Australian Product Information - SYNACTHEN® DEPOT (tetracosactide (tetracosactrin))

1. NAME OF THE MEDICINE

tetracosactide (tetracosactrin)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tetracosactide (tetracosactrin) is the first corticotrophic preparation to be produced entirely by synthesis and displays all the pharmacological properties of endogenous ACTH. It is a long-chain polypeptide composed of the first 24 of the 39 amino acids contained in the naturally occurring ACTH (corticotrophin) molecule.

In contrast to ACTH preparations obtained by extraction, the composition of tetracosactide (tetracosactrin) is not subject to variation, so that dosage can be expressed in terms of weight. For the purposes of clinical use, Synacthen 1 mg corresponds approximately to 100 international units of ACTH (as defined in the Third International Working Standard).

Synacthen Depot is administered only by the intramuscular route.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Injection, modified release

Milky white suspension.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Neurological Diseases

Acute exacerbations in patients suffering from multiple sclerosis. Hypsarrhythmia, and or infantile spasms.

4.2 DOSE AND METHOD OF ADMINISTRATION

By intramuscular injection only.

Before an injection of Synacthen Depot, the ampoule containing the relatively thin, slightly opalescent suspension should be shaken until it becomes uniformly cloudy. The preparation should be stored in a refrigerator (2 - 8°C).

Adults:

Initially 1mg daily; in acute or critical conditions, treatment can be initiated with 1mg every 12 hours. Once the acute manifestations have subsided, the usual maintenance dosage is 1mg every 2 or 3 days; in patients who respond well, it is often possible to reduce the dose to as little as 0.5mg every 2 or 3 days or 1mg weekly.

Infants:

Initially 0.25mg daily; for maintenance, 0.25mg every 2 to 8 days.

Small children:

Initially 0.25 to 0.5mg daily; for maintenance 0.25 to 0.5mg every 2 to 8 days.

Children of school age:

Initially 0.25 to 1mg daily; for maintenance 0.25 to 1mg every 2 to 8 days.

4.3 CONTRAINDICATIONS

- If the patient's case history discloses any record of hypersensitivity reactions to ACTH treatment, tetracosactide (tetracosactrin) must not be used either for diagnosis or for treatment.
- Hypersensitivity to tetracosactide (tetracosactrin) and / or ACTH of animal origin. Viral diseases or recent vaccination with live virus
- Acute psychoses
- Infections (unless antibiotics are being administered at the same time)
- Peptic ulcer
- Cushing's syndrome
- Heart failure (refractory)
- Pregnancy and breast feeding
- Adrenocortical insufficiency
- Adrenogenital syndrome
- In view of the increased risk of anaphylactic reactions, Synacthen Depot must not be employed to treat asthma or other allergic conditions.
- Diabetes mellitus
- Moderate or severe hypertension
- Since Synacthen Depot contains benzyl alcohol, it is contra-indicated in neonates (especially premature infants), in whom benzyl alcohol can cause severe poisoning.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In rare instances in patients without a history of allergy, but more frequently in the presence of a history of asthma or other forms of allergy, severe anaphylactic reactions have occurred, some with fatal outcome. Usually, such reactions were manifest within 30 minutes after administration of Synacthen Depot.

In patients who, in addition to the disease entity for which tetracosactide (tetracosactrin) is indicated, are also susceptible to allergies or are actually suffering from an allergic disorder (especially asthma), treatment with Synacthen Depot should only be resorted to if other therapeutic measures have failed to elicit the desired response and if the condition is severe enough to warrant such medication.

In these allergic patients the physician must be prepared in advance to treat any anaphylactic reaction occurring after the injection of Synacthen Depot.

Synacthen Depot should not be administered intravenously.

Hypersensitivity:

Before employing Synacthen Depot the physician must ascertain whether the patient is suffering from an allergic disorder (especially asthma) or is susceptible in general to allergies. He should also enquire whether the patient has been treated with ACTH preparations in the past, and if so, ensure that the treatment did not give rise to hypersensitivity reactions (see Section 4.3 CONTRAINDICATIONS).

Synacthen Depot should only be administered under medical supervision.

If local or systemic hypersensitivity reactions occur during or after an injection - eg. marked redness and pain at the injection site, urticaria, pruritus, flushing, severe malaise, or dyspnoea-treatment with tetracosactide (tetracosactrin) must be discontinued and all use of ACTH preparations avoided in the future.

Hypersensitivity reactions tend to occur within 30 minutes of injection. The patient should be kept under observation during this time. Should a serious anaphylactic reaction occur, despite all precautions, the following immediate measures must be taken: administer adrenaline (0.4 to 1mL of a 1mg/mL solution intramuscularly or 0.1 to 0.2mL of a 1mg/mL solution in 10mL physiological saline slowly intravenously, as well as large intravenous doses of water-soluble corticosteroids, repeating the dose if necessary.

Salt and water retention:

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 be required occasionally.

Pre-existing conditions:

Patients already receiving medication for diabetes mellitus or for moderate to severe hypertension must have their dosages readjusted if treatment with Synacthen Depot is instituted.

Use with caution in patients with non-specific ulcerative colitis, diverticulitis, recent intestinal anastomosis, renal insufficiency, hypertension, predisposition to thromboembolism, osteoporosis and myasthenia gravis.

The effect of therapy with Synacthen Depot may be increased in patients with hypothyroidism or cirrhosis of the liver.

Infectious diseases:

Synacthen Depot may activate latent amoebiasis. It is 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.

Synacthen Depot should be used cautiously in patients with ocular herpes simplex owing to possible corneal perforation.

Do not administer live virus vaccines to patients being treated with Synacthen Depot. Any other immunisation procedures must be undertaken with caution because of the decrease in antibody response.

Adrenocortical insufficiency:

Relative adrenocortical insufficiency can follow termination of prolonged ACTH treatment and may persist for several months after stopping treatment. The risk can be reduced by keeping the dose of Synacthen Depot to the lowest possible level for the shortest duration (see also Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Treatment should be withdrawn gradually.

In patients who suffer an injury or undergo surgery during or within one year after treatment, the associated stress may be managed by an increase or resumption of treatment with Synacthen Depot. Additional use of rapidly acting corticosteroids may be required. The lowest effective dose should be used and, if the dose has to be reduced, it should be done gradually.

Antibody formation:

There have been occasional instances of antibodies being formed in individuals during therapy with synthetic ACTH. The clinical significance of these is not clear.

Effects on the eye:

Prolonged therapy may be associated with development of posterior subcapsular cataracts and glaucoma.

Psychological disturbances:

Psychological disturbances may occur during treatment with Synacthen Depot (eg. euphoria, insomnia, mood swings, personality changes, severe depression or even frank psychotic manifestations). Existing emotional instability or psychotic tendencies may be aggravated.

Use in hepatic impairment

The effect of therapy with Synacthen Depot may be increased in patients with cirrhosis of the liver.

Use in renal impairment

Use with caution in patients with renal insufficiency.

Use in the elderly

No data available.

Paediatric use

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

In infants and small children treated with Synacthen Depot, echocardio-graphic recordings should be made regularly, because during long-term treatment with high doses reversible myocardial hypertrophy may occur.

Due to the presence of benzyl alcohol, Synacthen Depot is not recommended in infants and children up to 3 years old, as it may cause toxic reactions and allergic reactions.

Effects on laboratory tests

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - Lack of diagnostic accuracy.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 hypertension may need adjustment to their drug regimen if treatment with Synacthen Depot is instituted.

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.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy (Category D)

There have been some reports of miscarriage or fetal malformation occurring in pregnant women treated with tetracosactide (tetracosactrin), therefore Synacthen Depot must not be administered during pregnancy.

Australian characterisation of pregnancy definition: Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Use in lactation

The administration of tetracosactide (tetracosactrin) during lactation has not been reported. Any decision to initiate treatment with Synacthen Depot must be with recognition to the individual case history. Mothers must not breastfeed during the period of its use.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since Synacthen Depot may have an effect on the central nervous system, patients should be cautious when driving a vehicle or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Hypersensitivity reactions:

Synacthen Depot may provoke hypersensitivity reactions which tend to be more severe (anaphylactic shock) in patients susceptible to allergies, especially asthma (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Hypersensitivity reactions may include skin reactions at the injection site, dizziness, nausea, vomiting, urticaria, flushing, malaise, dyspnoea, angioneurotic oedema or Quincke's oedema.

A number of deaths have been reported in association with administration of Synacthen OR Synacthen Depot. The incidence of mortality in recipients is estimated to be about 0.002% which is very low and comparable to that associated with the use of penicillin. However, it should be borne in mind that the outcome has been fatal in 15% of all adverse reactions reported. Allergic reactions account for 74% of all reactions.

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

In rare cases the benzyl alcohol contained in Synacthen Depot may also give rise to hypersensitivity reactions, especially in children below 3 years of age (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Other adverse reactions:

Synacthen Depot induces the adrenal cortex to increase its production of glucocorticoids and mineralocorticoids, and androgens to a lesser extent. Side effects therefore tend to be of the type found with these corticosteroids:

Musculoskeletal:

Osteoporosis, muscle weakness, steroid myopathy, loss of muscle mass, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones, tendon rupture.

Gastrointestinal:

Abdominal discomfort / distension, peptic ulcer with possible perforation and haemorrhage, pancreatitis, ulcerative oesophagitis.

Dermatological:

Hyperpigmentation, acne, striae of the skin, thin fragile skin, petechiae and ecchymosis, facial erythema, increased sweating, suppression of skin test reactions, impaired wound healing, abscess.

Neurological:

Headache, vertigo, psychological changes, convulsions, increased intracranial pressure with papilloedema (pseudotumour cerebri), usually after treatment.

Endocrine:

Fluid retention, electrolyte disturbance (eg. hypernatraemia, hypokalaemia, hypokalaemic alkalosis, negative calcium balance), hirsutism, hyperglycaemia, glycosuria, Cushing's syndrome (moon face, plethora), suppression of growth in children, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress (eg. after trauma, surgery or illness); decreased carbohydrate tolerance, menstrual irregularities, increased appetite, weight gain.

Ophthalmic:

Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos.

Metabolic:

Negative nitrogen balance due to protein catabolism.

Cardiovascular:

Hypertension, necrotising angiitis, congestive heart failure, thromboembolism. In infants and small children treated over a prolonged period with high dosages, reversible myocardial hypertrophy may occur in isolated instances.

Haematological:

leucocytosis.

Immunological:

Lowered resistance to infectious agents.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdosage may lead to temporary water retention and to signs of excessive adrenocortical activity (Cushing's syndrome). In such circumstances Synacthen Depot should be withdrawn for a time or, alternatively, given in reduced doses either by halving the dosage or by prolonging the interval between injections to, say, 5 to 7 days, in adults.

In infants or children, tetracosactide (tetracosactrin) should be discontinued and case history and dosage schedule carefully reviewed.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Synacthen Depot has the same physiological action as endogenous ACTH; in the normally functioning adrenal cortex it stimulates the biosynthesis of glucocorticoids, mineralocorticoids and (to a lesser extent) androgens. This accounts for its therapeutic effect in conditions responsive to glucocorticoid treatment. Its pharmacological activity, however, is not comparable to that of the corticosteroids, because under ACTH treatment - in contrast to treatment with a single glucocorticoid - the tissues are exposed to a physiological spectrum of corticosteroids such as desoxycorticosterone, corticosterone, cortisol and aldosterone.

Prolonged treatment with high doses of ACTH induces hyperplasia and hypertrophy of the adrenal cortex and continuous high output of cortisol, corticosterone and weak androgens.

The binding sites of ACTH are located in the plasma membrane of the adrenocortical cells, where it becomes bound to a specific receptor. The hormone-receptor complex activates adenyl cyclase, thereby stimulating the production of cyclic AMP (adenosine monophosphate). Cyclic AMP activates protein kinase, which promotes the synthesis of pregnenolone from cholesterol. From pregnenolone the various corticosteroids are produced via a variety of enzymatic pathways.

Synacthen Depot is supplied as a suspension in which the active substance is adsorbed onto an inorganic zinc complex so that the formulation provides for a protracted release. Following an intramuscular injection of 1mg Synacthen Depot, the plasma cortisol concentration remains elevated for 24 to 36 hours.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Adsorption of tetracosactide (tetracosactrin) on to zinc phosphate provides for sustained release of the active substance from the intramuscular injection site. After an injection of 1mg Synacthen Depot i.m., the radioimmunologically determined plasma concentrations of tetracosactide (tetracosactrin) lie for 12 hours between 200 and 300 pg/mL.

Distribution

Tetracosactide (tetracosactrin) has an apparent distribution volume of approx. 0.4 litres/kg.

Metabolism

In the serum, tetracosactide (tetracosactrin) is broken down first by serum endopeptidases (such as trypsin, plasmin, thrombin, and kallikrein) into inactive oligopeptides and then by aminopeptidase into free amino acids. Its rapid elimination from the plasma is probably attributable not only to this relatively slow process of cleavage, but rather to the fact that the active substance becomes rapidly concentrated in the adrenals and kidneys.

Elimination

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Benzyl alcohol

Dibasic sodium phosphate dodecahydrate

Hydrochloric acid

Sodium chloride

Sodium hydroxide

Water for injection

Zinc chloride

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Protect from light and store in a refrigerator (2-8°C)

6.5 NATURE AND CONTENTS OF CONTAINER

Injection: 1mg/mL, 1mL ampoules; containers of 1 AUST R 11060.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Active ingredient: tetracosactide (tetracosactrin)

Empirical formula: $C_{136}H_{210}N_{40}O_{31}S$

Molecular weight: 2933.5

Amino acid sequence: Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly- Lys- Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro

CAS number

60189-34-6

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription only medicine

8. SPONSOR

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18 March 2020

Summary table of changes

Section changed	Summary of new information
All	Reformatted in line with the new form
Title; 1; 2; 3; 4; 5; & 6	Editorial
6.1	List of excipients added
8	Updates to sponsor and distributor details