

Azmacort[®]

(triamcinolone acetonide) Inhalation Aerosol

Rev. May 2003

Rx only

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(triamcinolone acetonide)

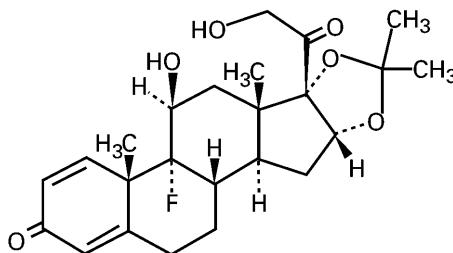
Inhalation Aerosol

For Oral Inhalation Only

Shake Well Before Using

DESCRIPTION

Triamcinolone acetonide, USP, the active ingredient in **Azmacort[®]** Inhalation Aerosol, is a corticosteroid with a molecular weight of 434.5 and with the chemical designation 9-Fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. (C₂₄H₃₁FO₆).



Azmacort Inhalation Aerosol is a metered-dose aerosol unit containing a microcrystalline suspension of triamcinolone acetonide in the propellant dichlorodifluoromethane and dehydrated alcohol USP 1% w/w. Each canister contains 60 mg triamcinolone acetonide. The canister must be primed prior to the first use. After an initial priming of 2 actuations, each actuation delivers 200 mcg triamcinolone acetonide from the valve and 100 mcg from the spacer-mouthpiece under defined *in vitro* test conditions. The canister will remain primed for 3 days. If the canister is not used for more than 3 days, then it should be reprimed with 2 actuations. There are at least 240 actuations in one **Azmacort** Inhalation Aerosol canister. **After 240 actuations, the amount delivered per actuation may not be consistent and the unit should be discarded.**

CLINICAL PHARMACOLOGY

Triamcinolone acetonide is a more potent derivative of triamcinolone. Although triamcinolone itself is approximately one to two times as potent as prednisone in animal models of inflammation, triamcinolone acetonide is approximately 8 times more potent than prednisone.

The precise mechanism of the action of glucocorticoids in asthma is unknown. However, the inhaled route makes it possible to provide effective local anti-inflammatory activity with reduced systemic corticosteroid effects. Though highly effective for asthma, glucocorticoids do not affect asthma symptoms immediately. While improvement in asthma may occur as soon as one week after initiation of **Azmacort** Inhalation Aerosol therapy, maximum improvement may not be achieved for 2 weeks or longer.

Based upon intravenous dosing of triamcinolone acetonide phosphate ester, the half-life of triamcinolone acetonide was reported to be 88 minutes. The volume of distribution (V_d) reported

was 99.5 L (SD \pm 27.5) and clearance was 45.2 L/hour (SD \pm 9.1) for triamcinolone acetonide. The plasma half-life of glucocorticoids does not correlate well with the biologic half-life.

The pharmacokinetics of radiolabeled triamcinolone acetonide [^{14}C] were evaluated following a single oral dose of 800 mcg to healthy male volunteers. Radiolabeled triamcinolone acetonide was found to undergo relatively rapid absorption following oral administration with maximum plasma triamcinolone acetonide and [^{14}C]-derived radioactivity occurring between 1.5 and 2 hours. Plasma protein binding of triamcinolone acetonide appears to be relatively low and consistent over a wide plasma triamcinolone acetonide concentration range as a function of time. The overall mean percent fraction bound was approximately 68%.

The metabolism and excretion of triamcinolone acetonide were both rapid and extensive with no parent compound being detected in the plasma after 24 hours post-dose and a low ratio (10.6%) of parent compound $\text{AUC}_{0-\infty}$ to total [^{14}C] radioactivity $\text{AUC}_{0-\infty}$. Greater than 90% of the oral [^{14}C]-radioactive dose was recovered within 5 days after administration in 5 out of the 6 subjects in the study. Of the recovered [^{14}C]-radioactivity, approximately 40% and 60% were found in the urine and feces, respectively.

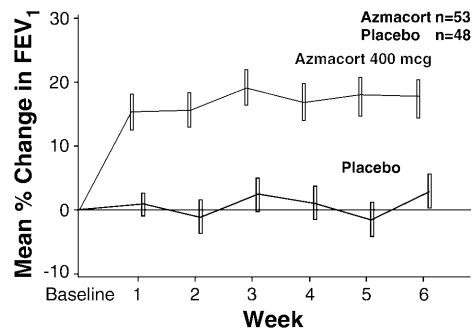
Three metabolites of triamcinolone acetonide have been identified. They are 6 β -hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6 β -hydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound due to (a) the dependence of anti-inflammatory activity on the presence of a 21-hydroxyl group, (b) the decreased activity observed upon 6-hydroxylation, and (c) the markedly increased water solubility favoring rapid elimination. There appeared to be some quantitative differences in the metabolites among species. No differences were detected in metabolic pattern as a function of route of administration.

CLINICAL TRIALS

Double-blind, placebo-controlled efficacy and safety studies have been conducted in asthma patients with a range of asthma severities, from those patients with mild disease to those with severe disease requiring oral steroid therapy.

The efficacy and safety of **Azmacort** Inhalation Aerosol given twice daily was demonstrated in two placebo-controlled clinical trials. In two separate studies, 222 asthmatic patients were randomized to receive either **Azmacort** Inhalation Aerosol 400 mcg twice daily or matching placebo for a treatment period of 6 weeks. Patients were adult asthmatics who were using inhaled beta₂-agonists on more than an occasional basis (at least three times weekly), either without or with inhaled corticosteroids, for control of their asthma symptoms. For the combined studies, 48% (52/109) patients randomized to placebo and 41% (46/113) patients randomized to **Azmacort** Inhalation Aerosol treatment were previously treated with inhaled corticosteroids.

Results of weekly lung function tests (FEV₁) from one of these trials is presented graphically below. Results of the second study are presented in tabular form as the changes in asthma measures from baseline to the end of the treatment period.



Mean Changes in Asthma Measures from Baseline to Endpoint^a
All-Treated Patients
Results from a Placebo-Controlled, 6 Week Study

Asthma Measure	Placebo (N=61)	Azmacort 400 mcg bid (N=60)
Percent Change in FEV ₁ (%)	2.8%	17.5%
Increase in Morning Peak Flow Rate (L/min)	6.7	45.9
Decrease in Albuterol Use (puffs/day)	0.6	3.4
Decrease in Daily Asthma Symptom Score (units/day) ^b	0.5	2.3

^aEndpoint Results are obtained from the last evaluable data, regardless of whether the patient completed 6 weeks of treatment

^bScale (0-6) with 0 = no symptom: Maximum Score (AM + PM) =12

In both studies, treatment with **Azmacort** Inhalation Aerosol (400 mcg twice daily) resulted in significant improvements in all clinical asthma measures (lung functions, asthma symptoms, use of as-needed beta₂-agonist medications) when compared to placebo.

INDICATIONS

Azmacort Inhalation Aerosol is indicated in the maintenance treatment of asthma as prophylactic therapy. **Azmacort** Inhalation Aerosol is also indicated for asthma patients who require systemic corticosteroid administration, where adding Azmacort may reduce or eliminate the need for the systemic corticosteroids.

Azmacort Inhalation Aerosol is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

Azmacort Inhalation Aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to triamcinolone acetonide or any of the other ingredients in this preparation contraindicates its use.

WARNINGS

Particular care is needed in patients who are transferred from systemically active corticosteroids to **Azmacort** Inhalation Aerosol because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosolized steroids in recommended doses. After withdrawal from systemic corticosteroids, a number of months is usually required for recovery of hypothalamic-pituitary-adrenal (HPA) function. For some patients who have received large doses of oral steroids for long periods of time before therapy with **Azmacort** Inhalation Aerosol is initiated, recovery may be delayed for one year or longer. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections, particularly gastroenteritis or other

conditions with acute electrolyte loss. Although **Azmacort** Inhalation Aerosol may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies only normal physiological amounts of corticosteroid systemically and does NOT provide the increased systemic steroid which is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been recently withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack.

Localized infections with *Candida albicans* have occurred infrequently in the mouth and pharynx. These areas should be examined by the treating physician at each patient visit. The percentage of positive mouth and throat cultures for *Candida albicans* did not change during a year of continuous therapy. The incidence of clinically apparent infection is low (2.5%). These infections may disappear spontaneously or may require treatment with appropriate antifungal therapy or discontinuance of treatment with **Azmacort** Inhalation Aerosol.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Azmacort Inhalation Aerosol is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing following dosing. If bronchospasm occurs following use of **Azmacort** Inhalation Aerosol, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with **Azmacort** Inhalation Aerosol should be discontinued and alternative treatment should be instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma which are not responsive to bronchodilators occur during the course of treatment with **Azmacort** Inhalation Aerosol. During such episodes, patients may require therapy with systemic corticosteroids.

The use of **Azmacort** Inhalation Aerosol with systemic prednisone, dosed either daily or on alternate days, could increase the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, **Azmacort** Inhalation Aerosol should be used with caution in patients already receiving prednisone treatment for any disease.

Transfer of patients from systemic steroid therapy to **Azmacort** Inhalation Aerosol may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS

During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function. (See **DOSAGE AND ADMINISTRATION**.) Although steroid withdrawal effects are usually transient and not severe,

severe and even fatal exacerbation of asthma can occur if the previous daily oral corticosteroid requirement had significantly exceeded 10 mg/day of prednisone or equivalent.

In responsive patients, inhaled corticosteroids will often permit control of asthmatic symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since triamcinolone acetonide is absorbed into the circulation and can be systemically active, the beneficial effects of **Azmacort** Inhalation Aerosol in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

Suppression of HPA function has been reported in volunteers who received 4000 mcg daily of triamcinolone acetonide by oral inhalation. In addition, suppression of HPA function has been reported in some patients who have received recommended doses for as little as 6 to 12 weeks. Since the response of HPA function to inhaled corticosteroids is highly individualized, the physician should consider this information when treating patients.

When used at excessive doses or at recommended doses in a small number of susceptible individuals, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, **Azmacort**[®] (triamcinolone acetonide) Inhalation Aerosol should be discontinued slowly, consistent with accepted procedures for reducing systemic steroid therapy and for management of asthma symptoms.

Azmacort Inhalation Aerosol should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, parasitic, or viral infections; or ocular herpes simplex.

The long-term local and systemic effects of **Azmacort** Inhalation Aerosol in human subjects are still not fully known. While there has been no clinical evidence of adverse experiences, the effects resulting from chronic use of **Azmacort** Inhalation Aerosol on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects including suppression of growth in children. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of a decrease in adrenal function.

Information for Patients: Patients being treated with **Azmacort** Inhalation Aerosol should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a complete disclosure of all possible adverse or intended effects.

Patients should use **Azmacort** Inhalation Aerosol at regular intervals as directed. Results of clinical trials indicate that significant improvement in asthma may occur by 1 week, but maximum benefit may not be achieved for 2 weeks or more. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

In clinical studies and post-marketing experience with **Azmacort** Inhalation Aerosol, local infections of the oropharynx with *Candida albicans* have occurred. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with **Azmacort** Inhalation Aerosol. However, at times therapy with **Azmacort** Inhalation Aerosol may need to be interrupted.

Patients should be instructed to track their use of **Azmacort** Inhalation Aerosol and to dispose of the canister after 240 actuations since reliable dose delivery cannot be assured after 240 doses.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

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