroid Comparison Chart

For the purpose of comparison, one 5 mg RAYOS tablet is the equivalent milligram dosage of the following various corticosteroids:

Betamethasone, 0.75 mg	Paramethasone, 2 mg
Cortisone, 25 mg	Prednisolone, 5 mg
Dexamethasone, 0.75 mg	Prednisone, 5 mg
Hydrocortisone, 20 mg	Triamcinolone, 4 mg
Methylprednisolone, 4 mg	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

3 DOSAGE FORMS AND STRENGTHS

Delayed-release Tablets

- RAYOS 1 mg prednisone: Pale yellowish-white, round, unscored delayed-release tablet embossed with “NP 1” on one side.

- RAYOS 2 mg prednisone: Yellowish-white, round, unscored delayed-release tablet embossed with “NP 2” on one side.
- RAYOS 5 mg prednisone: Light yellow, round, unscored delayed-release tablet embossed with “NP 5” on one side.

4 CONTRAINDICATIONS

RAYOS is contraindicated in patients who have known hypersensitivity to prednisone or to any of the excipients. Rare instances of anaphylaxis have occurred in patients receiving corticosteroid therapy [*see Adverse Reactions (6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Alterations in Endocrine Function

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing’s syndrome, and hyperglycemia. Monitor patients for these conditions with chronic use.

Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for corticosteroid insufficiency after withdrawal of treatment. Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving corticosteroids already, dosage may have to be increased.

Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. Mineralocorticoid supplementation is of particular importance in infancy.

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.

5.2 Increased Risks Related to Infection

Corticosteroids may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic infections. The degree to which the dose, route and duration of corticosteroid administration correlates with the specific risks of infection is not well characterized, however, with increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

Corticosteroids may mask some signs of infection and may reduce resistance to new infections.

Corticosteroids may exacerbate infections and increase risk of disseminated infections.

The use of prednisone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for management of the disease in conjunction with an appropriate anti-tuberculous regimen.

Chickenpox and measles can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In children or adults who have not had these diseases, particular care should be taken to avoid exposure. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

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 Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions.

Corticosteroids may increase risk of reactivation or exacerbation of latent infection.

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.

Corticosteroids may activate latent amebiasis. Therefore, 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 any patient with unexplained diarrhea.

Corticosteroids should not be used in cerebral malaria.

5.3 Alterations in Cardiovascular/Renal Function

Corticosteroids can cause elevation of blood pressure, salt, and water retention, and increased excretion of potassium and calcium. 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. These agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Literature reports suggest an apparent association between 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.

5.4 Use in Patients with Gastrointestinal Disorders

There is an increased risk of gastrointestinal perforation in patients with certain GI disorders. Signs of GI perforation, such as peritoneal irritation may be masked in patients receiving corticosteroids.

Corticosteroids should be used with caution if there is a probability of impending perforation, abscess, or other pyogenic infections; diverticulitis; fresh intestinal anastomoses; and active or latent peptic ulcer.

5.5 Behavioral and Mood Disturbances

Corticosteroids use may be associated with central nervous system effects 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.

5.6 Decrease in Bone Density

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the 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 children and adolescents and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy and bone density should be monitored in patients on long term corticosteroid therapy.

5.7 Ophthalmic Effects

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

The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes.

Intraocular pressure may become elevated in some individuals. If corticosteroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

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.

5.8 Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered; however, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison’s disease.

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 dose, because of possible hazards of neurological complications and a lack of antibody response.

5.9 Effect on Growth and Development

Long-term use of corticosteroids can have negative effects on growth and development in children.

Growth and development of pediatric patients on prolonged corticosteroid therapy should be carefully monitored.

5.10 Use in Pregnancy

Prednisone can cause fetal harm when administered to a pregnant woman. Human and animal studies suggest that use of corticosteroids during the first trimester of pregnancy is associated with an increased risk of orofacial clefts, intrauterine growth restriction, and decreased birth weight. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus [*see Use in Specific Populations (8.1)*].

5.11 Neuromuscular Effects

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

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), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

5.12 Kaposi's Sarcoma

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

6 ADVERSE REACTIONS

Common adverse reactions for corticosteroids include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

Allergic Reactions: Anaphylaxis, angioedema

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis

Dermatologic: Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scalp, edema, facial erythema, hyper or hypo-pigmentation, impaired wound healing, increased sweating, petechiae and ecchymoses, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria

Endocrine: Abnormal fat deposits, decreased carbohydrate tolerance, development of Cushingoid state, hirsutism, manifestations of latent diabetes mellitus and increased requirements for insulin or oral hypoglycemic agents in diabetics, menstrual irregularities, moon facies, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery or illness), suppression of growth in children

Fluid and Electrolyte Disturbances: Fluid retention, potassium loss, hypertension, hypokalemic alkalosis, sodium retention

Gastrointestinal: Abdominal distention, elevation in serum liver enzymes levels (usually reversible upon discontinuation), hepatomegaly, hiccups, malaise, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, ulcerative esophagitis

General: Increased appetite and weight gain

Metabolic: Negative nitrogen balance due to protein catabolism

Musculoskeletal: Osteonecrosis of femoral and humeral heads, charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures

Neurological: Arachnoiditis, convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually following discontinuation of treatment, insomnia, meningitis, mood swings, neuritis, neuropathy, paraparesis/paraplegia, paresthesia, personality changes, sensory disturbances, vertigo

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, and central serous chorioretinopathy

Reproductive: Alteration in motility and number of spermatozoa

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of RAYOS was evaluated in 375 rheumatoid arthritis patients in two controlled trials. Patients treated with RAYOS ranged in age from 20 to 80 years (median age 56 years), with 85% female, 99% Caucasian, 1% African-American, and <1% Asian.

Patients received RAYOS 3 mg to 10 mg once daily at 10 pm; the majority (84%) received ≤5 mg. The clinical trial experience did not raise new safety concerns beyond those already established for immediate-release prednisone.

6.2 Postmarketing Experience

Adverse reactions have been identified during post approval use of RAYOS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The postmarketing experience has not raised new safety concerns beyond those already established for immediate-release prednisone.

7 DRUG INTERACTIONS

7.1 Aminoglutehimide

Aminoglutethimide may lead to loss of corticosteroid-induced adrenal suppression.

7.2 Amphotericin B Injection

There have been cases reported in which concomitant use of Amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure *[see Drug Interactions (7.14)]*.

7.3 Anticholinesterase Agents

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.

7.4 Anticoagulant Agents

Co-administration 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.

7.5 Antidiabetic Agents

Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

7.6 Antitubercular Drugs

Serum concentrations of isoniazid may be decreased.

7.7 CYP 3A4 Inducers (e.g., Barbiturates, Phenytoin, Carbamazepine, and Rifampin)

Drugs such as barbiturates, phenytoin, ephedrine, and rifampin, which induce hepatic microsomal drug metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

7.8 CYP 3A4 Inhibitors (e.g., Ketoconazole, Macrolide Antibiotics)

Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60% leading to increased risk of corticosteroid side effects.

7.9 Cholestyramine

Cholestyramine may increase the clearance of corticosteroids.

7.10 Cyclosporine

Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

7.11 Digitalis

Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

7.12 Estrogens, Including Oral Contraceptives

Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

7.13 Nonsteroidal Anti-Inflammatory Drugs (NSAIDS) Including Aspirin and Salicylates

Concomitant use of aspirin or other nonsteroidal anti-inflammatory drugs and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids; this could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when corticosteroid is withdrawn.

7.14 Potassium-Depleting Agents (e.g., Diuretics, Amphotericin B)

When corticosteroids are administered concomitantly with potassium-depleting agents, patients should be observed closely for development of hypokalemia.

7.15 Skin Tests

Corticosteroids may suppress reactions to skin tests.

7.16 Toxoids and Live or Attenuated Vaccines

Patients on corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated 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 Warnings and Precautions (5.8)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category D [see Warnings and Precautions (5.10)]: Multiple cohort and case controlled studies in humans suggest that maternal corticosteroid use during the first trimester increases the rate of cleft lip with or without cleft palate from about 1/1000 infants to 3-5/1000 infants. Two prospective case control studies showed decreased birth weight in infants exposed to maternal corticosteroids in utero.

RAYOS was not formally evaluated for effects on reproduction. Published literature indicates prednisolone, the active metabolite of prednisone, has been shown to be teratogenic in rats, rabbits, hamsters, and mice with increased incidence of cleft palate in offspring. In teratogenicity studies, cleft palate along with elevation of fetal lethality (or increase in resorptions) and reductions in fetal body weight were seen in rats at maternal doses of 30 mg/kg (equivalent to 290 mg in a 60 kg individual based on mg/m^2 body surface

comparison) and higher. Cleft palate was observed in mice at a maternal dose of 20 mg/kg (equivalent to 100 mg in a 60 kg individual based on mg/m^2 comparison). Additionally, constriction of the ductus arteriosus has been observed in fetuses of pregnant rats exposed to prednisolone.

In humans, the risk of decreased birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses. It is likely that underlying maternal conditions contribute to intrauterine growth restriction and decreased birth weight, but it is unclear to what extent these maternal conditions contribute to the increased risk of orofacial clefts.

Prednisolone can cause fetal harm when used in pregnancy. RAYOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

8.3 Nursing Mothers

Prednisolone, the active metabolite of prednisone, is secreted in human milk. Reports suggest that prednisolone concentrations in human milk are 5 to 25% of maternal serum levels, and that total infant daily doses are small, about 0.14% of the maternal daily dose. The risk of infant exposure to prednisolone through breast milk should be weighed against the known benefits of breastfeeding for both the mother and baby.

Caution should be exercised when RAYOS is administered to a nursing woman. If RAYOS must be prescribed to a breastfeeding mother, the lowest dose should be prescribed to achieve the desired clinical effect. High doses of corticosteroids for long periods could potentially produce problems in infant growth and development and interfere with endogenous corticosteroid production.

8.4 Pediatric Use

The efficacy and safety of prednisone in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). However, some of these conclusions and other indications for pediatric use of corticosteroid, e.g., severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations. The adverse effects of prednisone in pediatric patients are similar to those in adults [*see Adverse Reactions (6)*]. 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.

Children who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in children than some commonly used tests of HPA axis function. The linear growth of children treated with corticosteroids by any route should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of other treatment alternatives. In order to minimize the potential growth effects of corticosteroids, children should be titrated to the lowest effective dose [*see Warnings and Precautions (5.9)*]

8.5 Geriatric Use

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience with prednisone has not identified differences in responses between the elderly and younger patients. However, the incidence of corticosteroid-induced side effects may be increased in geriatric patients and are dose-related. Osteoporosis is the most frequently encountered complication, which occurs at a higher incidence rate in corticosteroid-treated geriatric patients as compared to younger populations and in age-matched controls. Losses of bone mineral density appear to be greatest early on in the course of treatment and may recover over time after steroid withdrawal or use of lower doses (i.e., ≤ 5 mg/day). Prednisone doses of 7.5 mg/day or higher have been associated with an increased relative risk of both vertebral and nonvertebral fractures, even in the presence of higher bone density compared to patients with involution osteoporosis. Routine screening of geriatric patients, including regular assessments of bone mineral density and institution of fracture prevention strategies, along with regular review of prednisone indication should be undertaken to minimize complications and keep the prednisolone dose at the lowest acceptable level. Co-administration of certain bisphosphonates have been shown to retard the rate of bone loss in corticosteroid-treated males and postmenopausal females, and these agents are recommended in the prevention and treatment of corticosteroid-induced osteoporosis [*see Warnings and Precautions (5.6)*].

It has been reported that equivalent weight-based doses yield higher total and unbound prednisolone plasma concentrations and reduced renal and non-renal clearance in elderly patients compared to younger populations. 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, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

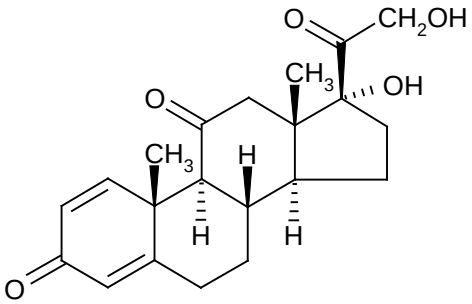
10 OVERDOSAGE

The effects of accidental ingestion of large quantities of prednisone over a very short period of time have not been reported, but prolonged use of the drug can produce mental symptoms, moon face, abnormal fat deposits, fluid retention, excessive appetite, weight gain, hypertrichosis, acne, striae, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, increased blood pressure, tachycardia, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, headache, weakness, menstrual disorders, accentuated menopausal symptoms, neuropathy, fractures, osteoporosis, peptic ulcer, decreased glucose tolerance, hypokalemia, and adrenal insufficiency. Hepatomegaly and abdominal distention have been observed in children.

Treatment of acute overdosage is by immediate gastric lavage or emesis followed by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy the dosage of prednisone may be reduced only temporarily, or alternate day treatment may be introduced.

11. DESCRIPTION

The active ingredient in RAYOS is prednisone (a corticosteroid). Corticosteroids are adrenocortical steroids, both naturally occurring and synthetic. The molecular formula for prednisone is $C_{21}H_{26}O_5$. The chemical name for prednisone is 17,21-dihydroxypregna-1,4-diene-3,11,20-trione, and the structural formula is:



Prednisone is a white to practically white, odorless, crystalline powder and has a molecular weight of 358.43. Prednisone is very slightly soluble in water; slightly soluble in alcohol, chloroform, dioxane, and methanol.

RAYOS is a delayed-release prednisone tablet. It consists of a prednisone-containing core tablet in an inactive shell, which delays the onset of in vitro drug dissolution by approximately 4 hours. Each tablet contains 1 mg, 2 mg, or 5 mg of prednisone, with the following inactive ingredients: dibasic calcium phosphate dihydrate, colloidal silicon dioxide, croscarmellose sodium, glycerol dibehenate, lactose monohydrate, magnesium stearate, povidone, yellow ferric oxide, and red ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Naturally occurring corticosteroids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, such as prednisone, are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Corticosteroids, such as prednisone, cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

Prednisone is a synthetic adrenocortical steroid drug with predominantly corticosteroid properties. Some of these properties reproduce the physiological actions of endogenous glucocorticosteroids, but others do not necessarily reflect any of the adrenal hormones' normal functions; they are seen only after administration of large therapeutic doses of the drug. The pharmacological effects of

prednisone which are due to its corticosteroid properties include: promotion of gluconeogenesis; increased deposition of glycogen in the liver; inhibition of the utilization of glucose; anti-insulin activity; increased catabolism of protein; increased lipolysis; stimulation of fat synthesis and storage; increased glomerular filtration rate and resulting increase in urinary excretion of urate (creatinine excretion remains unchanged); and increased calcium excretion.

Depressed production of eosinophils and lymphocytes occurs, but erythropoiesis and production of polymorphonuclear leukocytes are stimulated. Inflammatory processes (edema, fibrin deposition, capillary dilatation, migration of leukocytes and phagocytosis) and the later stages of wound healing (capillary proliferation, deposition of collagen, cicatrization) are inhibited.

Prednisone can stimulate secretion of various components of gastric juice. Suppression of the production of corticotropin may lead to suppression of endogenous corticosteroids. Prednisone has slight mineralocorticoid activity, whereby entry of sodium into cells and loss of intracellular potassium is stimulated. This is particularly evident in the kidney, where rapid ion exchange leads to sodium retention and hypertension.

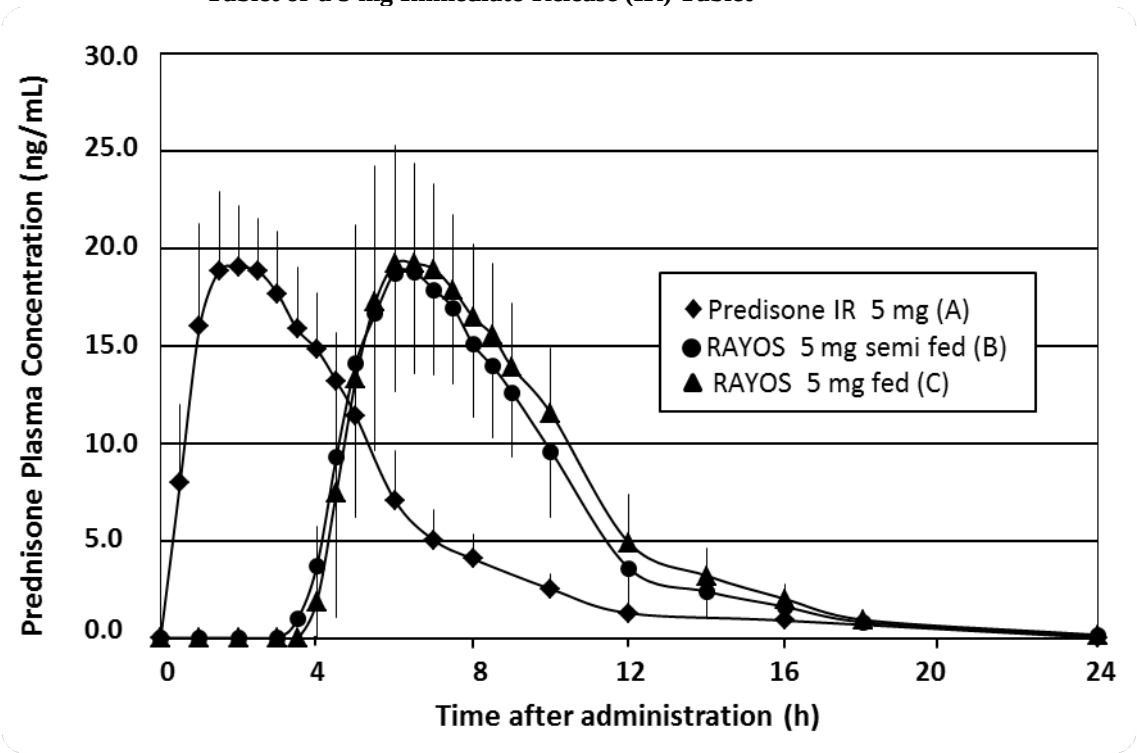
12.3 Pharmacokinetics

The pharmacokinetic profile of RAYOS has an approximately 4-hour lag time from that of immediate-release prednisone formulations. While the pharmacokinetic profile of RAYOS when given with food differs in terms of lag time from IR prednisone, its absorption, distribution, and elimination processes are comparable.

Absorption

Prednisone is released from RAYOS when taken with food approximately 4 hours after oral ingestion. This causes a delay in the time until peak plasma concentrations (T_{max}) are achieved. Median T_{max} of RAYOS in 27 healthy male subjects was 6.0 - 6.5 hours compared to 2.0 hours for an immediate-release (IR) formulation. Subsequently, prednisone was absorbed at the same rate as the IR formulation. Peak plasma concentrations (C_{max}) and exposure, as indicated by $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$, were comparable for both prednisone IR and RAYOS administered 2.5 hours after a light meal or with normal meal (Figure 1).

Figure 1: Mean Plasma Levels of Prednisone After a Single Dose of 5 mg Prednisone Administered as a 5 mg RAYOS Tablet or a 5 mg Immediate-Release (IR) Tablet



A: 5 mg IR tablet under fasting conditions, administered at 2 am, B: 5 mg RAYOS, administered 2.5 hours after a light evening meal, and C: 5 mg RAYOS administered immediately after dinner

In a study with 24 healthy subjects, oral absorption of prednisone from RAYOS was significantly affected by the intake of food. Under standard fasting conditions, both the maximum plasma concentration (C_{max}) and the bioavailability of RAYOS were significantly lower than under fed conditions, shortly after intake of a high fat meal.

RAYOS at dose levels of 1 mg, 2 mg, and 5 mg showed dose-proportionality in terms of peak and systemic exposure (C_{max}, $AUC_{0-\infty}$, and AUC_{0-last}) for the parent drug prednisone as well as for the active metabolite prednisolone.

Metabolism

Prednisone is completely converted to the active metabolite prednisolone, which is further metabolized mainly in the liver and excreted in the urine as sulfate and glucuronide conjugates. The exposure of prednisolone is 4-6 fold higher than that of prednisone.

Excretion

The terminal half-life of both prednisone and prednisolone from the administration of RAYOS was 2-3 hours, which is comparable to that from the IR formulation.

Special Populations

The effects of gender, age, renal impairment, and hepatic impairment on the pharmacokinetics of prednisone or prednisolone after administration of RAYOS have not been evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Prednisone was not formally evaluated in carcinogenicity studies. Review of the published literature identified carcinogenicity studies of prednisolone, the active metabolite of prednisone, at doses which were less than the typical clinical doses. In a 2-year study, male Sprague-Dawley rats administered prednisolone in drinking water at a dose of 368 mcg/kg/day (equivalent to 3.5 mg/day in a 60-kg individual based on a mg/m^2 body surface area comparison) developed increased incidences of hepatic adenomas. Lower doses were not studied, and therefore, a no effect level could not be identified. In an 18-month study, intermittent oral gavage administration of prednisolone did not induce tumors in female Sprague-Dawley rats when given 1, 2, 4.5, or 9 times per month at 3 mg/kg prednisone (equivalent to 29 mg in a 60-kg individual based on a mg/m^2 body surface area comparison).

Prednisone was not formally evaluated for genotoxicity. However, in published studies prednisolone was not mutagenic with or without metabolic activation in the Ames bacterial reverse mutation assay using *Salmonella typhimurium* and *Escherichia coli*, or in a mammalian cell gene mutation assay using mouse lymphoma L5178Y cells, according to current evaluation standards. In a published chromosomal aberration study in Chinese Hamster Lung (CHL) cells, a slight increase was seen in the incidence of structural chromosomal aberrations with metabolic activation at the highest concentration tested, however, the effect appears to be equivocal. Prednisolone was not genotoxic in an *in vivo* micronucleaus assay in the mouse, though the study design did not meet current criteria.

Prednisone was not formally evaluated in fertility studies. However, menstrual irregularities have been described with clinical use [*see Adverse Reactions (6)*].

14 CLINICAL STUDIES

The efficacy of RAYOS in the treatment of rheumatoid arthritis was assessed in one multicenter, double-blind, placebo-controlled, randomized, 12-week trial in patients ≥18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients were enrolled who were not currently treated with corticosteroids but had received non-biologic DMARD therapy for at least 6 months before receipt of study medication, and had an incomplete response to DMARD therapy alone. Patients were randomized in a 2:1 ratio to treatment with RAYOS 5 mg (n=231) or placebo (n=119) administered at 10 pm. A total of 350 patients were enrolled and ranged in age from 27 to 80 years (median age 57 years) with 84% females. Race was distributed as follows: 98% Caucasian, 1% African-American, and <1% Asian.

The percentage of patients with improvement in rheumatoid arthritis at 12 weeks using ACR response criteria (ACR20) was assessed as the primary endpoint, and ACR20, ACR50 and ACR70 responses for patients treated with RAYOS 5 mg versus placebo are shown in Table 1. The relative efficacy of RAYOS compared to immediate-release prednisone has not been established.

Table 1: ACR Responses (Percentage of Patients)

ACR Response at 12 Weeks	RAYOS 5 mg	Placebo	RAYOS 5 mg – Placebo (95% CI)
	N=231	N=119	
ACR20	47%	29%	17% (7.2, 27.6)
ACR50	22%	10%	12% (4.4, 19.6)
ACR70	7%	3%	4% (0.1, 8.7)

All missing values were imputed as non-responders.

The results of the components of the ACR response criteria are shown in Table 2.

Table 2: Components of ACR Response

Parameter	RAYOS 5 mg + DMARD N=231		Placebo + DMARD N=119	
	Baseline	Week 12	Baseline	Week 12
Tender joint count[a]	12.6 (6.2)	7.9 (6.8)	12.5 (5.9)	9.8 (6.7)
Swollen joint count[a]	8.4 (4.4)	4.8 (4.8)	8.6 (4.7)	6.1 (5.4)
Patient assessment of pain[b]	55.3 (21.9)	33.0 (24.5)	50.5 (23.3)	39.6 (24.7)
Patient global assessment[c]	57.4 (20.1)	36.2 (24.5)	50.9 (20.9)	43.0 (22.4)
Physician global assessment[c]	55.2 (16.1)	31.9 (19.7)	54.1 (17.4)	40.4 (21.8)
Disability index (HAQ-DI)[d]	1.3 (0.6)	1.1 (0.6)	1.3 (0.6)	1.2 (0.6)
ESR (mm/hr)	33.0 (16.6)	25.2 (16.8)	32.9 (20.0)	26.5 (19.7)
CRP (mg/dL)	9.3 (13.2)	7.5 (10.7)	11.8(18.0)	9.7 (12.1)

Mean (SD) is presented. Baseline values were carried forward for patients with missing data at Week 12.

[a] 28-joint count

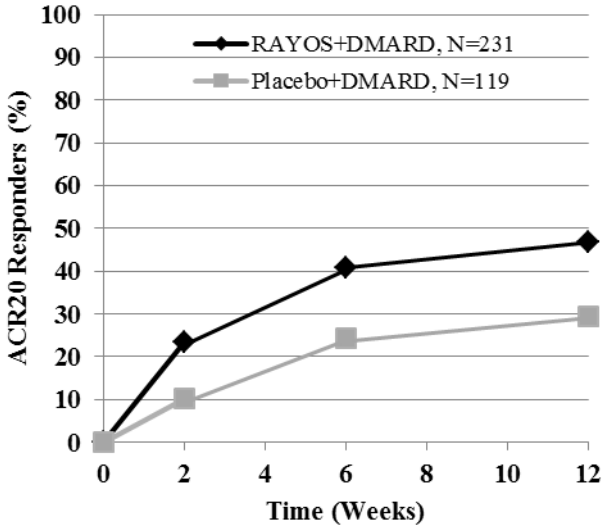
[b] Patient assessment of arthritis pain. Visual analog scale: 0 = no pain, 100 = very intensive pain

[c] Patient or physician global assessment of disease activity. Visual analog scale: 0 = not active at all, 100 = extremely active

[d] Health Assessment Questionnaire Disability Index; 0=best, 3=worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

The percentage of patients achieving ACR20 responses by visit is shown in Figure 2.

Figure 2: ACR20 Response Over 12 Weeks[a]



[a] The same patients may not have responded at each time point.

The percent change from baseline in the duration of morning stiffness at 12 weeks was assessed as a prespecified secondary endpoint. Patients treated with RAYOS had a median decrease in the duration of morning stiffness of 55% compared to 33% in placebo-treated patients (20% estimated median difference between treatment groups with 95% confidence interval [7, 32]). This corresponds to a median duration of morning stiffness of 46 minutes in the RAYOS group and 85 minutes in the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

RAYOS delayed-release tablets (1 mg prednisone) are pale yellowish-white, round, unscored tablets embossed with “NP 1” on one side and supplied as:

NDC Number	Size
75987-020-01	Bottle of 30 tablets
75987-020-02	Bottle of 100 tablets

RAYOS delayed-release tablets (2 mg prednisone) are yellowish-white, round, unscored tablets embossed with “NP 2” on one side and supplied as:

NDC Number	Size
75987-021-01	Bottle of 30 tablets
75987-021-02	Bottle of 100 tablets

RAYOS delayed-release tablets (5 mg prednisone) are light yellow, round, unscored tablets embossed with “NP 5” on one side and supplied as:

NDC Number	Size
75987-022-01	Bottle of 30 tablets
75987-022-02	Bottle of 100 tablets

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature].

Protect RAYOS tablets from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

17 PATIENT COUNSELING INFORMATION

Patients should be informed of the following information before initiating therapy with RAYOS and periodically during the course of ongoing therapy.

- Patients should be warned not to discontinue the use of RAYOS abruptly or without medical supervision, to advise any medical attendants that they are taking it, and to seek medical advice at once should they develop fever or other signs of infection. Patients should be told to take RAYOS exactly as prescribed, follow the instructions on the prescription label, and not stop taking RAYOS without first checking with their healthcare providers, as there may be a need for gradual dose reduction.
- Patients should discuss with their physician if they have had recent or ongoing infections or if they have recently received a vaccine.
- Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.
- There are a number of medicines that can interact with RAYOS. Patients should inform their healthcare provider of all the medicines they are taking, including over-the-counter and prescription medicines (such as phenytoin, diuretics, digitalis or digoxin, rifampin, amphotericin B, cyclosporine, insulin or diabetes medicines, ketoconazole, estrogens including birth control pills and hormone replacement therapy, blood thinners such as warfarin, aspirin or other NSAIDS, barbiturates), dietary supplements, and herbal products. If patients are taking any of these drugs, alternate therapy, dosage adjustment, and/or special test may be needed during the treatment.
- For missed doses, patients should be told to take the missed dose as soon as they remember. If it is almost time for the next dose, the missed dose should be skipped and the medicine taken at the next regularly schedule time. Patients should not take an extra dose to make up for the missed dose.
- Patients should be told to take RAYOS with food. Patients should be advised not to break, divide, or chew RAYOS.
- Patients should be advised of common adverse reactions that could occur with RAYOS use to include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

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