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

1. NAME OF THE MEDICINE

tetracosactide (tetracosactrin)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Synacthen is the first corticotrophic preparation to be produced entirely by synthesis and displays all of 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 Synacthen is not subject to variation, so that dosage can be expressed in terms of weight. For the purposes of clinical use, Synacthen 1mg corresponds approximately to 100 international units of ACTH (as defined in the Third International Working Standard). Studies have shown that a single test dose of Synacthen 250 micrograms (corresponding to 25 IU) administered by intramuscular injection is sufficient to elicit a marked rise in plasma cortisol within 30 minutes.

Synacthen ampoules contain 250 micrograms tetracosactide (tetracosactrin) (as the hexa-acetate salt) per 1 mL of solution.

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

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

As a diagnostic aid in the assessment of suspected adrenocortical hypofunction.

4.2 DOSE AND METHOD OF ADMINISTRATION

Refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Effects on laboratory tests and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for information on drugs that may interfere with test results.

Synacthen 30 Minute Test

This test is based on the increase in plasma cortisol recorded 30 minutes after an intramuscular injection of Synacthen 250 micrograms. Two blood specimens should be taken, the first immediately before and the second exactly 30 minutes after the injection of Synacthen. If the plasma cortisol rises to at least 200 nanomoles/L (70 micrograms/L) above the initial level, or if the plasma cortisol level attained 30 minutes after injection exceeds 500 nanomoles/L (180 micrograms/L), irrespective of the basal level, then adrenocortical function can be regarded as normal.

4.3 CONTRAINDICATIONS

- If the patient's case history discloses any record of hypersensitivity reactions to ACTH treatment, tetracosactide (tetracosactrin) must not be used.
- Hypersensitivity to tetracosactide (tetracosactrin) and / or ACTH of animal origin or to any component of the formulation.
- Synacthen must not be used to treat asthma or other allergic conditions due to the increased risk of anaphylactic reactions (also see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- 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).
- Treatment of primary adrenocortical insufficiency.
- Pregnancy and breast feeding.
- Adrenogenital syndrome.

In view of the increased risk of anaphylactic reactions, Synacthen as a diagnostic agent is not recommended in patients with asthma or other allergic conditions (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE- Hypersensitivity).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Synacthen should only be administered under medical supervision.

Hypersensitivity

Before employing Synacthen 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).

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 of administration of Synacthen. In these allergic patients, the Synacthen test should only be performed if no ACTH preparations have previously been given. The physician must at all events be prepared in advance to combat at once any anaphylactic reaction occurring after the injection of Synacthen.

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 1 mL of a 1 mg/mL solution intramuscularly or 0.1 to 0.2 mL of a 1 mg/mL solution in 10 mL physiological saline slowly intravenously), as well as large intravenous doses of water- soluble corticosteroids, repeating the dose if necessary.

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

Pre-existing conditions:

Synacthen should be used with caution in patients with diabetes mellitus or moderate to severe hypertension.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

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.

Because spironolactone metabolites fluoresce, erroneously high plasma cortisol concentrations may be reported in patients receiving spironolactone when fluorometric analysis is used but not when radioimmunoassay or competitive protein binding methods are used. Therefore, patients should not receive pretest doses of spironolactone on the day of testing when the fluorometric method is used. Since

prednisone, dexamethasone and betamethasone are not detectable by the fluorometric method, therapy with these drugs can be maintained.

In patients with increased plasma bilirubin concentrations or with free haemoglobin in their plasma, falsely elevated fluorescence measurements may occur.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Patients receiving cortisone or hydrocortisone on the test day may exhibit abnormally high baseline plasma cortisol concentrations and a paradoxical decrease in plasma cortisol concentrations following administration of Synacthen. Patients should not receive pretest doses of cortisone or hydrocortisone on the day of testing.

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.

Live virus immunisation procedures must not be undertaken during treatment with Synacthen because of the decrease in antibody response.

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 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 administer Synacthen as a diagnostic aid 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 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)

Frequency estimate: very common ≥10%; common ≥1% to <10%; uncommon ≥0.1% to <1%; rare ≥0.01% to <0.1%; very rare <0.01%.

Hypersensitivity Reactions

Rare: Synacthen 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). Hypersensitivity reactions may include skin reactions at the injection site, dizziness, nausea, vomiting, urticaria, flushing, malaise, dyspnoea, angioneurotic oedema or Quincke's oedema.

Adrenal Haemorrhage

Isolated cases have been reported with Synacthen.

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

There have not been any reports that administration of Synacthen, in recommended dosage as a diagnostic aid, has resulted in signs and symptoms associated with overdosage. However, for information on this subject, reference may be made to the Product Information for Synacthen Depot.

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 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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Distribution

Tetracosactide (tetracosactrin) has an apparent distribution volume of approx. 0.4 litres/kg. The half-lives of its elimination from the plasma following an intravenous injection are approximately 7 minutes in the first phase (lasting approximately 1 hour), approximately 37 minutes in the next phase (also lasting approximately 1 hour) and, thereafter, approximately 3 hours.

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 aminopeptidases 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

Appropriate studies have not been performed to evaluate mutagenic potential.

Carcinogenicity

Appropriate studies have not been performed to evaluate carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

acetic acid, sodium acetate, sodium chloride, water for injections.

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: 250 micrograms/mL, 1 mL ampoule; containers of 1. AUST R 11058

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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®= registered trademark

9. DATE OF FIRST APPROVAL

12 August 1999

10. DATE OF REVISION

17 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
8	Updates to sponsor and distributor details