Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Synacthen 250 micrograms/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance
One ampoule of 1 ml contains 250 micrograms of Tetracosactide (as tetracosactide acetate).

Excipient with known effect:
One ampoule of 1 ml contains 3.33 mg of sodium (as sodium acetate and sodium chloride).

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

This medicinal product is for diagnostic use only.
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). All plasma samples should be stored in a refrigerator until plasma cortisol level estimation.

Special populations

Renal impairment
No studies have been performed in patients with renal impairment.

Hepatic impairment
No studies have been performed in patients with hepatic impairment

Elderly population (aged 65 years and above)
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

- Hypersensitivity to tetracosactide and/or ACTH or to any of the excipients listed in section 6.1.
- Synacthen must not be used in patients with asthma or other allergic conditions due to the increased risk of anaphylactic reactions (see section 4.4).

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 4.3 Contraindications). In particular, the physician 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 60 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 as well as a large intravenous dose of a corticosteroid repeating the dose if necessary.
Caution is required in patients already receiving medication for diabetes mellitus or for moderate to severe hypertension (see section 4.5).

Lack of diagnostic accuracy
Post-administration total plasma cortisol levels during the Synacthen test may 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, and 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 the hypothalamic-pituitary-adrenal (HPA) axis.

The hydrocortisone product information prepared by the manufacturer should also be consulted.

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Observed interactions resulting in concomitant use not being recommended
As severe jaundice has been observed with concurrent use of Synacthen and valproate in pediatric population. Their concurrent use should be avoided.

Observed interactions to be considered
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 Warnings and precautions).

Anticipated interactions to be considered

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 Synacthen is given (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
There is no special recommendation.

Pregnancy
There are no or limited amount of data from the use of Synacthen in pregnant patients. Tetracosactide does not cross the placenta. Studies in animals are insufficient with respect to reproductive toxicity/teratogenicity. Synacthen is not recommended during pregnancy and should be used only if the expected benefit outweighs the potential risk to the fetus.

Breast-feeding
It is unknown whether tetracosactide/metabolites is excreted in human milk. A decision must be made whether to avoid breast-feeding during Synacthen diagnostic test, taking into account the benefit of breast feeding for the child and the benefit of diagnostic test for the woman. .

Fertility
There is no data available.

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

Adverse drug reactions (ADRs) may be related to tetracosactide or to the stimulation of glucocorticoids and mineralocorticoid secretion during the use of Synacthen.

The following adverse reactions 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 categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 1Adverse drug reactions from spontaneous reports and the literature (frequency not known) related to tetracosactide

Immune system disorders	Hypersensitivity*
Endocrine disorders	Adrenal hemorrhage

* 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 angioedema or Quincke's oedema (see section 4.4).

Adverse drug reactions related to glucocorticoid and mineralocorticoid effects
The ADRs related to glucocorticoid and mineralocorticoid effects are unlikely to be observed with short-term use of Synacthen as a diagnostic tool, but may be reported when Synacthen is used in therapeutic indications.

Table 2Adverse drug reactions from spontaneous reports and the literature (frequency not known) related to glucocorticoid and mineralocorticoid effects.

Infections and infestations	Infection susceptibility increased, abscess
Blood and 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; carbohydrate

	tolerance decreased, hyperglycaemia, manifestations of latent diabetes mellitus, hirsutism
Metabolism and nutrition disorders	Increased appetite, hypokalaemia, calcium deficiency, sodium retention, fluid retention
Psychiatric disorders	Mental disorder
Nervous system disorders	Headache, vertigo, convulsions Benign intracranial hypertension with papilloedema
Eye disorders	Posterior sub capsular cataracts, intraocular pressure increased, glaucoma, exophthalmos
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	Embolism, vasculitis necrotising, hypertension
Gastrointestinal disorders	Peptic ulcer hemorrhage, peptic ulcer perforation, pancreatitis, abdominal distension, oesophagitis ulcerative
Skin and subcutaneous tissue disorders	Skin atrophy, petechiae, ecchymosis, erythema, hyperhidrosis, acne, skin hyper pigmentation
Musculoskeletal, connective tissue and bone disorders	Osteoporosis, muscular weakness, myopathy, muscle atrophy, spinal fractures, osteonecrosis, pathological fracture, tendon rupture
General disorders and administration site conditions	Hypersensitivity [1)], weight increased, impaired healing, growth retardation
Investigations	Nitrogen balance negative, suppression of skin test reactions

[1)] also see section 4.8 Adverse drug reactions (paragraph "Adverse drug reactions related to tetracosactide") and section 4.4 Warnings and precautions.

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. Prolonged use of Synacthen is reported to have minimal suppression of hypothalamic-pituitary-adrenal axis as compared to long-term use of 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.

5.2 Pharmacokinetic properties

Absorption
Tetracosactide is rapidly absorbed from the i.m. injection site.

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.
Tetracosactide has an apparent volume of distribution of approximately 0.4 litres/kg.
Tetracosactide apparently does not cross the placenta and it is unknown whether tetracosactide passes into the breast milk.

Metabolism
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.

Elimination
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.

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 conventional studiesof genotoxicity, carcinogenic potential, toxicity toreproduction and development have been performed.

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°C-8°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

Alfasigma S.p.A
Via Ragazzi del '99, n. 5
40133 Bologna (BO)
Italy

8 MARKETING AUTHORISATION NUMBER

PA2206/002/001

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

March 2022