Synacthen Depot 1 mg/mL, suspension for injection

Name of the medicinal product

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

Qualitative and quantitative composition

2 Description and composition
Pharmaceutical form
A milky-white, suspension for intramuscular injection in a 1 mL ampoule.

Active substance
1 mg tetracosactide (β1–24-corticotrophin) adsorbed to zinc phosphate per ampoule (as hexaacetate).

For excipients, see section List of excipients.

Active moiety
Tetracosactide (β1–24-corticotrophin)

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

Clinical particulars
Therapeutic indications

3 Indications
The drug has been used in the following indications:
Collagen diseases, neurological diseases, chronic skin disorders.

Posology and method of administration

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 daily; 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.

Children

Pediatric patients
Due to the presence of benzylalcohol, Synacthen Depot is contraindicated in premature babies and in neonates (less than 1 month) and is not recommended in children below 3 years of age (see also section 5 Contraindications and section 6 Warnings and special precautions for use).

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

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

Children of school age: 5 to less than 12 years: Initially 0.25 to 1 mg daily administered intramuscularly daily; 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 (also see also sections 4 Dosage and Administration Posology and method of administration and Special warnings and special precautions for use).
- Acute psychosis.
- Infectious diseases.
- Peptic ulcer.
- Refractory heart failure.
- Cushing’s syndrome.
- Treatment of Primary adrenocortical insufficiency.
- Adrenogenital syndrome.
- Pregnancy and breast-feeding.

6  Warnings and precautions

Due to the presence of benzylalcohol, Synacthen Depot is not recommended in infants and children up to 3 years old, as it may cause toxic reactions and allergic reactions (also see sections Posology and method of administration and Contraindications).

Special warnings and precautions for use relevant to tetracosactide

- Hypersensitivity reactions (also see section 5 Contraindications)

... 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

Patients must not be vaccinated against smallpox during treatment with Synacthen Depot. Any other live virus immunization procedures must not be undertaken during treatment with Synacthen with caution because of the decrease in antibody response.

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 also section 7 Adverse drug reactions Undesirable effects).

Interaction with other medicinal products and other forms of interaction

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.

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

Pregnancy and lactation

Pregnancy

Synacthen Depot is contraindicated during pregnancy.

Lactation

Synacthen Depot is contraindicated while breast-feeding.

Effects on ability to drive and use machines

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

7 Undesirable effects Adverse drug reactions

Undesirable effects 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.

Undesirable effects Adverse drug reactions 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 Special warnings and special precautions for use).

**Adrenal haemorrhage:** Isolated cases have been reported with Synacthen Depot.

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

<table>
<thead>
<tr>
<th>Immune system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
</tr>
<tr>
<td><strong>Endocrine disorders</strong></td>
</tr>
<tr>
<td>Adrenal haemorrhage</td>
</tr>
</tbody>
</table>

...

**Undesirable effects 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 of age (see also sections 5 Contraindications and section 6 Special warnings and special precautions for use).

**Undesirable effects 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>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Increased susceptibility to infection, abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system-disorders</td>
<td>Leukocytosis</td>
</tr>
<tr>
<td>Endocrine-disorders</td>
<td>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</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Increased appetite, hypokalaemia, calcium deficiency, sodium retention, fluid retention</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Mental disorder 1)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, vertigo, convulsions</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Benign intracranial pressure with papilloedema, usually after treatment</td>
</tr>
<tr>
<td></td>
<td>Posterior sub-capsular cataracts, increased intraocular pressure, glaucoma, exophthalmoses</td>
</tr>
</tbody>
</table>
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, weight increased, impaired healing, growth retardation

Investigations
Negative nitrogen balance due to protein catabolism, suppression of skin test reactions

1) also see section Special warnings and special precautions for use
2) also see section Special warnings and special precautions for use and section Undesirable effects (paragraph Undesirable effects related to tetracosactide)

Table 7.2 Adverse drug reactions from spontaneous reports and literature (frequency not known) related to glucocorticoid and mineralocorticoid effects

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess, infection susceptibility increased</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytosis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endocrine disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalaemia, calcium deficiency, sodium retention, fluid retention, increased appetite</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental disorder</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Convulsions, benign intracranial pressure increased with papilloedema, usually after treatment; vertigo, headache</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular pressure increased, glaucoma, cataract subcapsular, exophthalmoses</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure congestive,</td>
<td></td>
</tr>
<tr>
<td>Reversible cardiac hypertrophy may occur in isolated cases in infants and small children treated over</td>
<td></td>
</tr>
</tbody>
</table>
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 hyper pigmentation

**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 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 Precaution).

**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.

...

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 breastfeeding woman.

Fertility

There is no data available.

10 Overdose

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.

Pharmacological properties

11 Clinical pharmacology

Pharmacodynamic properties

Pharmacotherapeutic group

Pharmacotherapeutic group: Anterior pituitary lobe hormones and analogues – ACTH

ATC code

ATC code: H01AA02.

Mechanism of action (MOA)/Pharmacodynamics (PD)

... 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.

...
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) properties

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 β$_{1-24}$-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.

Preclinical safety data

13 Non-clinical safety data

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

Pharmaceutical particulars

14 Pharmaceutical information
List of excipients

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

... Shelf-life

3 years.

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.

Nature and content of container

1 mL colourless glass ampoules of glass type I.

Instructions for use and handling, and disposal

The ampoule should be shaken before use.

Manufacturer

Nycomed Austria GmbH, Austria

For Novartis Pharma AG, Basel, Switzerland

Licensee Holder

Novartis Pharma Services AG,
36 Shacham St., Petach-Tikva