Prescribing Information

NOVARTIS

SYNACTHEN® DEPOT 1 mg/mL

(tetracosactide hexaacetate)

Suspension for Injection

1. Trade name

SYNACTHEN® DEPOT 1 mg/mL, suspension for injection.

2. Description and composition

Pharmaceutical form

A milky-white, suspension for intramuscular injection in a 1 mL ampoule.

Active substance

1 mg tetracosactide (beta$^{1\text{-}24}$-corticotrophin) adsorbed to zinc phosphate per ampoule (as hexaacetate).

Active moiety

Tetracosactide (beta$^{1\text{-}24}$-corticotrophin)

Excipients

One ampoule of Synacthen Depot 1 mg/1 mL contains the following excipients: zinc chloride anhydrous pure, benzylalcohol (10 mg), sodium chloride, disodium hydrogen phosphate dihydrate, water for injections.

3. Indications

Collagen diseases, neurological diseases, chronic skin disorders.

4. Dosage and administration

Dosage

Therapeutic use

Treatment is initiated with daily doses of Synacthen Depot and continued with intermittent doses after about 3 days.

Adults

The initial dose is 1 mg daily administered intramuscularly; in acute cases and in oncological indications, treatment can be started with 1 mg every 12 hours. Once the acute manifestations have subsided, the usual dosage is 1 mg every 2 to 3 days; in patients who respond well, the dosage may be reduced to as little as 0.5 mg every 2 to 3 days or 1 mg weekly.

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.

Pediatric patients

Due to the presence of benzylalcohol, Synacthen Depot is contraindicated in premature babies and in neonates (less than 1 month) (see also section 5 Contraindications and section 6 Warnings and precautions).

1 month to less than 2 years: Initially 0.25 mg daily administered intramuscularly; the maintenance dose is 0.25 mg every 2 to 8 days.

2 to less than 5 years: Initially 0.25 to 0.5 mg daily administered intramuscularly; the maintenance dose is 0.25 to 0.5 mg every 2 to 8 days.

5 to less than 12 years: Initially 0.25 to 1 mg daily administered intramuscularly; the maintenance dose is 0.25 to 1 mg every 2 to 8 days.

Geriatric patients

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

Method of administration

The ampoule should be shaken before use and the injection is to be given intramuscularly (see Instructions for use and handling in section 14 Pharmaceutical information).

5. Contraindications

- Known hypersensitivity to tetracosactide and/or ACTH or to any of the excipients.
- Synacthen Depot must not be used to treat asthma or other allergic conditions due to the increased risk of anaphylactic reactions (see also section 6 Warnings and precautions).
- Premature babies and neonates (less than 1 month), due to the presence of benzylalcohol (see also section 4 Dosage and administration).
- Acute psychosis.
- Infectious diseases.
- Peptic ulcer.
- Refractory heart failure.
- Cushing's syndrome.
- Treatment of primary adrenocortical insufficiency.
- Adrenogenital syndrome.

6. Warnings and precautions

Synacthen Depot should only be administered under medical supervision.

Synacthen Depot should not be administered intravenously.

Special warnings and precautions for use relevant to tetracosactide

- Hypersensitivity reactions (also see section 5 Contraindications)

Patients who are also susceptible to allergies (especially asthma) should not be treated with Synacthen Depot unless other therapeutic measures have failed to elicit the desired response and the condition is severe enough to warrant such medication.

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 local or systemic hypersensitivity reactions occur, during or after an injection (e.g. marked erythema and pain at the injection site, urticaria, pruritus, flushing, severe malaise, or dyspnoea), treatment with tetracosactide must be discontinued and any use of ACTH preparations avoided in the future.

When hypersensitivity reactions occur, they tend to set in within 30 minutes after the injection. The patient should therefore be kept under observation during this time. Adrenaline (0.4 to 1 mL of a 1 mg/mL solution i.m. or 0.1 to 0.2 mL of a 1 mg/mL solution in 10 mL physiological saline **slowly** i.v.) and corticosteroids i.v. in large doses, repeated if necessary, should be given immediately in the event of a serious anaphylactic reaction.

Special warnings and precautions for use relevant to glucocorticoid and mineralocorticoid effects

Salt and water retention in response to Synacthen Depot can often be avoided or eliminated by prescribing a low-salt diet. During prolonged treatment, potassium substitution may occasionally be required.

The effect of tetracosactide therapy may be increased in patients with hypothyroidism or cirrhosis of the liver.

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

Psychological disturbances may occur under treatment with tetracosactide (e.g. euphoria, insomnia, mood swings, personality changes and severe depression, or even frank psychotic manifestations). Existing emotional instability or psychotic tendencies may be aggravated.

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

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.

Synacthen Depot should not be used in the presence of active infectious or systemic diseases, when the use of live vaccine is contemplated or in the presence of a reduced immune response, unless adequate disease-specific therapy is being given.

Live virus immunization procedures must not be undertaken during treatment with Synacthen because of the decrease in antibody response.

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.

Echocardiography should be performed regularly in infants and small children since reversible cardiac hypertrophy may occur during long-term treatment with high doses (see also section 7 Adverse drug reactions).

If Synacthen Depot is used in any of the following conditions, the risks of treatment should be weighed against the possible benefits: ulcerative colitis, diverticulitis, recent intestinal anastomosis, renal insufficiency, hypertension, predisposition to thromboembolism, osteoporosis, myasthenia gravis.

In patients who suffer an injury or undergo surgery during or within one year after treatment, the associated stress should be managed by an increase in or resumption of treatment with Synacthen Depot. Additional use of rapidly acting corticosteroids may be required. Use the lowest effective dose to control the condition under treatment. If the dose has to be reduced, this should be done gradually. Relative insufficiency of the pituitary-adrenal axis is induced by prolonged administration, and may persist for several months after stopping treatment, so appropriate adrenocortical therapy should be considered.

7. Adverse drug reactions

Adverse drug reactions may be related to tetracosactide, to the presence of benzylalcohol or to the stimulation of glucocorticoids and mineralocorticoid secretion during the use of Synacthen Depot.

Adverse drug reactions related to tetracosactide

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 which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 7-1 Adverse drug reactions from spontaneous reports and literature (frequency not known) related to tetracosactide

Immune system disorders
Hypersenstivity*
Endocrine disorders
Adrenal haemorrhage

* Tetracosactide can provoke hypersensitivity reactions, 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, malaise, dyspnoea, and angioneurotic oedema or Quincke's oedema (see also section 6 Warnings and precautions).

Adverse drug reactions related to benzylalcohol

The benzylalcohol contained as an excipient in Synacthen Depot may provoke toxic reactions and allergic reactions in children below 3 years old (see also section 5 Contraindications and section 6 Warnings and precautions).

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 (see Table 7-2).

Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known) related to glucocorticoid and mineralocorticoid effects

Infections and infestations
Abscess, infection susceptibility increased
Blood and lymphatic system disorders
Leukocytosis
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, hirsutism
Metabolism and nutrition disorders
Hypokalaemia, calcium deficiency, sodium retention, fluid retention, increased appetite
Psychiatric disorders
Mental disorder[1)]
Nervous system disorders
Convulsions, benign intracranial pressure increased with papilloedema, usually after treatment; vertigo, headache
Eye disorders
Intraocular pressure increased, glaucoma, cataract subcapsular, exophthalmoses
Cardiac disorders
Cardiac failure congestive, Reversible cardiac hypertrophy may occur in isolated cases in infants and small children treated over a prolonged period with high doses
Vascular disorders
Vasculitis necrotising, thromboembolism, hypertension
Gastrointestinal disorders
Pancreatitis, peptic ulcer with possible perforation and haemorrhage, oesophagitis ulcerative, abdominal distension
Skin and subcutaneous tissue disorders
Skin atrophy, petechiae and ecchymosis, erythema, hyperhidrosis, acne and skin hyperpigmentation
Musculoskeletal and connective tissue disorders
Aseptic necrosis of femoral and humeral heads, spinal compression fractures, muscle atrophy, myopathy, osteoporosis, muscular weakness, pathological fracture of long bones, tendon rupture
General disorders and administration site conditions
Hypersensitivity reactions[2)] , growth retardation, weight increased, impaired healing
Investigations
Nitrogen balance negative due to protein catabolism, suppression of skin test reactions

[1)] also see section 6 Warnings and precautions

[2)] also see section 6 Warnings and precautions and section 7 Adverse drug reactions (paragraph "Adverse drug reactions related to tetracosactide")

8. Interactions

Observed interactions resulting in concomitant use not being recommended
Severe jaundice has been observed for concurrent use of Synacthen and valproate in pediatric population. Their concurrent use should be avoided.

Observed interactions to be considered
Concurrent use of Synacthen and other anticonvulsants (e.g. phenytoin, clonazepam, nitrazepam, phenobarbital, primidone) may increase the risk of liver damage; thus, Synacthen should be used with caution at minimum possible doses and for minimum duration for concurrent treatment.

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 also section 6 Warnings and precautions).

Anticipated interactions to be considered
Since Synacthen Depot increases the adrenocortical production of glucocorticoids and mineralocorticoids, drug interactions of the type seen with these corticosteroids may occur.

Patients already receiving medication for diabetes mellitus or for moderate to severe hypertension must have their dosage adjusted if treatment with Synacthen Depot is started.

9. Women of child-bearing potential, pregnancy, breast-feeding and fertility

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

Pregnancy
There is a limited amount of data on the use of Synacthen in pregnant patients. Data from animal studies are insufficient with respect to reproductive toxicity/teratogenicity. Synacthen should be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus.

Breast-feeding
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 is administered to a breast-feeding woman.

Fertility
There is no data available.

10. Overdosage

Signs and symptoms
If signs of water retention (increase in body weight) or excessive adrenocortical activity (Cushing's syndrome) appear, Synacthen Depot should be withdrawn for a while or given in lower doses, either by halving the dose or by prolonging the interval between injections, e.g. to 5 to 7 days.

Management
There is no known antidote. Symptomatic treatment is indicated.

11. Clinical pharmacology

Pharmacotherapeutic group
Anterior pituitary lobe hormones and analogues – ACTH

ATC code
H01AA02

Mechanism of action (MOA) / Pharmacodynamics (PD)
Tetracosactide consists of the first 24 amino acids occurring in the natural adrenocorticotrophic hormone (ACTH). Like ACTH, it stimulates adrenocortical production of glucocorticoids and mineralocorticoids, and to a lesser extent androgens, which explains its therapeutic effect in conditions responsive to glucocorticoid treatment. However, its pharmacological activity is not comparable to that of corticosteroids, because under ACTH treatment - in contrast to treatment with a single glucocorticoid - the tissues are exposed to a physiological spectrum of corticosteroids. Increasing doses of Synacthen Depot does not increase the pharmacodynamic response, however increases the duration of action. Prolonged use of Synacthen is reported to have minimal suppression of hypothalamic-pituitary-adrenal axis as compared to long-term corticosteroids.

The site of action of ACTH is the plasma membrane of the adrenocortical cells, where it binds to a specific receptor. The hormone-receptor complex activates adenylate cyclase, stimulating the production of cyclic AMP (adenosine monophosphate) and so promoting the synthesis of pregnenolone from cholesterol. From pregnenolone the various corticosteroids are produced via different enzymatic pathways.

After 1 mg of Synacthen Depot i.m., the cortisol levels increase and the highest values are recorded during the first 8 to 12 hours after the injection. The increased cortisol levels are maintained up to 24 h and return to basal levels after around 36-48 h.

Pharmacokinetics (PK)
Absorption
Adsorption of tetracosactide to zinc phosphate ensures sustained release of the active substance from the intramuscular injection site. Free tetracosactide 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 range between 200 and 300 pg/mL and are maintained for 12 hours.

Distribution
Tetracosactide 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 has an apparent distribution volume of about 0.4 L/kg.

Tetracosactide apparently does not cross the placenta and it is unknown whether tetracosactide passes into the breast milk.

Biotransformation / Metabolism
In serum, tetracosactide is rapidly degraded by enzymatic hydrolysis, first to inactive oligopeptides, then to free amino acids. Its rapid elimination from plasma is probably attributable not so much to this relatively slow process as to the fact that the active substance is rapidly concentrated in the adrenals and kidneys.

Elimination
Following an intravenous dose of ^{131}I-labelled beta$^{1\text{-}24}$-corticotrophin, 95 to 100% of the radioactivity is excreted in the urine within 24 hours.

12. Clinical studies

No recent clinical trial was conducted with Synacthen Depot.

13. Non-clinical safety data

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

14. Pharmaceutical information

Incompatibilities
Not applicable.

Special precautions for storage
Store in the original package or keep the ampoules in the outer carton. (Protect from light).

Store in a refrigerator (at 2°C to 8°C).

Synacthen Depot must be kept out of reach and sight of children.

Instructions for use and handling
The ampoule should be shaken before use.

Registration Number
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For Novartis Pharma AG, Basel, Switzerland

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