Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Synacthen 250 micrograms/ml solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance

250 micrograms of Tetracosactide. Each ml contains Tetracosactide 250 micrograms, as tetracosactide acetate.

Excipients

Contains 3.33 mg of sodium (as sodium acetate and sodium chloride) per ml.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a diagnostic test for the investigation of adrenocortical insufficiency.

4.2 Posology and method of administration

Adults

This preparation of Synacthen is intended for administration for diagnostic purposes only as a single intramuscular or intravenous dose; it is not to be used for repeated therapeutic administration.

The 30-minute Synacthen diagnostic test
This test is based on measurement of the plasma cortisol concentration immediately before and exactly 30 minutes after an intramuscular or intravenous injection of 250mcg (1ml) Synacthen. Adrenocortical function can be regarded as normal if the post-injection rise in plasma cortisol concentration amounts to at least 200nmol/litre (70mcg/litre).

Use in the elderly

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

Use in children

An intravenous dose of 250mcg/1.73 m^2 body surface area has been suggested. Thus for children aged 5-7 years, approximately half the adult dose will be adequate. For more accurate dosing of other ages, standard body surface area tables should be consulted.

4.3 Contraindications

- Known hypersensitivity to tetracosactide and/or ACTH or to any of the excipients.
- Acute psychosis.
- Infectious diseases.
- Peptic ulcer.
- Refractory heart failure.
- Cushing's syndrome.
- Primary adrenocortical insufficiency.
- Adrenogenital syndrome.
- Synacthen is contraindicated in patients with allergic disorders (e.g. asthma).
- Pregnancy and breast-feeding.

4.4 Special warnings and precautions for use

Before using Synacthen, the doctor should make every effort to find out whether the patient is suffering from, or has a history of allergic disorders, (see Section 4.4 Contraindications). In particular, he should enquire whether the patient has previously experienced adverse reactions to ACTH, Synacthen or other drugs.

Synacthen should only be administered under the supervision of appropriate senior hospital medical staff (e.g. consultants). The patient should only be treated in a unit having the appropriate resuscitative facilities immediately available. The patient should be kept under observation for at least 30 minutes post dose to ensure early detection of hypersensitivity reactions.

If local or systemic hypersensitivity reactions occur after the injection (for example, marked redness and pain at the injection site, urticaria, pruritus, flushing, faintness or dyspnoea), Synacthen or other ACTH preparations 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 occurring, the following measures must be taken immediately: administer adrenaline (0.4-1ml of a 0.1% solution intramuscularly or 0.1-0.2ml of a 0.1% solution in 10ml physiological saline slowly intravenously) as well as a large intravenous dose of a corticosteroid (for example 100-500mg hydrocortisone, three or four times in 24 hours) repeating the dose if necessary. The hydrocortisone product information prepared by the manufacturer should also be consulted.

4.5 Interaction with other medicinal products and other forms of interaction

Since Synacthen brings about an increase in adrenocortical production of glucocorticoids and mineralocorticoids, drug interactions of the type seen with these corticosteroids may occur. Patients receiving medication for diabetes mellitus or for moderate to severe hypertension must have their dosage adjusted if treatment with Synacthen is started.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Synacthen is contraindicated during pregnancy.

Lactation

Synacthen is contraindicated while breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 4.4).

Adrenal haemorrhage
Isolated cases have been reported with Synacthen.

Infections and infestations	Increased susceptibility to infection, abscess
Blood and the lymphatic system disorders	Leukocytosis
Endocrine disorders	Menstruation irregular, Cushing’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
Metabolism and nutrition disorders	Increased appetite, hypokalaemia, calcium deficiency, sodium retention, fluid retention
Psychiatric disorders	Mental disorder[1)]
Nervous system disorders	Headache, vertigo, convulsions Benign intracranial pressure with papilloedema, usually after treatment
Eye disorders	Posterior sub capsular cataracts, increased intraocular pressure, glaucoma, exophthalmoses
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[2)], weight increased, impaired healing, growth retardation
Investigations	Negative nitrogen balance due to protein catabolism, suppression of skin test reactions

[1)] also see section 4.4

[2)] also see section 4.8 and section 4.4

4.9 Overdose

Overdosage is unlikely to be a problem when the product is used as a single dose for diagnostic purposes.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anterior pituitary lobe hormones and analogues - ACTH - ATC code: H01AA02

Tetracosactide, the active substance of Synacthen, consists of the first 24 amino acids occurring in the natural corticotrophic hormone (ACTH) sequence and displays the same physiological properties as ACTH. Like ACTH, it stimulates adrenocortical production of glucocorticoids and mineralocorticoids and, to a lesser extent, androgens.

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.

5.2 Pharmacokinetic properties

Tetracosactide has an apparent volume of distribution of approximately 0.4 litres/kg.

Following an intravenous injection, elimination of the compound from the plasma consists of 3 phases. The half-lives of these phases are approximately 7 minutes (0-1 hour), 37 minutes (1-2 hours) and 3 hours thereafter.

In the serum, tetracosactide is broken down by serum endopeptidases into inactive oligopeptides and then by aminopeptidases into free amino acids. The rapid elimination from plasma is probably not attributable to this relatively slow cleavage process, but rather to the rapid concentration of the active substance in the adrenal glands and kidneys. Following an intravenous dose of ^{131}I-labelled tetracosactide, 95-100% of the radioactivity is excreted in the urine within 24 hours.

5.3 Preclinical safety data

No studies have been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid
Sodium acetate
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 5 years.
The product should be used immediately after opening.

6.4 Special precautions for storage

Store in a refrigerator (2-8^{o}C).

Keep the ampoules in the outer carton.

6.5 Nature and contents of container

Type I (Ph. Eur.) clear glass 1ml ampoule. The product is presented as a pack of 5 ampoules of 1ml.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sigma-Tau Industrie Farmaceutiche Riunite S.p.A
Viale Shakespeare
47 – 00144 Rome
Italy

8 MARKETING AUTHORISATION NUMBER

PA1931/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1978

Date of last renewal: 1st April 2008

10 DATE OF REVISION OF THE TEXT

February 2014