

PRODUCT MONOGRAPH

PrSYNACTHEN® DEPOT

Tetracosactide Zinc Injection, Mfr. Std.
(also known as cosyntropin injection)

1 mg/mL tetracosactide

Adrenocorticotrophic Hormone (synthetic ACTH)

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PHARMACOLOGICAL CLASSIFICATION

(Adrenocorticotrophic Hormone (synthetic ACTH))

ACTIONS AND CLINICAL PHARMACOLOGY

Natural adrenocorticotropin is a straight-chain polypeptide containing 39 amino acids which, by convention, are numbered from the N-terminal end of the molecule. The sequence of amino-acid occupying positions 25 to 33 varies among species and it is this part of the molecule which is most antigenic when ACTH of foreign origin is administered to man. In contrast, the N-terminal 24 amino-acid sequence is common to all species and is relatively non-antigenic, and it is only these amino-acids which are involved in its biological activities.

The most important physiological effects of ACTH involve the adrenal cortex and include the maintenance of adrenal weight and the control of adrenal corticosteroid synthesis and release. In its absence, adrenal blood flow is diminished, adrenal atrophy invariably ensues and cortisol secretion is markedly reduced. In addition to controlling corticosteroid secretion, ACTH also increases the synthesis and release of the other adrenal steroids, namely aldosterone and the adrenal androgens. It also has some degree of melanotropic activity and lipolytic effect.

SYNACTHEN DEPOT (tetracosactide zinc injection), a long-acting synthetic β 1-24-corticotropin, exhibits the same activity as natural ACTH with regard to all its biological activities. The complex results in a product whose absorption in man is effected over a longer period of time as compared to corticotropin. Therefore, therapy may be maintained with less frequent administration.

The long-term administration of SYNACTHEN DEPOT produces the same effects as those produced by cortisone, cortisol and their synthetic analogues. In addition, there is also hypertrophy and hyperplasia of the adrenal cortex, in contrast to the effect of the exogenous corticoids.

INDICATIONS AND CLINICAL USE

1. Diagnostic Use for the Investigation of Adrenocortical Insufficiency

SYNACTHEN DEPOT (tetracosactide zinc injection) is intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency. To determine the functional reserve of the adrenal cortex, a 5-hour test can be performed using SYNACTHEN DEPOT. Plasma-

cortisol should be estimated before and 4-6 hours after an I.M. injection of 1 mg SYNACTHEN DEPOT.

2. Therapeutic Use

- **Collagen Diseases:** Acute rheumatic fever; rheumatoid arthritis; lupus erythematosus; periarteritis nodosa, psoriatic arthritis; scleroderma; rheumatoid spondylitis; Still's disease.
- **Dermatologic Diseases:** Exfoliative dermatitis; dermatomyositis; pemphigus.
- **Endocrine Diseases:** Panhypopituitarism.
- **Eye Diseases:** Choroiditis; conjunctivitis; iritis; keratitis; optic neuritis; sympathetic ophthalmia; uveitis.
- **Hemolytic Diseases:** Acquired hemolytic jaundice.
- **Other Diseases:** Nephrotic syndrome; ulcerative colitis; Bell's palsy; acute exacerbations of multiple sclerosis, and as adjuvant treatment in cases of acute gout.

CONTRAINDICATIONS

- Known or suspected hypersensitivity to tetracosactide (also known as cosyntropin) and/or ACTH of animal origin or to any of the excipients of SYNACTHEN DEPOT (tetracosactide zinc injection).
- SYNACTHEN DEPOT must not be used to treat asthma or other allergic conditions due to the increased risk of anaphylactic reactions (see WARNINGS and PRECAUTIONS).
- Premature babies and neonates (less than 1 month), due to the presence of benzyl alcohol (see WARNINGS and DOSAGE AND ADMINISTRATION).
- Acute psychosis.
- Untreated bacterial, fungal and viral infections.
- Active or latent peptic ulcer.
- Refractory congestive heart failure.
- Cushing's syndrome.
- Treatment of primary adrenocortical insufficiency.
- Adrenogenital syndrome.

WARNINGS

SYNACTHEN DEPOT (tetracosactide zinc injection), MUST NOT BE GIVEN INTRAVENOUSLY.

BENZYL ALCOHOL: Due to the presence of benzyl alcohol, SYNACTHEN DEPOT is not recommended in infants and children between 1 month of age and 3 years old, as it may cause toxic reactions and allergic reactions.

In rare cases, particularly in patients subject to asthma and/or other forms of allergy - severe anaphylactic reactions may occur. Such reactions set in usually within 30 minutes after administration of SYNACTHEN DEPOT.

If SYNACTHEN DEPOT is used in any of the following conditions, the risks should be weighed against the possible benefits: non-specific ulcerative colitis; diverticulitis; recent intestinal anastomosis; renal insufficiency; hypertension; thromboembolic tendencies; acute or chronic infections, especially varicella or vaccinia; exanthematous and fungal diseases; osteoporosis and myasthenia gravis.

The administration of ACTH for three consecutive days may cause sodium and water retention with the risk of edema while the marked and prolonged increase in circulating corticosteroid levels that may occur in patients with bilateral adrenal hyperplasia, can cause a severe exacerbation of the symptoms of Cushing's syndrome. On extremely rare occasions, adrenal crisis has supervened during prolonged ACTH stimulation in patients with marked adrenal insufficiency. For this reason, some clinicians give 1 mg of dexamethasone daily through the 3 days on which SYNACTHEN DEPOT is given to provide steroid cover. This does not interfere with the test

PRECAUTIONS

Endocrine and Metabolism:

The blood pressure and weight should be carefully observed. Urinalysis should be done at intervals; if sugar is present the fasting blood glucose should be determined. Salt and water retention in response to SYNACTHEN DEPOT (tetracosactide zinc injection) can often be avoided or eliminated by prescribing a low-sodium diet; diuretics may be employed when strict sodium restriction is impossible.

Potassium supplement should be administered in cases of prolonged use.

Although the action of tetracosactide (also known as cosyntropin) is similar to that of exogenous adrenocortical steroids, the quantity of endogenous corticosteroids produced by the adrenal glands may be variable.

The lowest effective dose of tetracosactide should be used to control the condition under treatment. When reduction of the dosage is indicated, this should be gradual. Relative insufficiency of the pituitary-adrenal axis is induced by prolonged administration; therefore gradual reduction of tetracosactide dosage is essential. On discontinuation of therapy this type of insufficiency may persist for several months. During this period in cases of stressful conditions appropriate adrenocortical therapy should be considered.

It is advisable to verify the adrenal responsiveness before and during tetracosactide therapy. An enhanced effect of corticotropin therapy has been observed in patients with hypothyroidism and in those with cirrhosis of the liver.

Immune:

Prolonged repeated tetracosactide administration may increase the risk of hypersensitivity reaction.

Before employing SYNACTHEN DEPOT the physician must ascertain whether the patient is suffering from an allergic disorder (especially asthma) or is susceptible in general to allergies (see CONTRAINDICATIONS and WARNINGS). The physician should also enquire whether the patient has been treated with ACTH preparations in the past, and, if so, make sure that the treatment gave rise to no hypersensitivity reactions (see CONTRAINDICATIONS).

Allergic reactions may occur in response to SYNACTHEN DEPOT, which tend to be more severe in patients susceptible to allergies (especially asthma) (see CONTRAINDICATIONS). Because of the possibility of an allergic reaction occurring with SYNACTHEN DEPOT, the injection should be given under medical supervision and the patient kept under observation for about 1 hour. Self-injection by patients is not recommended. Should any prodromal signs occur, stop further treatment.

Allergic reactions of this type include: marked redness and pain at the injection site, dizziness, nausea, vomiting, urticaria, pruritus, flushings, severe malaise, dyspnea or angioneurotic edema or Quincke's edema. If local or systemic hypersensitivity reactions occur during or after an injection, treatment with tetracosactide must be discontinued and all use of ACTH preparations avoided in the future.

Live virus immunization procedures must not be undertaken during treatment with SYNACTHEN DEPOT because of the decrease in antibody response and possible hazard of neurological complications.

Infection:

Infections must be treated simultaneously with appropriate antibiotics; the signs and symptoms of inflammation may be masked by the anti-inflammatory effects of cortisol produced by the over-active adrenal glands.

SYNACTHEN DEPOT may activate latent amoebiasis. It is therefore recommended that latent or active amoebiasis be ruled out before initiating therapy.

If SYNACTHEN DEPOT is indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary because the disease may be reactivated. During prolonged therapy, such patients should receive chemoprophylaxis.

Ophthalmologic:

Prolonged use of tetracosactide may be associated with development of posterior subcapsular cataracts and glaucoma.

SYNACTHEN DEPOT should be used cautiously in patients with ocular herpes simplex owing to possible corneal perforation.

Peri-Operative Considerations:

Patients who are subjected to the stress of surgical operations or trauma while being treated, or within one year after treatment has been terminated, should have their SYNACTHEN DEPOT therapy augmented or reinstated and continued for the duration of the stress period and immediately following it. In stressful conditions, additional use of rapidly acting corticosteroids may be required.

Psychiatric:

Psychological disturbances such as euphoria, depression, insomnia, psychosis, mood swings, and personality changes may occur during therapy. Existing emotional disorders or psychoses may be aggravated.

Special Populations

Patients with Special Diseases and Conditions: Patients receiving medication for diabetes mellitus or for hypertension must have the dosage of their medication readjusted if treatment with SYNACTHEN DEPOT is instituted.

Since SYNACTHEN DEPOT increases the adrenocortical production of glucocorticoids and mineralocorticoids, drug interactions of the type seen with these corticosteroids may occur.

An enhanced effect of corticotropin therapy has been observed in patients with hypothyroidism and in those with cirrhosis of the liver.

Hepatic Impairment: No studies have been performed in patients with hepatic impairment.

Renal Impairment: No studies have been performed in patients with renal impairment.

Pediatrics (>3 years of age): In children undergoing long-term treatment, growth should be monitored as SYNACTHEN DEPOT can inhibit growth in children.

Small children treated with SYNACTHEN DEPOT, echocardiographic recordings should be made regularly, because during long-term treatment with high doses reversible cardiac hypertrophy may occur.

Geriatrics (> 65 years of age): There is no such information available which would necessitate dosage modification in elderly (65 years of age and above).

Women of child-bearing potential: There is no special recommendation.

Pregnant Women: Safety in pregnant women has not been established. There are no adequate and well controlled studies of SYNACTHEN DEPOT in pregnant women. Data from animal studies are insufficient with respect to reproductive toxicity/teratogenicity. Therefore the use of SYNACTHEN DEPOT during pregnancy requires that the benefits of the drug be carefully weighed against the potential risk to the mother and embryo or fetus.

Nursing Women: It is unknown whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SYNACTHEN DEPOT is administered to a breastfeeding woman.

Fertility: There are no data available.

Lack of diagnostic accuracy

Post administration total plasma cortisol levels during the SYNACTHEN DEPOT test might be misleading in some special clinical situations due to altered cortisol binding globulin levels. These situations include patients on oral contraceptives, post operative patients, critical illness, severe liver

disease, nephrotic syndrome. Hence, in these circumstances, alternative parameters (e.g., salivary cortisol, free cortisol index, plasma free cortisol) can be used to assess the integrity of HPA axis.

Monitoring and Laboratory Tests

Before using SYNACTHEN DEPOT the physician must ascertain whether the patient is susceptible to allergies (especially asthma). It is also important to establish whether the patient has been treated with ACTH preparations in the past, and if so to confirm that the treatment did not trigger any hypersensitivity reactions.

If SYNACTHEN DEPOT is indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary because the disease may be reactivated. During prolonged therapy, such patients should receive chemoprophylaxis.

Provided the dosage is carefully individualised, SYNACTHEN DEPOT is unlikely to inhibit growth in children. Nevertheless, growth should be monitored in children undergoing long-term treatment (see PRECAUTIONS, Special Populations).

Echocardiography should be performed regularly in small children since reversible cardiac hypertrophy may occur during long-term treatment with high doses (see PRECAUTIONS, Special Populations and POST-MARKET ADVERSE DRUG REACTIONS).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse drug reactions may be related to tetracosactide (also known as cosyntropin) zinc hydroxide, to the presence of benzyl alcohol or the stimulation of glucocorticoids and mineralocorticoid secretion during the use of SYNACTHEN DEPOT (tetracosactide zinc injection).

Adverse drug reactions related to benzyl alcohol

In rare cases the benzyl alcohol contained SYNACTHEN DEPOT may also give rise to hypersensitivity reactions. The benzyl alcohol contained as an excipient in SYNACTHEN DEPOT may provoke toxic reactions and allergic reactions especially in children below 3 years old (see CONTRAINDICATIONS and PRECAUTIONS)

Post-Market Adverse Drug Reactions

Adverse drug reactions related to tetracosactide zinc hydroxide

The following adverse reactions have been derived from post-marketing experience via spontaneous cases reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Within each system organ class, adverse drug reactions are presented in order of decreasing seriousness.

Endocrine disorders

Adrenal haemorrhage

Immune system disorders

Hypersensitivity*

* Tetracosactide zinc hydroxide can provoke hypersensitivity reactions (see CONTRAINDICATIONS and WARNINGS), which tend to be more severe (anaphylactic shock) in patients susceptible to allergies (especially asthma). Hypersensitivity reactions may include skin reactions at the injection site, dizziness, nausea, vomiting, urticaria, pruritus, flushing, dyspnea, and angioneurotic edema or Quincke's edema.

Adverse drug reactions related to glucocorticoid and mineralocorticoid effects

The adverse drug reactions related to glucocorticoid and mineralocorticoid effects are unlikely to be observed with short-term use of SYNACTHEN DEPOT as a diagnostic tool, but may be reported when SYNACTHEN DEPOT is used in therapeutic indications.

Blood and lymphatic system disorders: Leukocytosis, prolonged ACTH may result in antibody formation.

Cardiac disorders: Cardiac failure congestive, reversible myocardial hypertrophy may occur in isolated cases in infants and small children treated over a prolonged period with high doses

Endocrine disorders: Cushing's syndrome, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, e.g. after trauma, surgery, or illness; menstruation irregular, carbohydrate tolerance decreased, hyperglycaemia, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics, hirsutism

Eye disorders: Intraocular pressure increased, glaucoma, cataract subcapsular, exophthalmoses

Gastrointestinal disorders: Pancreatitis, peptic ulcer with possible perforation and haemorrhage, oesophagitis ulcerative, abdominal distension

General disorders and administration site conditions: Hypersensitivity reactions, growth retardation (suppression of growth in children), weight increased, impaired wound healing

Infections and infestations: Abscess, infection susceptibility increased.

Investigations: Nitrogen balance negative due to protein catabolism, suppression of skin test reactions, loss of stimulatory effect

Metabolism and nutrition disorders: Hypokalaemic alkalosis, calcium deficiency, sodium retention, fluid retention, potassium loss, increased appetite

Musculoskeletal and connective tissue disorders: Aseptic necrosis of femoral and humeral heads, vertebral compression fractures, muscle atrophy (loss of muscle mass), steroid myopathy, osteoporosis, muscular weakness, pathological fracture of long bones, tendon rupture

Nervous system disorders: Convulsions, intracranial pressure increased with papilloedema usually after treatment, vertigo, headache

Psychiatric disorders: Psychic changes, mental disorders

Skin and subcutaneous tissue disorders: Skin atrophy, thin fragile skin, petechiae and ecchymosis, erythema, hyperhidrosis, acne and skin hyperpigmentation

Vascular disorders: Vasculitis necrotizing, thromboembolism, hypertension

DRUG INTERACTIONS

Drug-Drug Interactions

Valproate: Severe jaundice has been observed with concurrent use of SYNACTHEN DEPOT (tetracosactide zinc injection) and valproate in pediatric population. Their concurrent use should be avoided.

Other anticonvulsants: Concurrent use of SYNACTHEN DEPOT and other anticonvulsants (e.g. phenytoin, clonazepam, nitrazepam, phenobarbital, primidone) may increase the risk of liver damage, thus, SYNACTHEN DEPOT should be used with caution at minimum possible doses and for minimum duration for concurrent treatment.

Oral contraceptives: Endogenous and synthetic estrogens can cause an increase in total cortisol levels and therefore, it is considered appropriate to use alternative methods (e.g., salivary cortisol, free cortisol index, plasma free cortisol) for interpretation of the results of the HPA axis examination (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Diagnostic Use for the Investigation of Adrenocortical Insufficiency

One mg of SYNACTHEN DEPOT (tetracosactide zinc injection), injected intramuscularly at about 10 a.m. Plasma 11-hydroxycorticosteroids to be measured before and 4-6 hours after the injection.

Performance of Adrenal Function Tests:

1. The 30-Minute SYNACTHEN DEPOT Screening Test

Preparation:

The subject need not be fasted. The procedure should be started at about 10:00 a.m. and can be performed as an out-patient procedure.

Procedure:

- i. A 5-7 mL blood sample is taken for determination of plasma cortisol levels at time 0. This will serve as a base against which to compare later values.
- ii. 1 mg of SYNACTHEN DEPOT is given by intramuscular injection immediately after the blood sample has been taken.
- iii. A further 5-7 mL blood sample is taken exactly 30 minutes after the injection.

NOTE: Some clinicians take an additional sample 45-60 minutes after the injection (in case the 30- minute sample is lost or the assay is invalid for any reason).

Interpretation of Results:

In normal subjects the plasma cortisol level at 30 minutes reaches at least 20 µg/100 mL (0.55 µmol/L) with an increment which exceeds 7 µg/100 mL (0.19 µmol/L).

NOTE: This simple procedure should be used only for screening purposes with any abnormal results requiring confirmation by more prolonged ACTH stimulation. However, a normal response does exclude primary adrenocortical insufficiency, and may also be of value in the serial assessment of adrenocortical function in patients who are, or were, receiving corticosteroid therapy.

2. The 5-Hour SYNACTHEN DEPOT Test

Preparation:

The subject need not be fasted. The procedure should be started at about 10:00 a.m., at least 30 minutes after the insertion of an indwelling catheter.

Procedure:

- i. A 5-7 mL blood sample is taken for determination of plasma cortisol levels at time 0. This will serve as a base against which to compare later values.
- ii. 1 mg of SYNACTHEN DEPOT is given by intramuscular injection immediately after the blood sample has been taken.
- iii. Further samples are taken after 0.5, 1, 2, 3, 4 and 5 hours for plasma cortisol assay. This assay of several samples avoids a single, possibly inaccurate result which might lead to an erroneous conclusion.

NOTE: The amount of SYNACTHEN DEPOT used exceeds the amount required to induce a maximum adrenocortical response, ensuring an accurate assessment of the reserve capacity of the adrenal cortex.

Interpretation of Results:

In normal subjects, plasma cortisol levels more than double in the first hour, and then rise more slowly. After five hours normal values lie within the range of 37 to 66 µg/100 mL (1.02 - 1.82 µmol/L). All the plasma samples should be stored in a refrigerator until plasma cortisol level estimation.

3. The 3-Day SYNACTHEN DEPOT Test

Preparation:

For Procedure A, hospitalization is not required, nor does the patient need to be fasted. Admission to hospital is usually required for Procedure B, however, the patient can eat a normal diet and remain ambulant during his in-patient stay.

Procedure A:

A 30-minute SYNACTHEN DEPOT test (see section on 30-Minute SYNACTHEN DEPOT Test) is performed at 9:00 a.m. on day 1. The patient then receives 1 mg of SYNACTHEN DEPOT injected intramuscularly on days 2 and 3. On day 4 a second 30-minute SYNACTHEN DEPOT test is performed at 10:00 a.m.

Procedure B:

Urinary cortisol levels are determined on complete 24-hour collections for 5 consecutive days. The first two days serve as a control period. Starting on day 3 the patient is given, once daily, intramuscular injections of 1 mg SYNACTHEN DEPOT.

Day 1	Day 2	Day 3	Day 4	Day 5
Daily Urinary Cortisol Determinations				
1 mg I.M. daily SYNACTHEN DEPOT at 9:30 a.m.				

Interpretation of Results:

NOTE: Prolonged ACTH stimulation tests offer advantages over the shorter tests only in differentiating between primary and secondary adrenocortical insufficiency. No response is found in patients with the primary type (Addison's disease) whereas, with prolonged stimulation, in the great majority of patients there is a marked but delayed corticosteroid response in secondary adrenal atrophy.

Procedure A provides this information, i.e. a marked improvement in the second 30-minute SYNACTHEN DEPOT test is consistent with secondary adrenocortical insufficiency whereas no improvement is found in the primary type. As concerns procedure B, in normal subjects, urinary cortisol excretion at least doubles on the first day of SYNACTHEN DEPOT stimulation (i.e. day 3) and continues to increase during the remainder of the test.

Therapeutic Use

In general, the correct dose is the smallest one given at the longest possible interval necessary to produce control of the clinical disorder.

The average dose is 0.5 - 1 mg I.M. twice a week, tailoring the dose according to the individual requirements. In acute cases, or after prolonged steroid therapy, 1 mg I.M. daily for three days. However, the interval should be extended as soon as an adequate response is obtained.

Once the acute manifestations have subsided or for chronic conditions, the dose should be adjusted according to the patient's needs. Some may be best maintained on a dose of 0.5 - 1 mg every 2 or 3 days while others may respond better to 2 mg at weekly, or even longer intervals.

Pediatric patients: Due to the presence of benzyl alcohol, SYNACTHEN DEPOT is contraindicated in premature babies and in neonates (less than 1 month) and is not recommended in infants and children between 1 month of age and 3 years old (see CONTRAINDICATIONS and WARNINGS).

The following dosage schedule is suggested for children:

Age	Initial Dosage	Maintenance Dosage
3 - 6 years	0.25 - 0.5 mg/day intramuscularly	0.25 - 0.5 mg every 2 - 8 days
7 - 15 years	0.25 - 1 mg/day intramuscularly	0.25 - 1 mg every 2 - 8 days

Geriatric patients: There is no information available which would necessitate dosage modification in elderly (65 years of age and above).

Transferring from Corticoids

Administer 1 mg SYNACTHEN DEPOT daily to elicit full adrenal response. At the same time withdraw the steroid gradually, reducing by a quarter the original dose on successive days. Once the steroid has been withdrawn, adjust SYNACTHEN DEPOT dosage to individual patient's requirements.

Transferring from ACTH of Animal Origin

One mg of SYNACTHEN DEPOT has approximately the same corticotropic activity as 100 international units of ACTH (as defined in the 3rd International Working Standard). This equivalence is not, however, valid for depot preparations since the effect of SYNACTHEN DEPOT lasts appreciably longer than ACTH gel and considerably longer than ACTH in carboxymethyl cellulose. To transfer a patient receiving, for example, 40 units ACTH gel daily, give 0.5 mg SYNACTHEN DEPOT I.M. instead on alternate days. The response should then be assessed and the dosage adjusted, preferably by lengthening the interval between injections.

Special Populations

Renal impairment: No studies have been performed in patients with renal impairment.

Hepatic impairment: No studies have been performed in patients with hepatic impairment.

Route of Administration

The preferred route of administration is by intramuscular injection, slowly and deeply into the gluteal region.

The ampoules should be slightly shaken until the suspension shows a uniform appearance.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Edema, hypertension or signs of excessive adrenocortical activity (Cushings's syndrome) during therapy usually indicate overdosage. In such cases the dosage should be reduced, frequency of administration decreased (i.e. to 5-7 days), or the drug withdrawn according to the severity of the condition.

There is no known antidote for corticotropin. Toxic effects should be treated symptomatically.

For management of a suspected drug overdose contact your regional Poison Control Center.

PHARMACOLOGY

Animal Pharmacology:

Synacthen was found in Sayers' test, as well as other tests, to display potent ACTH activity of 106 ± 14 IU/mg.

Following hypophysectomy, the weight of the adrenals steadily diminishes. Treatment with SYNACTHEN DEPOT (tetracosactide zinc injection), on the other hand, leads to a dose-dependent increase in the weight of the adrenals in hypophysectomised rats. The protracted effect of SYNACTHEN DEPOT also has been demonstrated by reference to the decrease in the weight of the thymus which it produces, a decrease brought about by the prolonged thymolytic action of the adrenocortical hormones secreted in response to the stimulus provided by SYNACTHEN DEPOT.

Human Pharmacology:

The effect of a single intramuscular injection of aqueous SYNACTHEN is short-lived, lasting about 90 minutes. In SYNACTHEN DEPOT the active substance is present in the form of a tetracosactide/zinc complex insoluble in water, i.e. suspension of zinc salts on which the tetracosactide is precipitated. For every 1 mg tetracosactide the preparation contains 2.5 mg zinc²⁺. This pharmaceutical formulation guarantees protracted release of the active substance at the site of injection. It also prevents, or at least retards, breakdown of the active substance by tissue enzymes.

Under physiological conditions the plasma cortisol level varies between 5 and 20 µg/100 mL (0.14 - 0.55 µmol/L), the highest values being recorded early in the morning. Following an intramuscular injection of 1 mg of SYNACTHEN DEPOT, the plasma cortisol concentration rises by 20 to 40 µg/100 mL (0.55 - 1.10 µmol/L), the extent of the rise depending on the initial level. The highest values are recorded during the first 4 to 12 hours after the injection. The plasma cortisol does not decline to base-line values until after 24 to 36 hours.

The dose-response curves for SYNACTHEN DEPOT suggest that the major factor influencing the duration of action is total dosage. An increase from 0.5 to 1 mg has an effect in increasing the initial response at 3 1/2 hours. Increasing the dose from 1 to 2 mg does not provoke a greater response, but sustains the enhanced plasma 11-OHCS levels from the evening of the first day throughout the second day. Comparing the effect of intramuscular injection with subcutaneous injection at a dose of 1 mg the pattern of response is almost identical. After 1 mg of SYNACTHEN DEPOT I.M., the cortisol levels increases and the highest values are recorded during the first 4 to 8 hours after the injection. The plasma corticosteroid response was maintained for up to 12 hours and return to basal levels after around 36-48 hours.

The adrenocorticotropin action of SYNACTHEN DEPOT has been compared in two doses (1 and 2 mg) with 80 units of a gelatin preparation of natural corticotropin. In terms of maximum plasma cortisol concentrations attained, 1 mg of SYNACTHEN DEPOT was approximately equivalent to 80 units of corticotropin gel, both doses stimulating the adrenal glands maximally, but the gel must be given twice daily and SYNACTHEN DEPOT once daily to maintain stimulation. Mean plasma

cortisol levels had returned to normal by 24 hours after the corticotropin gel and by 48 hours after both doses of SYNACTHEN DEPOT.

While the growth hormone release is inhibited by the prolonged administration of corticosteroids, it is not affected by long-term corticotropin therapy.

The effect of long-term treatment with SYNACTHEN DEPOT on the hypothalamic-pituitary-adrenal axis was assessed by the following tests: nyctohemeral variation in plasma corticosteroids, insulin-induced hypoglycemia, lysine- vasopressin and intramuscular depot tetracosactide. Both plasma immuno-reactive ACTH and fluorogenic corticosteroids were measured to analyze the hypothalamic-pituitary-adrenal response in terms of the pituitary as well as the adrenal components. No suppression of hypothalamic-pituitary-adrenal function took place. Increasing doses of SYNACTHEN DEPOT does not increase the pharmacodynamics response, but it increases the duration of action.

Pharmacokinetics

Absorption

Adsorption of tetracosactide zinc hydroxide to zinc phosphate ensures sustained release of the active substance from the intramuscular injection site. Free tetracosactide zinc hydroxide is rapidly absorbed from the I.M. injection site. After an injection of 1 mg SYNACTHEN DEPOT I.M., the radioimmunologically determined plasma concentrations of tetracosactide zinc hydroxide range between 200 and 300 pg/mL and are maintained for 12 hours.

Distribution

Corticotropin is rapidly distributed and concentrated in the adrenals and kidneys, which lead to rapid decrease in its plasma levels. There is no evidence of binding of ACTH to any particular plasma protein. Tetracosactide zinc hydroxide has an apparent distribution volume averaging about 43% of body weight.

Metabolism

In serum, tetracosactide zinc hydroxide is rapidly degraded by enzymatic hydrolysis, first to inactive oligopeptides, then to free amino acids. The plasma half-life of tetracosactide zinc hydroxide in control subjects was found to have a mean value of 7 minutes.

Elimination

Following an intravenous dose of ¹³¹I-labelled beta¹⁻²⁴-corticotrophin, 95 to 100% of the radioactivity is excreted in the urine within 24 hours.

STABILITY AND STORAGE RECOMMENDATIONS

Store in a refrigerator (2 - 8°C); protect from light.

Store in the original package or keep the ampoules in the outer carton.
SYNACTHEN DEPOT must be kept out of sight and reach of children.

AVAILABILITY OF DOSAGE FORMS

SYNACTHEN DEPOT (tetracosactide zinc injection) 1 mg/mL: Each 1 mL ampoule of milky-white suspension for intramuscular injection contains 1 mg tetracosactide as zinc hydroxide complex. Available in cartons of 1 ampoule.

SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance:

H-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-OH

Tetracosactide Zinc complex

Chemical Name: β^{1-24} -corticotroph in (tetracosactide)

Molecular Formula: $[C_{136}H_{210}N_{40}O_{31}S]Zn$ complex

Molecular Weight: 2933.5

Description: White to pale yellow, flocculent, hygroscopic powder (lyophilisate) containing 6 molecules of acetic acid (bound to the basic peptide group), and varying amounts of water.

Solubility: Freely soluble in water, dilute acids and dilute alkalis, practically insoluble in non-polar solvents.

Composition:

SYNACTHEN DEPOT (tetracosactide zinc injection) 1 mg/mL ampoule: Each mL of sterile suspension contains the medicinal ingredient tetracosactide (1 mg) absorbed on amorphous zinc hydroxide-phosphate precipitate forming a water insoluble complex and the following non-medicinal ingredients: benzyl alcohol (10 mg), sodium chloride, sodium hydroxide (to adjust pH), sodium phosphate, and sterile water for injection (1 mL). Approximately 2.5 mg of Zn^{2+} is present per mL.

CLINICAL TRIALS

No recent clinical trial was conducted with SYNACTHEN DEPOT.

TOXICOLOGY

Non-clinical safety data

No studies have been performed to evaluate the mutagenic or carcinogenic potential of tetracosactide zinc hydroxide. No standard animal studies on fertility and reproduction toxicity have been performed with tetracosactide zinc hydroxide.

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PART III: CONSUMER INFORMATION

PrSYNACTHEN® DEPOT
Tetracosactide Zinc Injection, Mfr. Std.
(also known as cosyntropin injection)
1mg/ml tetracosactide

This leaflet is part III of a three-part "Product Monograph" published when SYNACTHEN DEPOT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SYNACTHEN DEPOT. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

SYNACTHEN DEPOT is used:

- in the treatment of certain conditions that are responsive to corticoids, and
- in the test to find out if the adrenal glands, small glands next to the kidneys, are working as well as they should.

What it does:

SYNACTHEN DEPOT belongs to a group of medicines called pituitary hormones and analogues.

SYNACTHEN DEPOT works by stimulating the adrenal glands to increase the production of natural "steroid" hormones.

When it should not be used:

This product should be given under medical supervision.

You should not be given SYNACTHEN DEPOT:

- **In premature babies and neonates (less than one month)**
- If you are allergic (hypersensitive) to tetracosactide (also known as cosyntropin), or a corticotrophin (ACTH), or any of the other ingredients of SYNACTHEN DEPOT listed under the heading "What the important nonmedicinal ingredients are;"
- If you have any untreated infectious disease.
- If you have an acute mental illness (acute psychosis).
- If you have or have had a duodenal or stomach ulcer.
- If you have a heart disease.
- If you have Cushing's syndrome, a condition of the adrenal glands causing weight gain, rounded face and high blood pressure.
- If your adrenal glands not working properly (adrenocortical insufficiency, or adrenogenital syndrome)

Do not use SYNACTHEN DEPOT in premature babies and children up to 3 years old. Since SYNACTHEN DEPOT contains benzyl alcohol as a preservative which can cause Gasping Syndrome and may result in death.

Do not use SYNACTHEN DEPOT to treat asthma or other allergic conditions as this may result in anaphylactic reactions (very serious allergic reactions.)

If any of these conditions apply to you, tell your doctor as you should not be treated with SYNACTHEN DEPOT.

What the medicinal ingredient is:

Tetracosactide (also known as cosyntropin)

What the important nonmedicinal ingredients are:

Benzyl alcohol (10 mg), sodium chloride, sodium hydroxide, sodium phosphate, sterile water for injection.

What dosage forms it comes in:

SYNACTHEN DEPOT is supplied as a suspension in a 1 mL ampoule for injection into a muscle (intramuscular injection). One 1 mL ampoule contains 1 mg of tetracosactide in the form of a tetracosactide/zinc complex.

WARNINGS AND PRECAUTIONS

SYNACTHEN DEPOT is not recommended for use in children less than 3 years old, since it contains benzyl alcohol, which can cause toxic reactions and allergic reactions (gasping syndrome). SYNACTHEN DEPOT can cause salt and water retention; you may need a low-salt diet during the treatment.

BEFORE you use SYNACTHEN DEPOT talk to your doctor or pharmacist if you have any of the following conditions:

- underactive thyroid gland (hypothyroidism);
- severe liver disease (cirrhosis);
- kidney problems;
- high blood pressure;
- inflammation of the bowel (e.g. ulcerative colitis or diverticulitis);
- blood clotting problems (thromboembolism);
- thinning of the bones (osteoporosis);
- extreme muscle weakness (myasthenia gravis);
- pregnancy or breast-feeding;

You should also tell your doctor if you are going to have a surgery or to receive a vaccine.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These include the following medicines:

- medicines to treat seizure such as valproate, phenytoin, clonazepam, primidone, phenobarbital;
- hormonal birth control pills.

PROPER USE OF THIS MEDICATION

Usual dose:

Adult:

Starting dose: 1 mg is given once daily as an injection into a muscle.

Maintenance dose: 0.5 mg to 1 mg twice a week depending on how you respond to the treatment.

The treatment should be stopped gradually to help maintain the normal function of adrenal glands.

For diagnostic test use: 1 mg is given as a single injection into a muscle, before one or more blood samples are taken. These blood samples will show whether your adrenal glands are functioning as well as they should.

Children:

The starting dose for children depends on the age of the child.

3 to 6 years old:

Starting dose: 0.25mg to 0.5 mg is given once daily as an injection in a muscle.

Maintenance dose is 0.25mg to 0.5mg every 2-8 days depending on how the child responds to the treatment.

7 to 15 years old:

Starting dose: 0.25mg to 1 mg is given once daily as an injection in a muscle.

Maintenance dose is 0.25mg to 1 mg every 2-8 days depending on how the child responds to the treatment.

Overdose:

In case of a suspected drug overdose, contact your doctor, or nurse, or regional Poison Control Centre immediately, even if there are no symptoms..

Missed Dose:

If you miss your scheduled dose, call your doctor or nurse immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

SYNACTHEN DEPOT may cause the following side effects:

- **Endocrine disorders:** menstrual (period) problems, Cushings' syndrome (a condition of the adrenal glands causing weight gain, rounded face and high blood pressure), dysfunction of the adrenal glands (adrenocortical problem), increased blood sugar levels, increased body and facial hair.
- **Fluid and metabolic disturbances:** low calcium level in the blood (hypocalcaemia), low potassium level in the blood (hypokalaemia), high sodium level in the blood (hypernatraemia), swelling of hands, ankles or feet (fluid build-up in the body).
- **Neurological disorders:** mood changes, fits, headache, dizziness.
- **Ophthalmic disorders:** decreased or blurred vision, glaucoma (a condition in which the pressure of fluid in the eye is high), exophthalmus (protruding eyeballs).
- **Cardiac and vascular disorders:** high blood pressure, heart

disease involving shortness of breath, swelling of the feet or legs due to fluid build-up in the body (oedema due to heart failure), reversible enlargement of the heart muscle, blockage of a blood vessel by a clot (thromboembolism), necrotising vasculitis.

- **Gastrointestinal disorders:** ulcer in stomach or duodenum, inflammation of the pancreas (pancreatitis), inflammation of the oesophagus (food pipe), stomach or abdominal pain or discomfort.
- **Skin disorders:** allergic reaction (see above also section "Some effects could be serious"), thinning of the skin, red or purple flat, pinhead spots under the skin, bruising, redness of the skin, acne.
- **Muscle and bone disorders:** muscle cramps or pain, muscle weakness, thinning of the bones (osteoporosis), destruction of bone tissue (aseptic necrosis of femoral and humeral heads), tendon rupture.
- **Others:** breathlessness, increased susceptibility to infection, excessive sweating, weight gain, growth retardation in children, increased white blood cells.

If any of these side effects persist or are troublesome, **tell your doctor.**

If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Unknown Frequency	If you have an allergic reaction. Symptoms of an allergic reaction may include redness or pain at the injection site, rash, itching, hives or flushing,			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Unknown Frequency	dizziness, nausea or vomiting, difficulty breathing, swelling of the face, lips, tongue or other parts of the body			✓
	If you are bleeding of the adrenal gland, a small gland above the kidneys. Symptoms of bleeding of the adrenal gland are sudden acute abdominal and flank pain.			✓

This is not a complete list of side effects. For any unexpected effects while taking SYNACTHEN DEPOT, contact your doctor or pharmacist.

HOW TO STORE IT

If you are storing SYNACTHEN DEPOT at home, keep it in the refrigerator (2-8°C).

Do not use after the expiry date shown on the box.

Store in the original package.

Keep out of the sight and reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Valeo Pharma Inc., at:

Toll-free telephone: 1-855-694-0151

Or by written request at: 16667 Boul. Hymus
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Or by e-mail at: info@valeopharma.com

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