

# NEW ZEALAND DATA SHEET

## **SYNACTHEN DEPOT<sup>®</sup> i.m.<sup>®</sup>** **(tetracosactide hexaacetate)** 1 mg/mL Suspension for Injection

### **Trade Name**

SYNACTHEN DEPOT i.m.<sup>®</sup> 1 mg/mL suspension for injection

### **Description and composition**

#### **Pharmaceutical form(s)**

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

#### **Active substance**

1 mg tetracosactide (beta<sup>1-24</sup>-corticotrophin) adsorbed to zinc phosphate per ampoule (as hexaacetate).

#### **Active moiety**

Tetracosactide (beta<sup>1-24</sup>-corticotrophin)

#### **Excipients**

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

Information might differ in some countries.

### **Indications**

#### **Therapeutic use:**

- **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.

**Diagnostic use for the investigation of adrenocortical insufficiency:**

A 5-hour test can be performed using Synacthen Depot when the 30-minute test with Synacthen i.m./i.v. gives inconclusive results, or if the aim is to determine the functional reserve of the adrenal cortex (see Synacthen i.m./i.v. data sheet).

## **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 Contraindications and 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).

## Diagnostic use for the investigation of adrenocortical insufficiency.

**5-hour Synacthen Depot test:** Plasma cortisol is measured immediately before and 0.5, 1, 2, 3, 4, and 5 hours after an injection of 1 mg Synacthen Depot i.m.

If adrenocortical function is normal, baseline plasma cortisol (normally >200 nmol/L) doubles in the first hour and then continues to rise slowly, as follows:

**Table 1** Hourly cortisol levels

Time	nmol/L
1 <sup>st</sup> hour	600-1250 nmol/L
2 <sup>nd</sup> hour	750-1500 nmol/L
3 <sup>rd</sup> hour	800-1550 nmol/L
4 <sup>th</sup> hour	950-1650 nmol/L
5 <sup>th</sup> hour	1000-1800 nmol/L

If plasma cortisol rises more slowly than indicated above, this may be the result of: Addison's disease; secondary adrenocortical insufficiency due to a disorder of hypothalamo-pituitary function, or overdose of corticosteroids. For further differentiation between primary and secondary adrenocortical hypofunction, a 3-day test can be performed using Synacthen Depot. All the plasma samples should be stored in a refrigerator until plasma cortisol level estimation.

## 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 Pharmaceutical information).

## 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 (also see Warnings and precautions)
- Premature babies and neonates (less than 1 month), due to the presence of benzylalcohol (see also Dosage and administration ).
- Acute psychosis
- Infectious diseases.
- Peptic ulcer.
- Refractory heart failure.
- Cushing's syndrome.
- Treatment of primary adrenocortical insufficiency.

- Adrenogenital syndrome.

## 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 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 (0.4-1 mL of a 1 mg/mL solution i.m. or 0.1 to 0.2 mL of a 1mg/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.

### 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 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.

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 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 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.

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

<b>Immune system disorders</b>
Hypersensitivity*
<b>Endocrine disorders</b>
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 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 Contraindications and 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 2).

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

<p><b>Infections and infestations</b> Abscess, infection susceptibility increased</p> <p><b>Blood and lymphatic system disorders</b> Leukocytosis</p> <p><b>Endocrine disorders</b> 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><b>Metabolism and nutrition disorders</b> Hypokalaemia, calcium deficiency, sodium retention, fluid retention, increased appetite</p> <p><b>Psychiatric disorders</b> Mental disorder<sup>1)</sup></p> <p><b>Nervous system disorders</b> Convulsions, benign intracranial pressure increased with papilloedema, usually after treatment; vertigo, headache</p> <p><b>Eye disorders</b> Intraocular pressure increased, glaucoma, cataract subcapsular, exophthalmoses</p> <p><b>Cardiac disorders</b> Cardiac failure congestive, Reversible cardiac hypertrophy may occur in isolated cases in infants and small children treated over a prolonged period with high doses</p> <p><b>Vascular disorders</b> Vasculitis necrotising, thromboembolism, hypertension</p> <p><b>Gastrointestinal disorders</b> Pancreatitis, peptic ulcer with possible perforation and haemorrhage, oesophagitis ulcerative, abdominal distension,</p> <p><b>Skin and subcutaneous tissue disorders</b> Skin atrophy, petechiae and ecchymosis, erythema, hyperhidrosis, acne and skin hyperpigmentation</p> <p><b>Musculoskeletal and connective tissue disorders</b></p>
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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<sup>2)</sup>, 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*

2. *also see Warnings and precautions and Adverse drug reactions (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 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.

## 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 breastfeeding 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 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.

## **Clinical Pharmacology**

### **Pharmacotherapeutic group**

Anterior pituitary lobe hormones and analogues – ACTH

### **ATC code**

H01AA02

### **Mechanisms 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 increases 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**

Absorption 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 <sup>131</sup>I-labelled beta<sup>24</sup>-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 depot.

## **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**

Not applicable.

### **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 Depot must be kept out of reach and sight of children.

**Nature and content of container**

1 mL colourless glass ampoules of glass type I.

**Instructions for use and handling**

The ampoule should be shaken before use.

**Medicine classification**

Prescription Medicine

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