NOVARTIS

Drug Regulatory Affairs

# SYNACTHEN i.m./i.v.Ò

## (tetracosactide hexaacetate)

250 micrograms/mL Solution for injection or infusion

## Basic Prescribing Information

**NOTICE**

**The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.**

**National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Prescribing Information or European SPCs) may differ in several respects, including but not limited to the characterisation of risk and benefits.**


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| Author(s): | Sandra Jullian |
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# 1 Name of the medicinal product

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

# 2 Qualitative and quantitative composition

250 micrograms tetracosactide ($ß^{1-24}$-corticotrophin) per ampoule (as hexaacetate).

For excipients, see section 6.1.

# 3 Pharmaceutical form

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

# 4 Clinical particulars

## 4.1 Therapeutic indications

- **Diagnostic use:** for the investigation of adrenocortical insufficiency.
- **Therapeutic use**: alternative to Synacthen Depot in cases where i.v. injection or infusion of tetracosactide is preferable to i.m. injection.

Unlike Synacthen Depot, Synacthen has a short duration of action and can be administered both i.m. and i.v.

## 4.2 Posology and method of 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.

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 BPI).

- **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 section 6.2*)*.

## 4.3 Contraindications

- Known hypersensitivity to tetracosactide and/or ACTH or to any of the excipients.
- Acute psychosis.
- Infectious diseases.
- Peptic ulcer.
- Refractory heart failure.
- Cushing's syndrome.

- Primary adrenocortical insufficiency.
- Adrenogenital syndrome.
- Pregnancy and breast-feeding.
- Synacthen must not be used to treat asthma or other allergic conditions due to the increased risk of anaphylactic reactions (also see section 4.4).

## 4.4 Special warnings and special precautions for use

Synacthen should only be administered under medical supervision.

### Special warnings and precautions for use relevant to tetracosactide

**Hypersensitivity reactions (also see section 4.3)**

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.

### 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.

Patients should not be vaccinated against smallpox during treatment with Synacthen. Any other immunisation procedures must be undertaken with caution 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 myocardial hypertrophy may occur during long-term treatment with high doses (also see section 4.8).

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.

## 4.5 Interaction with other medicinal products and other forms of interaction

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.

Synacthen contains an active substance that may interfere with routine drug testing in athletes.

## 4.6 Pregnancy and lactation

### Pregnancy

Synacthen is contraindicated during pregnancy.

### Lactation

Synacthen is contraindicated while breast-feeding.

## 4.7 Effects on ability to drive and use machines

Since Synacthen may have an effect on the central nervous system, patients should be very cautious when driving vehicles or usingmachines.

## 4.8 Undesirable effects

Undesirable effects may be related to tetracosactide or to the stimulation of glucocorticoids and mineralocorticoid secretion during the use of Synacthen.

### Undesirable effects related to tetracosactide

**Hypersensitivity reactions**: 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 section 4.4).

**Adrenal haemorrhage**: isolated cases have been reported with Synacthen.

### Undesirable effects related to glucocorticoid and mineralocorticoid effects

The undesirable effects 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 1).

## Table 1

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| **Infections and infestations** | Increased susceptibility to infection, abscess |
| **Blood and the lymphatic system disorders** | Leukocytosis |
| **Endocrine disorders** | Menstruation irregular, Cushings's syndrome, secondary adrenocortical and pituitary unresponsiveness. Particularly in times of stress, e.g. after trauma, surgery, or illness; decreased carbohydrate tolerance, hyperglycaemia, manifestations of latent diabetes mellitus, hirsutism |
| **Metabolism and nutrition disorders** | Increased appetite, hypokalaemia, calcium deficiency, sodium retention, fluid retention |
| **Psychiatric disorders** | Mental disorder[1)] |
| **Nervous system disorders** | Headache, vertigo, convulsions |
| | Benign intracranial pressure with papilloedema, usually after treatment |
| **Eye disorders** | Posterior sub capsular cataracts, increased intraocular pressure, glaucoma, exophthalmoses |
| **Cardiac disorders** | Cardiac failure congestive, blood pressure increase |
| | Reversible myocardial hypertrophy may occur in isolated cases in infants and small children treated over a prolonged period with high doses |
| **Vascular disorders** | Thromboembolism, necrotising vasculitis |
| **Gastrointestinal disorders** | Peptic ulcer with possible perforation and haemorrhage, pancreatitis, abdominal distension, oesophagitis ulcerative |
| **Skin and subcutaneous tissue disorders** | Skin atrophy, petechiae and ecchymosis, erythema, hyperhidrosis, acne and skin hyper pigmentation |
| **Musculoskeletal, connective tissue and bone disorders** | Osteoporosis, muscular weakness, myopathy steroid, loss of muscle mass, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones, tendon rupture |
| **General disorders and administration site conditions** | Hypersensitivity reactions[2)], weight increased, impaired healing, growth retardation |
| **Investigations** | Negative nitrogen balance due to protein catabolism, suppression of skin test reactions |

[1)] also see section 4.4

[2)] also see section 4.8 and section 4.4 (paragraph "Undesirable effects relevant to tetracosactide")

## 4.9 Overdose

### 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.

# 5 Pharmacological properties

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anterior pituitary lobe hormones and analogues – ACTH – ATC code: H01AA02.

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.

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.

## 5.2 Pharmacokinetic properties

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

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).

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.

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

## 5.3 Preclinical safety data

No studies have been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

# 6 Pharmaceutical particulars

## 6.1 List of excipients

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

## 6.2 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.

## 6.3 Shelf life

5 years.

## 6.4 Special precautions for storage

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

Store in a refrigerator (2-8°C).

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

## 6.5 Nature and content of container

1 mL colourless glass ampoules of glass type I.

## 6.6 Instructions for use and handling, and disposal

Not applicable.