SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Synacthen Ampoules 250mcg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tetracosactide (as acetate) 250 micrograms per ampoule.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

A clear colourless aqueous solution for intramuscular injection or intravenous infusion in a 1 mL clear glass ampoule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 250micrograms (1ml) Synacthen. Adrenocortical function can be regarded as normal if the post-injection rise in plasma cortisol concentration increases by 200 nmol/litre (70 micrograms/litre), i.e. if the value 30 minutes after injection is >500 nmol/litre (180 micrograms/litre), adrenocortical function is regarded as normal. All the plasma samples should be stored in a refrigerator until plasma cortisol level estimation.

Where the 30-minute test has yielded inconclusive results, or where it is desired to determine the functional reserve of the adrenal cortex, a 5-hour test can be performed with Synacthen Depot (see separate Summary of Product Characteristics). Furthermore, a 3-day test with Synacthen Depot may be used to differentiate between primary and secondary adrenocortical insufficiency.

Children: An intravenous dose of 250micrograms/1.73m² body surface area has been suggested. Thus for children aged 5 to 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.

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

4.3 Contraindications

Known hypersensitivity to tetracosactide and/or ACTH or to any of the excipients listed in section 6.1 List of excipients.

Synacthen is contra-indicated in patients with allergic disorders (e.g. asthma) (see Section 4.4 Special warnings and precautions for use), acute psychosis, infectious diseases, peptic ulcer, refractory heart failure, Cushing's syndrome, treatment of primary adrenocortical insufficiency and adrenocongenital syndrome.

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 "Contra-indications"). 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).

If local or systemic hypersensitivity reactions occur after the injection (for example, marked redness and pain at the injection site, urticaria, pruritus, flushing, faintness, severe malaise or dyspnoea), Synacthen or other ACTH preparations must be discontinued and should be avoided in the future. Hypersensitivity reactions tend to occur within 30 minutes of an 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, the patient should be treated appropriately with adrenaline and steroids.

Synacthen Ampoules should not be used in the presence of active infectious or systemic diseases, when the use of live vaccine is contemplated or in the presence of a reduced immune response, unless adequate disease specific therapy is being given.

Use with care in patients with hypertension and thromboembolic tendencies.

Use cautiously in patients with ocular herpes simplex owing to possible corneal perforation.

The increased production of adrenal steroids may result in corticosteroid type effects:

- Psychological disturbances may be triggered (e.g. euphoria, insomnia, mood swings, personality changes and severe depression, or even frank psychotic manifestations). Existing emotional instability or psychotic tendencies may be aggravated
- Latent infections (e.g. amoebiasis, tuberculosis) may become activated
- Ocular effects may be produced (e.g. glaucoma, cataracts)
- Dosage adjustments may be necessary in patients being treated for diabetes or hypertension
- If Synacthen is used in any of the following conditions, the risks of treatment should be weighed against the possible benefits: ulcerative colitis, diverticulitis, recent intestinal anastomosis, kidney failure, hypertension, predisposition to thromboembolism, osteoporosis, myasthenia gravis.

The solution for injection contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially ‘sodium- free’.

Lack of diagnostic accuracy
Post administration total plasma cortisol levels during 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.

4.5 Interaction with other medicinal products and other forms of interaction

Severe jaundice has been observed for concurrent use of Synacthen and valproate in paediatric population. Their concurrent use should be avoided.

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 oestrogens 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 precaution for use).

Since Synacthen increases the adrenocortical production of glucocorticoids and mineralocorticoids, drug interactions of the type seen with these corticosteroids may occur (see Section 4.4 Special warnings and precautions for use). Patients already receiving medication for diabetes mellitus or for moderate to severe hypertension must have their dosage adjusted if treatment with Synacthen is started.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There is limited amount of data in the use of tetracosactide in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see Section 5.3 Preclinical safety data). Synacthen should be used during pregnancy only if the expected benefit outweighs the potential risk to the foetus.

Breast-feeding

It is not known whether tetracosactide enters breast milk or not. Because many drugs are excreted in human milk, caution should be exercised when Synacthen is administered to a breastfeeding woman.

Fertility

Animal studies are insufficient with respect to reproductive toxicity (see Section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness.

4.8 Undesirable effects

Undesirable effects may be related to tetracosactide or to the stimulation of glucocorticoids and mineralocorticoid secretion during the use of Synacthen.

The following undesirable effects 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 categorised as not known. Undesirable effects are listed according to system organ classes in MedDRA. Within each system organ class, undesirable effects are presented in order of decreasing seriousness.

Table 1. Undesirable effects (frequency not known) related to tetracosactide

Immune system disorders: Hypersenstivity*
Endocrine disorders: Adrenal haemorrhage

*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, angioneurotic oedema and Quincke's oedema.

The undesirable effects 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. Should information be required on the side effects reported with therapeutic use of tetracosactide acetate, see Synacthen Depot Ampoules 1 mg/ml Summary of Product Characteristics.

Table 2 Undesirable effects (frequency not known) related to glucocorticoid and mineralocorticoid effects

Infections and infestations Abscess. Infection susceptibility increased
Blood and the lymphatic system disorders

Leukocytosis

Endocrine disorders

Cushing's syndrome, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, e.g. after trauma, surgery or illness; menstruation irregular, carbohydrate tolerance decreased, hyperglycaemia, manifestations of latent diabetes mellitus, hirsutism

Metabolism and nutrition disorders

xalaemia, calcium deficiency, sodium retention, fluid retention, increased appetite

Psychiatric disorders

Mental disorder[1)]

Nervous system disorders

Convulsions, benign intracranial pressure increased with papilloedema, usually after treatment; vertigo, headache

Eye disorders

cular pressure increased, glaucoma, posterior sub capsular cataracts , exophthalmoses

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

Vasculitis necrotising, thromboembolism, hypertension

Gastrointestinal disorders

Pancreatitis, peptic ulcer with possible perforation and haemorrhage, oesophagitis ulcerative, abdominal distension

Skin and subcutaneous tissue disorders

Skin atrophy, petechiae and ecchymosis, erythema, hyperhidrosis, acne and skin hyper pigmentation

Musculoskeletal and connective tissue disorders

Aseptic necrosis of femoral and humeral heads, spinal compression fracture, muscle atrophy, myopathy , osteoporosis, muscular weakness, pathological fracture of long bones, tendon rupture

General disorders and administration site conditions

sensitivity reactions [2)]), growth retardation, weight increased, impaired healing

Investigations

ive nitrogen balance due to protein catabolism, suppression of skin test reactions

[1)] Also see section 4.4 Special warnings and precautions for use

[2)]) Also see 4.4. Special warnings and precautions for use and Table 1 Undesirable effects related to tetracosactide.

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation 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 via the Yellow Card Scheme by connecting to the following website: www.mhra.gov.uk/yellowcard.

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 acetate consists of the first 24 amino acids occurring in the ACTH sequence and displays the same physiological properties as ACTH. In the adrenal cortex, it stimulates the biosynthesis of glucocorticoids, 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 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

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, though some non-specific interaction with albumin has been reported. Tetracosactide acetate has an apparent volume of distribution of approximately 0.4L/kg.

Biotransformation
In the serum, tetracosactide acetate 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 tetracosactide acetate from the plasma consists of 3 phases. The half-lives of these phases are approximately 7 minutes (0 to 1 hour), 37 minutes (1 to 2 hours) and 3 hours thereafter.
Following an iv dose of ^{131}I-labelled tetracosactide acetate, 95 to 100% of the radioactivity is excreted in the urine within 24 hours.

5.3 Preclinical safety data

No studies have been performed to evaluate the mutagenic or carcinogenic potential of tetracosactide. No animal studies on fertility and reproduction toxicity have been performed with tetracosactide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid,
Sodium acetate,
Sodium chloride,
Water for injection.

6.2 Incompatibilities

None known.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Synacthen should be protected from light and stored in a refrigerator (2 - 8°C).

6.5 Nature and contents of container

The ampoules are colourless glass Ph.Eur type I.

Synacthen Ampoules comes in cardboard boxes of 1 ampoule and 5 ampoules of 1 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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SS14 3FR
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8 MARKETING AUTHORISATION NUMBER(S)

PL 43252/0026

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25 June 1998

10 DATE OF REVISION OF THE TEXT

27/11/2024