Synacthen Depot Ampoules 1 mg/ml

Summary of Product Characteristics Updated 02-Jul-2021 | Atnahs Pharma UK Ltd

1. Name of the medicinal product

Synacthen Depot Ampoules 1mg/ml

2. Qualitative and quantitative composition

Tetracosactide acetate 1mg/ml

Excipient(s) with known effect

Contains benzyl alcohol (10mg/ml).

Each ampoule contains a total of 3.32 mg of sodium.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Suspension for injection.

Tetracosactide acetate is absorbed on to zinc phosphate. A sterile, milky white suspension, which settles on standing, in a clear glass ampoule.

4. Clinical particulars

4.1 Therapeutic indications

Therapeutic use: Synacthen Depot should normally only be used for short-term therapy in conditions for which glucocorticoids are indicated in principle, for example, in ulcerative colitis and Crohn's disease, juvenile rheumatoid arthritis, or as adjunct therapy in patients with rheumatoid arthritis and osteoarthrosis. Synacthen Depot may be particularly useful in patients unable to tolerate oral glucocorticoid therapy or in patients where normal therapeutic doses of glucocorticoids have been ineffective.

Diagnostic use: As a diagnostic aid for the investigation of adrenocortical insufficiency.

4.2 Posology and method of administration

Posology

Therapeutic use: Initially, daily doses of Synacthen Depot should be given but after approximately 3 days, intermittent doses may be given.

Adults: Initially 1mg intramuscularly daily or 1mg every 12 hours in acute cases. After the acute symptoms of the disease have disappeared, treatment may be continued at a dose of 1mg every 2 to 3 days; in patients who respond well, the dosage may be reduced to 0.5mg every 2 to 3 days or 1mg per week.

Paediatric population:

Premature babies or neonates (less than 1 month): Due to the presence of benzyl alcohol, Synacthen Depot is contraindicated in premature babies and in neonates (less than one month). (See section 4.3 Contraindications).

Children aged 3 to 5 years: Initially 0.25 to 0.5mg intramuscularly daily; the maintenance dose is 0.25 to 0.5mg every 2 to 8 days.

Children aged 5 to 12 years: Initially 0.25 to 1mg intramuscularly daily; the maintenance dose is 0.25 to 1mg every 2 to 8 days.

Elderly:

There is no evidence to suggest that dosage should be different in the elderly.

Diagnostic use: In cases of suspected adrenocortical insufficiency, where the 30-minute diagnostic test with Synacthen ampoules (see Synacthen Ampoules 250 mcg Summary of Product Characteristics) has yielded inconclusive results or where it is desired to determine the functional reserve of the adrenal cortex, a 5-hour test with Synacthen Depot may be performed.

Adults: This test is based on measurement of the plasma cortisol concentration before and exactly 30 minutes, 1, 2, 3, 4 and 5 hours after an intramuscular injection of 1mg Synacthen Depot. 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:

Hourly cortisol levels:

Time	nmol/L
1st hour	600 – 1250 nmol/L

2nd hour	750 – 1500 nmol/L
3rd hour	800 – 1550 nmol/L
4th hour	950 – 1650 nmol/L
5th 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.

A 3-day test with Synacthen Depot may be used to differentiate between primary and secondary adrenocortical insufficiency.

All the plasma samples should be stored in a refrigerator until plasma cortisol level estimation.

Children: No paediatric dosage has been established

Elderly: There is no evidence to suggest that dosage should be different in the elderly.

Method of administration

Synacthen Depot is intended for intramuscular injection. The ampoule should be shaken before use.

4.3 Contraindications

Hypersensitivity to tetracosactide or ACTH or to any of the excipients listed in section 6.1 List of excipients.

In view of the increased risk of anaphylactic reactions, Synacthen Depot should not be used in patients known to have asthma and/or other forms of allergy (see section 4.4 Special warnings and precautions for use).

Acute psychoses, infectious diseases, Cushing's syndrome, peptic ulcer, refractory heart failure, treatment of primary adrenocortical insufficiency and adrenogenital syndrome.

Synacthen Depot must not be used for premature babies or neonates (less than 1 month) due to the presence of benzyl alcohol (see section 4.2 Posology and method of administration).

Synacthen Depot must not be administered intravenously.

4.4 Special warnings and precautions for use

Before using Synacthen Depot, the doctor should make every effort to find out whether the patient is suffering from, or has a history of, allergic disorders. In particular, he should enquire whether the patient has previously experienced adverse reactions to ACTH, Synacthen Depot or other drugs.

Synacthen Depot should only be administered under medical supervision.

If local or systemic hypersensitivity reactions occur during or after an injection (for example, marked redness and pain at the injection site, urticaria, pruritus, flushing, faintness, severe malaise or dyspnoea), Synacthen Depot or other ACTH preparations must be discontinued and should be avoided in the future. Hypersensitivity reactions tend to occur within 30 minutes of the injection. The patient should therefore be kept under observation during this time.

Preparation should be made in advance to combat any anaphylactic reaction that may occur after an injection of Synacthen. In the event of a serious anaphylactic reaction, the patient should be treated appropriately with adrenaline and steroids.

Synacthen Depot should not be used in the presence of active infectious or systemic diseases, when the use of live vaccine is contemplated or in the presence of a reduced immune response, unless adequate disease specific therapy is being given.

Use with care in patients with non-specific ulcerative colitis, diverticulitis, recent intestinal anastomosis, kidney failure, hypertension, thromboembolic tendencies, osteoporosis and myasthenia gravis.

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

The increased production of adrenal steroids may result in corticosteroid type effects:

- Salt and water retention can occur and may respond to a low salt diet. Potassium supplementation may be necessary during long term treatment

- Psychological disturbances may be triggered (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

- Use 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.

- Ocular effects may be produced (e.g. glaucoma, cataracts).

- Provided the dose is chosen to meet the individual's needs, Synacthen Depot is unlikely to inhibit growth in children. Nevertheless, growth should be monitored in children undergoing long-term treatment. In infants and children aged up to 5 years, reversible myocardial hypertrophy may occur in very rare cases following long-term treatment with high doses. Therefore echocardiographic recordings should be made regularly.

- Dosage adjustments may be necessary in patients being treated for diabetes or hypertension.

An enhanced effect of tetracosactide acetate therapy may occur in patients with hypothyroidism and in those with cirrhosis of the liver.

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.

This medicine contains 10mg of benzyl alcohol in each 1ml ampoule which is equivalent to 1mg/ml.

Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates (“gasping syndrome”). The minimum amount of benzyl alcohol at which toxicity may occur is not known.

Synacthen Depot contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium- free'.

Lack of diagnostic accuracy

Post administration total plasma cortisol levels during 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.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions are likely with drugs whose actions are affected by adrenal steroids (see Section 4.4 Special warnings and precautions for use).

Severe jaundice has been observed for concurrent use of Synacthen and valproate in paediatric population. Their concurrent use should be avoided.

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 oestrogens 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 Section 4.4 Special warnings and precautions for use).

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.

4.6 Fertility, pregnancy and lactation

Women of child bearing potential

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. Synacthen should be used during pregnancy only if the expected benefit outweighs the potential risk to the foetus.

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.

4.7 Effects on ability to drive and use machines

Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness.

4.8 Undesirable effects

Since Synacthen Depot stimulates the adrenal cortex to increase the output of glucocorticoids and mineralocorticoids, side effects associated with excessive adrenocorticotropic activity may be encountered**,** as well as those related to tetracosactide, and to the presence of benzyl alcohol in the formulation.

The following undesirable effects 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 categorised as not known. Undesirable effects are listed according to system organ classes in MedDRA. Within each system organ class, undesirable effects are presented in order of decreasing seriousness.

Table 1 Undesirable effects (frequency not known) related to tetracosactide

Immune system disorders:
Hypersenstivity*
Endocrine disorders:
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, angioneurotic oedema and Quincke's oedema (see Section 4.4 Special warnings and precautions for use).

Undesirable effects related to benzyl alcohol

The benzyl alcohol contained as an excipient in Synacthen Depot may provoke toxic and anaphylactoid reactions in children aged under 3 years.

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 Depot as a diagnostic tool, but may be reported when Synacthen Depot is used for therapeutic indications.

Table 2 Undesirable effects (frequency not known) related to glucocorticoid and mineralocorticoid effects

Infections and infestations:
Abscess, infection susceptibility increased
Blood and lymphatic system disorders:
Leukocytosis
Endocrine disorders:
Cushing'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
Metabolism and nutrition disorders:
Hypokalaemia, calcium deficiency, sodium retention, fluid retention, increased appetite, hypokalaemic alkalosis
Psychiatric disorders*:*
Mental disorder[1]
Nervous system disorders:
Convulsions, benign intracranial pressure increased with papilloedema usually after treatment, vertigo, headache
Eye disorders:

Intraocular pressure increased, glaucoma, posterior subcapsular cataracts, exophthalmoses.

Cardiac disorders:

Cardiac failure congestive

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:

*S*kin atrophy, petechiae, ecchymosis, erythema, hyperhidrosis, acne, 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 reactions[2], growth retardation, weight increase, impaired healing.

Investigations:

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

[1]Also see Section 4.4 Special warnings and precautions for use.

[2]Also see Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects (paragraph Undesirable effects related to tetracosactide).

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme by connecting to the following website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Relating to therapeutic usage of Synacthen Depot:

Overdosage may lead to fluid retention and signs of excessive adrenocorticotropic activity (Cushing's Syndrome). In such cases, Synacthen Depot should either be withdrawn temporarily, given in lower doses or the interval between injections should be prolonged (e.g. 5 to 7 days).

Treatment: There is no known antidote. Treatment should be symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

ATC Code: H01 AA02

Tetracosactide acetate consists of the first 24 amino acids occurring in the natural corticotropic hormone (ACTH) sequence and displays the same physiological properties as ACTH. In the adrenal cortex, it stimulates the biosynthesis of glucocorticoids, 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.

5.2 Pharmacokinetic properties

Absorption

Tetracosactide acetate is absorbed on to a zinc phosphate complex which ensures the sustained release of the active substance from the intramuscular injection site. After an intramuscular injection of 1mg Synacthen Depot, the radioimmunologically determined plasma concentrations of tetracosactide acetate range between 200 to 300pg/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, though some non-specific interaction with albumin has been reported. Tetracosactide acetate has an apparent volume of distribution of approximately 0.4litres/kg.

Biotransformation

In the serum, tetracosactide acetate is broken down by serum endopeptidases into inactive oligopeptides and then by aminopeptidases into 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 tetracosactide acetate, 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 the mutagenic or carcinogenic potential of tetracosactide. No animal studies on fertility and reproduction toxicity have been performed with tetracosactide.

6. Pharmaceutical particulars

6.1 List of excipients

Zinc chloride anhydrous pure

Disodium phosphate dodecahydrate,

Benzyl alcohol

Sodium chloride

Sodium hydroxide

Water for injections.

6.2 Incompatibilities

None known

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Synacthen Depot comes in cardboard boxes of 1 ampoule and 10 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The ampoule should be shaken before use.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

PL 43252/0027

9. Date of first authorisation/renewal of the authorisation

25 June 1998

10. Date of revision of the text

14/10/2020

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