SYNACTHEN® DEPOT  
(tetracosactrin zinc phosphate complex)

DESCRIPTION

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 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.

PHARMACOLOGICAL ACTIONS

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.
**Pharmacokinetics**

Adsorption of 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 tetracosactrin lie for 12 hours between 200 and 300 pg/mL.

Tetracosactrin has an apparent distribution volume of approx. 0.4 litres/kg.

In the serum, 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.

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.

**INDICATIONS**

**Neurological Diseases**

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

**CONTRAINDICATIONS**

If the patient's case history discloses any record of hypersensitivity reactions to ACTH treatment, tetracosactrin must not be used either for diagnosis or for treatment.

Hypersensitivity to 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.

**WARNINGS**

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 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.

**PRECAUTIONS**

**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 "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 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.

**Use in children**
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, echocardiographic recordings should be made regularly, because during long-term treatment with high doses reversible myocardial hypertrophy may occur.

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.

**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 "Dosage and 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.

**Effect 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.

**Use in Pregnancy (Category D)**
There have been some reports of miscarriage or fetal malformation occurring in pregnant women treated with tetracosactrin, therefore Synacthen Depot must not be administered during pregnancy.
**Use in Lactation**
The administration of 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.

**Interactions with Other Drugs**

**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 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.
ADVERSE REACTIONS

Hypersensitivity reactions:
Synacthen Depot may provoke hypersensitivity reactions which tend to be more severe (anaphylactic shock) in patients susceptible to allergies, especially asthma (see "WARNINGS"). 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 CONTRAINdicATIONS and PRECAUTIONS).

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.

**DOSAGE AND 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.

**OVERDOSAGE**

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, tetracosactrin should be discontinued and case history and dosage schedule carefully reviewed.

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

**PRESENTATION AND PACK**

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

Novartis Pharmaceuticals Australia Pty Ltd
54 Waterloo Road
North Ryde NSW 2113

® = Registered trademark

Approved by Therapeutic Goods Administration: 24 August 1992
Safety related changes notified: 7 December 2011
Date of most recent amendment: 22 December 2011