

SUMMARY OF PRODUCT CHARACTERISTICS**1. NAME OF THE MEDICINAL PRODUCT****Synacthen Depot 1mg/ml suspension for injection****2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ampoule contains 1 mg tetracosactide (beta¹⁻²⁴-corticotrophin) (as hexaacetate) adsorbed to zinc phosphate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Milky white suspension for intramuscular injection, in a 1 ml ampoule.

4. CLINICAL PARTICULARS**4.1 Therapeutic indications**Therapeutic use:

Infantile myoclonic encephalopathy with hypsarrhythmia.

Diagnostic use for the investigation of adrenocortical insufficiency:

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

4.2 Posology and method of administrationTherapeutic use:

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

As Synacthen Depot contains benzyl alcohol it is contraindicated in premature babies and neonates (less than 1 month) and is not recommended for use in children aged under 3 years (see section 4.3 and section 4.4).

Babies (aged up to 1 year): Initially 0.25 mg daily administered intramuscularly; the maintenance dose is 0.25 mg every 2 to 8 days.

Small children: 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.

School-age children: Initially 0.25 to 1 mg daily administered intramuscularly; the maintenance dose is 0.25 to 1 mg every 2 to 8 days.

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 >70 µg/100 ml) doubles in the first hour and then continues to rise slowly, as follows:

1st hour	215-450 µg/100 ml
2nd hour	270-540 µg/100 ml
3rd hour	290-560 µg/100 ml
4th hour	340-590 µg/100 ml
5th hour	360-650 µg/100 ml

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. In the case of primary adrenocortical insufficiency, plasma cortisol levels are no more than 25 µg/100 ml, even after three injections.

4.3 Contraindications

- Known hypersensitivity to ACTH and/or tetracosactide or to any of the excipients
- Premature babies and neonates (less than 1 month), as Synacthen Depot contains benzyl alcohol (see also section 4.2 and section 4.4).
- Acute psychosis
- Infectious diseases.
- Peptic ulcer.
- Refractory heart failure.
- Cushing's syndrome.
- Primary adrenocortical insufficiency.
- Adrenogenital syndrome.
- Pregnancy and breastfeeding.
- Synacthen Depot must not be used to treat asthma or other allergic conditions due to the increased risk of anaphylactic reactions (see section 4.4).

4.4 Special warnings and precautions for use

Synacthen Depot should only be administered under medical

supervision.

Synacthen Depot should not be administered intravenously. Because Synacthen Depot contains benzyl alcohol, it is not recommended for use in babies and children aged under 3 years because it can cause toxic and allergic reactions (see also section 4.2 and section 4.3).

Special warnings and precautions for use relevant to tetracosactide Hypersensitivity reactions (see section 4.3)

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 administering Synacthen Depot the doctor must ascertain whether the patient is susceptible to allergies (especially asthma). The doctor must also establish whether the patient has been treated with ACTH preparations in the past, and if so confirm that the treatment did not trigger any hypersensitivity reaction.

If local or systemic hypersensitivity reactions occur during or after an injection (for example, marked redness and pain at the injection site, urticaria, pruritus, hot flush, severe malaise or dyspnoea), administration of tetracosactide must be discontinued and use of ACTH preparations should be avoided in the future.

When hypersensitivity reactions occur, this tends to happen within 30 minutes of the injection. It is therefore recommended that the patient be kept under observation during this time. In the event of a serious anaphylactic reaction, adrenaline should be given immediately (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.

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 a low-salt diet. During prolonged treatment, potassium replacement 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 cataract and glaucoma.

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

Synacthen Depot should be used with caution in patients with herpes simplex affecting the eyes owing to the risk of 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.

All immunisations should be performed with caution due to the reduced antibody response.

Provided the dosage is carefully adjusted to the individual, Synacthen Depot is unlikely to inhibit growth in children. Nevertheless, growth should be monitored in children undergoing long-term treatment.

Echocardiograms should be performed regularly in infants and small children since reversible myocardial hypertrophy may occur during long-term treatment with high doses (see section 4.8).

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 fast-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 Depot increases the adrenocortical production of glucocorticoids and mineralocorticoids, interactions of the type seen with corticosteroids may occur with certain drugs.

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.

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Synacthen Depot contains an active ingredient that may affect routine screening performed in athletes.

4.6 Fertility, pregnancy and lactation

Pregnancy

Synacthen Depot is contraindicated during pregnancy.

Breastfeeding

Synacthen Depot is contraindicated while breastfeeding.

4.7 Effects on ability to drive and use machines

Since Synacthen Depot can potentially affect the central nervous system, patients should be very cautious when driving or using machines.

4.8 Adverse effects

Adverse drug reactions may be related to tetracosactide, benzyl alcohol or to the stimulation of glucocorticoid and mineralocorticoid secretion during the use of Synacthen Depot.

Adverse drug reactions related to tetracosactide

Hypersensitivity reactions

Tetracosactide can trigger 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, vasomotor reactions, malaise, dyspnoea and Quincke's oedema (see section 4.4).

Adrenal haemorrhage

Isolated cases have been reported with use of Synacthen Depot.

Adverse drug reactions related to benzyl alcohol

Synacthen Depot contains benzyl alcohol as an excipient which can trigger toxic reactions and allergic reactions in children under 3 years old (see section 4.3 and section 4.4).

Adverse drug reactions related to glucocorticoid and mineralocorticoid effects

The adverse drug reactions related to glucocorticoid and mineralocorticoid effects are unlikely to occur 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 below).

<i>Infections and infestations</i>	Increased susceptibility to infection, abscess
<i>Blood and lymphatic system disorders</i>	Leukocytosis
<i>Endocrine disorders</i>	Irregular periods, Cushing's syndrome, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, e.g. after trauma, surgery or illness; reduced carbohydrate tolerance, hyperglycaemia, symptoms of latent diabetes mellitus, hirsutism
<i>Metabolism and nutrition disorders</i>	Increased appetite, hypokalaemia, calcium deficiency, sodium retention, fluid retention
<i>Psychiatric disorders</i>	Mental disorder ¹
<i>Nervous system disorders</i>	Headache, dizziness, seizures Benign intracranial pressure with papilloedema, usually after treatment
<i>Eye disorders</i>	Posterior subcapsular cataract, increased intraocular pressure, glaucoma, exophthalmus
<i>Cardiac disorders</i>	Congestive heart failure, hypertension Reversible myocardial hypertrophy may occur in isolated cases in infants and small children treated over a prolonged period with high doses
<i>Vascular disorders</i>	Thromboembolism, necrotising vasculitis

<i>Gastrointestinal disorders</i>	Peptic ulcer with possible perforation and haemorrhage, pancreatitis, abdominal distension, ulcerative oesophagitis
<i>Skin and subcutaneous tissue disorders</i>	Skin atrophy, petechiae and ecchymosis, erythema, hyperhidrosis, acne and skin hyperpigmentation
<i>Musculoskeletal and connective tissue disorders</i>	Osteoporosis, muscular weakness, steroid myopathy, muscle atrophy, spinal compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones, tendon rupture.
<i>General disorders and administration site conditions</i>	Hypersensitivity reactions ² , weight gain, impaired healing, growth retardation.
<i>Investigations</i>	Nitrogen balance negative due to protein catabolism, suppression of skin test reactions

¹ See section 4.4

² See section 4.4 and section 4.8 (paragraph 'Adverse effects related to tetracosactide').

4.9 Overdose

Signs and symptoms

If signs of water retention (weight gain) or excessive adrenocortical activity (Cushing's syndrome) appear, Synacthen Depot should be temporarily withdrawn 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

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, tetracosactide stimulates adrenocortical biosynthesis of glucocorticoids and mineralocorticoids, and to a lesser extent androgens, which explains its therapeutic effect in conditions treated with glucocorticoids. 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 all physiological corticosteroids together.

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

5.2 Pharmacokinetic properties

Adsorption of tetracosactide to zinc phosphate ensures sustained release of the active substance from the intramuscular injection site. Following 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.

The apparent volume of distribution of tetracosactide is around 0.4 l/kg.

Tetracosactide is rapidly broken down in serum by enzymatic hydrolysis, initially into inactive oligopeptides and thereafter into free amino acids.

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

5.3 Preclinical safety data

No studies have been performed to evaluate the carcinogenic or mutagenic potential of tetracosactide or any disruption of fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Zinc chloride, disodium phosphate dihydrate, sodium chloride, benzyl

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alcohol (10 mg), water for injection.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2 to 8°C). Protect from light.

6.5 Nature and contents of container

Pack of one 1 ml type I clear glass ampoule.

6.6 Special precautions for disposal and other handling

The ampoule should be shaken before use.

7. MARKETING AUTHORISATION HOLDER

Alfasigma S.p.A.
Viale Sarca, n. 223
20126 Milan (MI)
Italy

8. MARKETING AUTHORISATION NUMBER

BE050915

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

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Date of latest renewal: 12.02.2014

10. DATE OF REVISION OF THE TEXT

August 2017