

NEW ZEALAND DATA SHEET

SYNACTHEN[®] **Tetracosactide Hexaacetate** **250 micrograms/mL Solution for Injection or Infusion**

Trade Name

SYNACTHEN i.m./i.v.[®] 250 micrograms/mL solution for injection or infusion

Description and composition

Pharmaceutical form(s)

A clear colourless aqueous solution for intramuscular injection or intravenous infusion in a 1 mL ampoule.

Active substance

250 micrograms tetracosactide (beta¹⁻²⁴-corticotrophin) per ampoule (as hexaacetate).

Active moiety

Tetracosactide (beta¹⁻²⁴-corticotrophin).

Excipients

One ampoule of Synacthen i.m./i.v. 250 micrograms/mL contains: acetic acid, sodium acetate, sodium chloride, water for injections.

Information might differ in some countries.

Indications

Diagnostic use:

For the investigation of adrenocortical insufficiency.

Therapeutic use:

Alternative to Synacthen Depot in the following indications where i.v. injection or infusion of tetracosactide is preferable to i.m. injection.

Neurological diseases

Acute exacerbations in patients suffering from multiple sclerosis.

West syndrome (Infantile myoclonic encephalopathy with hypsarrhythmia).

Rheumatic diseases

Short-term therapy in conditions for which glucocorticoids are normally indicated; in patients showing poor gastrointestinal tolerance of oral glucocorticoids; where glucocorticoids in normal doses have not elicited an adequate response.

Skin diseases

Long-term treatment of skin disorders responsive to glucocorticoids - e.g. pemphigus, severe chronic eczema, erythrodermal or pustular forms of psoriasis.

Diseases of the gastrointestinal tract

Ulcerative colitis; regional enteritis.

Oncology

As adjuvant therapy to improve the tolerability of chemotherapy.

Dosage and administration

Diagnostic use:

30-minute Synacthen test: Plasma cortisol is measured immediately before and exactly 30 minutes after an injection of 250 micrograms Synacthen i.m. or i.v. If plasma cortisol increases by >200 nmol/L (70 micrograms/L), i.e. if the value 30 minutes after injection is >500 nmol/L (180 micrograms/L), adrenocortical function is regarded as normal. All the plasma samples should be stored in a refrigerator kept until plasma cortisol level estimation.

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.

Geriatric patients

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

If the 30-minute test gives inconclusive results, or if the aim is to determine the functional reserve of the adrenal cortex, the 5-hour test may be performed using Synacthen Depot (see Synacthen Depot Data Sheet).

Therapeutic use:

For therapeutic indications, Synacthen can be administered as an i.v. injection or as an infusion in glucose solution (5% or 12.5%) or NaCl (0.9%) (see also Pharmaceutical information).

Contraindications

- Known hypersensitivity to tetracosactide and/or ACTH or to any of the excipients.
- Synacthen must not be used to treat asthma or other allergic conditions due to the increased risk of anaphylactic reactions (also see Warnings and precautions).
- Acute psychosis.
- Infectious diseases.
- Peptic ulcer.
- Refractory heart failure.
- Cushing's syndrome.
- Treatment of primary adrenocortical insufficiency.
- Adrenogenital syndrome.

Warnings and precautions

Synacthen should only be administered under medical supervision.

Special warnings and precautions for use relevant to tetracosactide

Hypersensitivity reactions (also see Contraindications)

Patients who are also susceptible to allergies (especially asthma) should not be treated with Synacthen unless other therapeutic measures have failed to elicit the desired response and the condition is severe enough to warrant such medication. The Synacthen test should only be performed in such patients if they have not received ACTH preparations previously. The physician must be prepared to take immediate measures should an anaphylactic reaction occur after injection of Synacthen.

Before using Synacthen 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 dose if necessary, should be given immediately in the event of a serious anaphylactic reaction.

Lack of diagnostic accuracy

Post administration total plasma cortisol levels during the Synacthen 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.

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

Salt and water retention in response to Synacthen 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 should be used cautiously in patients with ocular herpes simplex owing to possible corneal perforation.

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

If Synacthen 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.

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

Provided the dosage is carefully individualised, Synacthen 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 Adverse drug reactions).

If Synacthen 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. 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.

Adverse drug reactions

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

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

<p>Immune system disorders Hypersensitivity*</p> <p>Endocrine disorders Adrenal haemorrhage</p>

* 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 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 as a diagnostic tool, but may be reported when Synacthen is used in therapeutic indications (see Table 2).

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

<p>Infections and infestations Abscess, infection susceptibility increased</p> <p>Blood and the lymphatic system disorders Leukocytosis</p> <p>Endocrine disorders Cushings'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</p> <p>Metabolism and nutrition disorders Hypokalaemia, calcium deficiency, sodium retention, fluid retention, increased appetite</p> <p>Psychiatric disorders Mental disorder¹⁾</p> <p>Nervous system disorders Convulsions, benign intracranial pressure increased with papilloedema, usually after treatment; vertigo, headache</p> <p>Eye disorders Intraocular pressure increased, glaucoma, Posterior sub capsular cataracts, exophthalmoses</p> <p>Cardiac disorders Cardiac failure congestive</p>

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 reactions²⁾, growth retardation, weight increased, impaired healing,

Investigations

Nitrogen balance negative due to protein catabolism, suppression of skin test reactions

1) also see *Warnings and precautions section*

2) also see *Warnings and precautions section and Adverse drug reactions section (paragraph "Adverse drug reactions related to tetracosactide")*

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 *Warnings and precautions*).

Anticipated interactions to be considered

Since Synacthen 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 is started.

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.

Overdosage

Signs and symptoms

If signs of water retention (increase in body weight) or excessive adrenocortical activity (Cushing's syndrome) appear, Synacthen should either be withdrawn for a while or given in lower doses.

Management

There is no known antidote. Symptomatic treatment is indicated.

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. Prolonged use of Synacthen is reported to have minimal suppression of hypothalamic-pituitary-adrenal axis as compared to long-term use of 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.

Pharmacokinetics (PK)

Absorption

Tetracosactide is rapidly absorbed from the i.m. injection site.

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

The plasma elimination half-life following i.v. injection is about 7 minutes in the first hour (first phase), about 37 minutes in the next hour (second phase), and thereafter about 3 hours (terminal phase).

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

Clinical studies

No recent clinical trial was conducted with Synacthen i.m./i.v.

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.

Pharmaceutical information

Incompatibilities

- Ringer acetate solution is not suitable for infusions.

- Only freshly prepared solutions should be used, and for stability reasons the duration of an infusion must not exceed 4 hours.
- It is not advisable to add Synacthen to blood or plasma transfusions, as it may be broken down by enzymes in the blood.

Special precautions for storage

Store in the original package or keep the ampoules in the outer carton.

Store in a refrigerator (2-8°C).

Information might differ in some countries.

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

Nature and content of container

10 1 mL colourless glass ampoules of glass type I.

Instructions for use and handling

Not applicable.

Special precautions for disposal

Not applicable.

Medicine classification

Prescription Medicine

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