STERAPRED® 5 mg Uni-Pak
(Prednisone Tablets, 5 mg U.S.P.)

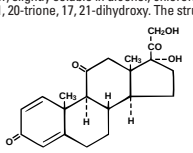
STERAPRED® 5 mg 12 DAY Uni-Pak
(Prednisone Tablets, 5 mg U.S.P.)

STERAPRED® DS Uni-Pak
(Prednisone Tablets, 10 mg U.S.P.)

STERAPRED® DS 12 DAY Uni-Pak
(Prednisone Tablets, 10 mg U.S.P.)

Rx Only

DESCRIPTION: STERAPRED 5 mg, STERAPRED 5 mg 12 DAY, STERAPRED DS, STERAPRED DS 12 DAY tablets contain prednisone U.S.P. which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Prednisone is a white to practically white, odorless, crystalline powder. It is very slightly soluble in water; slightly soluble in alcohol, chloroform, dioxane, and methanol. The chemical name for prednisone is pregna-1, 4-diene-3, 11, 20-trione, 17, 21-dihydroxy. The structural formula is represented below:



$C_{21}H_{26}O_5$
Molecular Weight: 358.43

Each tablet, for oral administration, contains 5 mg or 10 mg of prednisone USP (anhydrous). In addition, each tablet contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, crospovidone, docusate sodium, magnesium stearate and sodium benzoate.

CLINICAL PHARMACOLOGY: Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS AND USAGE: STERAPRED 5 mg, STERAPRED 5 mg 12 DAY, STERAPRED DS, STERAPRED DS 12 DAY tablets are indicated in the following conditions:

1. **Endocrine Disorders:**
   Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance)
   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:
   Psoriatic arthritis
   Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
   Ankylosing spondylitis
   Acute and subacute bursitis
   Acute nonspecific tenosynovitis
   Acute gouty arthritis
   Post-traumatic osteoarthritis
   Synovitis of osteoarthritis
   Epicondylitis
3. **Collagen Disease:**
   During an exacerbation or as maintenance therapy in selected cases of:
   Systemic lupus erythematosus
   Systemic dermatomyositis (polymyositis)
   Acute rheumatic carditis
4. **Dermatologic Diseases:**
   Pemphigus
   Bullous dermatitis herpetiformis
   Severe erythema multiforme (Stevens-Johnson syndrome)
   Exfoliative dermatitis
   Mycosis fungoides
   Severe psoriasis
   Severe seborrheic dermatitis
5. **Allergic States:**
   Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:
   Seasonal or perennial allergic rhinitis
   Bronchial asthma
   Contact dermatitis
   Atopic dermatitis
   Serum sickness
   Drug hypersensitivity reactions
6. **Ophthalmic Diseases:**
   Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
   Allergic corneal marginal ulcers
   Herpes zoster ophthalmicus
   Anterior segment inflammation
   Diffuse posterior uveitis and choroiditis
   Sympathetic ophthalmia
   Allergic conjunctivitis
   Keratitis
   Chorioretinitis
   Optic neuritis
   Iritis and iridocyclitis
7. **Respiratory Diseases:**
   Symptomatic sarcoidosis
   Loeffler's syndrome not manageable by other means
   Berylliosis
   Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
   Aspiration pneumonitis
8. **Hematologic Disorders:**
   Idiopathic thrombocytopenic purpura in adults
   Secondary thrombocytopenia in adults
   Acquired (autoimmune) hemolytic anemia
   Erythroblastopenia (RBC anemia)
   Congenital (erythroid) hypoplastic anemia
9. **Neoplastic Diseases:**
   For palliative management of:
   Leukemias and lymphomas in adults
   Acute leukemia of childhood
10. **Edematous States:**
    To induce a diuresis or remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus
11. **Gastrointestinal Diseases:**
    To tide the patient over a critical period of the disease in:
    Ulcerative colitis
    Regional enteritis
12. **Nervous System:**
    Acute exacerbations of multiple sclerosis
13. **Miscellaneous:**
    Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
    Trichinosis with neurologic or myocardial involvement

CONTRAINDICATIONS: Prednisone tablets are contraindicated in systemic fungal infections and known hypersensitivity to components.

WARNINGS:

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

Corticosteroids may mask some signs of infection, and new infections may appear during their use. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location of 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.[1]

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.[2] There may be decreased resistance and inability to localize infection when corticosteroids are used.

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.

Usage in pregnancy:

Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving immunosuppressive doses of corticosteroids. The use of STERAPRED 5 mg, STERAPRED 5 mg 12 DAY, STERAPRED DS, STERAPRED DS 12 DAY tablets 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 anti-tuberculous 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.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. 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 pooled intramuscular 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 may be considered. 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 Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

PRECAUTIONS:

Information For Patients:

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

General Precautions:

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. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroids should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

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.

Steroids should be used with caution in nonspecific ulcerative colitis; if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomosis; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

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

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 corticosteroids 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. (See **DOSAGE AND ADMINISTRATION**).

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

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

Drug Interactions:

The pharmacokinetic interactions listed below are potentially clinically important. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity. Corti-costeroids may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when corticosteroid is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anti-coagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

ADVERSE REACTIONS:

Fluid and Electrolyte Disturbances:

Sodium retention
Fluid retention
Congestive heart failure in susceptible patients
Potassium loss
Hypokalemic alkalosis
Hypertension

Musculoskeletal:

Muscle weakness
Steriod myopathy
Loss of muscle mass
Osteoporosis
Tendon rupture, particularly of the Achilles tendon
Vertebral compression fractures
Aseptic necrosis of femoral and humeral heads
Pathologic fracture of long bones

Gastrointestinal:

Peptic ulcer with possible perforation and hemorrhage
Abdominal distention
Pancreatitis
Ulcerative esophagitis

Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

Dermatologic:

Impaired wound healing
Thin fragile skin
Petechiae and ecchymoses
Facial erythema
Increased sweating
May suppress reactions to skin tests

Metabolic:

Negative nitrogen balance due to protein catabolism

Neurological:

Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment
Convulsions
Vertigo
Headache

Endocrine:

Menstrual irregularities
Development of Cushingoid state
Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
Suppression of growth in children
Decreased carbohydrate tolerance
Manifestations of latent diabetes mellitus
Increased requirements for insulin or oral hypoglycemic agents in diabetics

Ophthalmic:

Posterior subcapsular cataracts
Increased intraocular pressure
Glaucoma
Exophthalmos

Additional Reactions:

Urticaria and other allergic, anaphylactic or hypersensitivity reactions.

DOSAGE AND ADMINISTRATION:

The initial dosage of STERAPRED 5 mg, STERAPRED 5 mg 12 DAY, STERAPRED DS, STERAPRED DS 12 DAY (Prednisone Tablets) may vary from 5 mg to 60 mg of prednisone per day depending on the specific disease entity being treated. 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 of time there is a lack of satisfactory clinical response, prednisone 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 prednisone for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

Multiple Sclerosis:

In the treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisone for a week followed by 80 mg every other day for one (1) month have been shown to be effective. (Dosage range is the same for prednisone and prednisolone).

Alternate-Day Therapy: Alternate-day therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticoid is administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms and growth suppression in children.

The rationale for this treatment schedule is based on two major premises: (a) the anti-inflammatory or therapeutic effect of corticoids persists longer than their physical presence and metabolic effects and (b) administration of the corticosteroid every other morning allows for re-establishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the off-steroid day.

A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increasing amounts of corticotropin (ACTH) while a rise in free cortisol inhibits ACTH secretion. Normally the HPA system is characterized by diurnal (circadian) rhythm. Serum levels of ACTH rise from a low point about 10 p.m. to a peak level about 6 a.m. Increasing levels of ACTH stimulate adrenocortical activity resulting in a rise in plasma cortisol with maximal levels occuring between 2 a.m. and 8 a.m. This rise in cortisol dampens ACTH production and in turn adrenocortical activity. There is a gradual fall in plasma corticoids during the day with lowest levels occurring about midnight.

The diurnal rhythm of the HPA axis is lost in Cushing's disease, a syndrome of adrenocortical hyperfunction characterized by obesity with centripetal fat distribution, thinning of the skin with easy bruisability, muscle wasting with weakness, hypertension, latent diabetes, osteoporosis, electrolyte imbalance, etc. The same clinical findings of hyperadrenocorticism may be noted during long-term pharmacologic dose corticoid therapy administered in conventional daily divided doses. It would appear, then, that a disturbance in the diurnal cycle with maintenance of elevated corticoid values during the night may play a significant role in the development of undesirable corticoid effects. Escape from these constantly elevated plasma levels for even short periods of time may be instrumental in protecting against undesirable pharmacologic effects.

During conventional pharmacologic dose corticosteroid therapy, ACTH production is inhibited with subsequent suppression of cortisol production by the adrenal cortex. Recovery time for normal HPA activity is variable depending upon the dose and duration of treatment. During this time the patient is vulnerable to any stressful situation. Although it has been shown that there is considerably less adrenal suppression following a single morning dose of prednisolone (10 mg) as opposed to a quarter of that dose administered every 6 hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used. Further, it has been shown that a single dose of certain corticosteroids will produce adrenocortical suppression for two or more days. Other corticoids, including methylprednisolone, hydrocortisone, prednisone, and prednisolone, are considered to be short acting (producing adrenocortical suppresion for 1-1/4 to 1-1/2 days following a single dose) and thus are recommended for alternate-day therapy.

The following should be kept in mind when considering alternate-day therapy:

1. Basic principles and indications for corticosteroid therapy should apply. The benefits of alternate-day therapy should not encourage the indiscriminate use of steroids.
2. Alternate-day therapy is a therapeutic technique primarily designed for patients in whom long term pharmacologic corticoid therapy is anticipated.
3. In less severe disease processes in which corticoid therapy is indicated, it may be possible to initiate treatment with alternate-day therapy. More severe disease states usually will require daily divided high dose therapy for initial control of the disease process. The initial suppressive dose level should be continued until satisfactory clinical response is obtained, usually four to ten days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible particularly when subsequent use of alternate-day therapy is intended. Once control has been established, two courses are available: (a) change to alternate-day therapy and then gradually reduce the amount of corticoid given every other day, or (b) following control of the disease process, reduce the daily dose of corticoid to the lowest effective level as rapidly as possible and then change over to an alternate-day schedule. Theoretically, course (a) may be preferable.
4. Because of the advantages of alternate-day therapy, it may be desirable to try patients on this form of therapy who have been on daily corticoids for long periods of time (e.g., patients with rheumatoid arthritis). Since these patients may already have suppressed HPA axis, establishing them on alternate-day therapy may be difficult and not always successful. However, it is recommended that regular attempts be made to change them over. It may be helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose if difficulty is encountered. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.
5. As indicated above, certain corticosteroids, because of their prolonged suppresive effect on adrenal activity, are not recommended for alternate-day therapy (e.g., dexamethasone and betamethasone).
6. The maximal activity of the adrenal cortex is between 2 a.m. and 8 a.m., and it is minimal between 4 p.m. and midnight. Exogenous corticosteroids suppress adrencortical activity the least, when given at the time of maximal activity (a.m.)
7. In using alternate-day therapy it is important, as in all therapeutic situations, to individualize and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of alternate-day therapy will help the patient to understand and tolerate the possible flare-up of symptoms which may occur in the latter part of the off-steroid day. Other symptomatic therapy may be added or increased at this time if needed.
8. In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticoid dose for control. Once control is again established, alternate-day therapy may be reinstituted.
9. Although many of the undesirable features of corticosteroid therapy can be minimized by alternate-day therapy, as in any therapeutic situation, the physician must carefully weigh the benefit-risk ratio for each patient in whom corticoid therapy is being considered.

HOW SUPPLIED:

5 mg — Each white, round, flat, scored tablet is imprinted "DAN" above and below the score and "5052" on the reverse side of the tablet. Sterapred 5 mg is supplied in a 21 tablet Uni-Pak (NDC 0259-0390-21); Sterapred 5 mg 12 DAY is supplied in a 48 tablet Uni-Pak (NDC 0259-0391-48).

10 mg — Each white, round, flat, scored tablet is imprinted "DAN" above and below the score and "5442" on the reverse side of the tablet. Sterapred DS is supplied in a 21 tablet Uni-Pak (NDC 0259-0364-21); Sterapred DS 12 DAY is supplied in a 48 tablet Uni-Pak (NDC 0259-0389-48).

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light and moisture.

REFERENCES

[1] Fekety R. Infections associated with corticosteroids and immunosuppressive therapy. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases*. Philadelphia: WBSaunders Company 1992:1050-1.

[2] Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticoids. *Rev Infect Dis* 1989: 11(6):954-63.

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