Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Synarel 200 micrograms/dose Nasal Spray Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution containing 2mg/ml of nafarelin (as acetate) supplied in bottles fitted with a metered spray pump that delivers 200 micrograms of nafarelin base per spray.

This medicine contains 0.01 mg benzalkonium chloride in each spray (0.1 mL per spray) which is equivalent to 0.1 mg/mL.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Nasal spray, solution
A clear, colourless to slightly yellow, aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Synarel is indicated for the hormonal management of endometriosis, including pain relief and reduction of endometriotic lesions.

Synarel may also be used in the hormonal management of symptomatic uterine fibroids prior to a planned myomectomy or hysterectomy, including the relief of clinical symptoms and the reduction of uterine and fibroid volume.

Synarel may be used in controlled ovarian stimulation programmes prior to *in vitro* fertilisation, under the supervision of an infertility specialist.

4.2 Posology and method of administration

Synarel is for administration by the intranasal route only

Endometriosis and uterine fibroids:
Treatment should be started between days 2 and 4 of the menstrual cycle.

The recommended daily dose of Synarel is 200mcg taken twice daily (400mcg/day) as one spray to one nostril in the morning and one spray into the other nostril in the evening.
The recommended duration of therapy is six months for the management of endometriosis and three months for the management of uterine fibroids.

Controlled ovarian stimulation prior to in vitro fertilisation:
In the use of Synarel associated with controlled ovarian stimulation prior to *in vitro* fertilisation, the long protocol should be employed, whereby Synarelis continued through a period of transient gonadotrophin stimulation lasting 10-15 days (the 'flare effect') through to pituitary desensitisation (down-regulation).
Down-regulation may be defined as serum oestradiol ≤ 50pg/ml and serum progesterone ≤1ng/ml, and the majority of patients down-regulate within 4 weeks.

The recommended daily dose of Synarel is 400mcg taken twice daily as one spray to each nostril in the morning, and one spray each nostril in the evening (800mcg/day).

Once down-regulation is achieved, controlled ovarian stimulation with gonadotrophins, e.g. hMG, is commenced, and the Synarel dosage maintained until the administration of hCG at follicular maturity (usually a further 8-12 days).

If patients do not down-regulate within 12 weeks of starting Synarel, it is recommended that Synarel therapy be discontinued and the cycle cancelled.

Treatment may begin in either the early follicular phase (day 2) or the mid-luteal phase (usually day 21).

Bottles contain either 30 or 60 doses and should not be used for a greater number of doses. The 60 dose-unit bottle is sufficient for 30 days' treatment at 400mcg (2 sprays) per day, and 15 days treatment at 800mcg (4 sprays) per day.

The 30 dose-unit bottle is sufficient for 15 days' treatment at 400mcg (2 sprays) per day, and 7 days' treatment at 800mcg (4 sprays) per day. Patients should therefore be advised that continued use after this time may result in delivery of an insufficient amount of nafarelin.

4.3 Contraindications

Synarel should not be administered to patients who are:
1. Hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs or any of the excipients of Synarel listed in section 6.1
2. Have undiagnosed abnormal vaginal bleeding;
3. Are pregnant or may become pregnant;
4. Are breast-feeding;
5. Have hormone-dependent neoplasms

4.4 Special warnings and precautions for use

Synarel should be used under the supervision of a specialist with appropriate monitoring facilities.

Experience with the treatment of endometriosis has been limited to women 18 years of age and older.

In clinical studies the majority of women have only received up to six-months treatment with Synarel. Retreatment cannot be recommended since safety data for retreatment are not available.

When regularly used at the recommended dose, nafarelin inhibits ovulation. In the event of missed doses there may be breakthrough ovulation and a potential for conception. Patients should be advised to use non-hormonal, barrier methods of contraception. Therefore, if a patient becomes pregnant during treatment, administration of the drug must be discontinued and the patient must be informed of a potential risk to foetal development and/or miscarriage. As there is a risk of miscarriage in the patient population, a causal association with nafarelin acetate is uncertain.

Administration of nafarelin in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 8 weeks after treatment is discontinued. Diagnostic tests of pituitary-gonadal function conducted during the treatment and 4 to 8 weeks after discontinuation of nafarelin therapy may therefore be misleading. There may be an exacerbation of symptoms of pain and increase in nodular mass and pressure during the first weeks of treatment.

As with other drugs in this class ovarian cysts have been reported to occur in adult women in the first two months of therapy with Synarel. Many, but not all of these events occurred in patients with polycystic ovarian disease. These cystic enlargements may resolve spontaneously, generally by about four to six weeks of therapy, but in some cases may require discontinuation of drug and/or surgical intervention.

After a course of therapy, if further treatment of endometriosis and fibroids with nafarelin acetate is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits.

In adults, after six months of nafarelin acetate treatment there was very little, if any, decrease in the mineral content of the distal radius and second metacarpal. There was a reduction in vertebral trabecular bone density and total vertebral mass, averaging 8.7% and 4.3%, respectively. Substantial recovery of bone occurred during the post-treatment period. Total vertebral

bone mass, measured by dual photon absorptiometry (DPA) decreased by a mean of 5.9% at the end of treatment. Mean total vertebral mass, re-examined by DPA six months after completion of treatment, was 1.4% below pre-treatment levels.

If the use of a nasal decongestant is required at the time of nafarelin administration, it is recommended that the nasal decongestant be used at least 30 minutes after nafarelin dosing (see section 4.5).

Sneezing during or immediately after dosing may impair absorption of Synarel. If sneezing occurs upon administration, repeating the dose may be advisable.

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as nafarelin. Patients should be informed accordingly and treated as appropriate if symptoms occur.

Controlled ovarian stimulation prior to in vitro fertilisation;

As with other GnRH agonists, there have been reports of ovarian hyperstimulation syndrome (OHSS), associated with the use of nafarelin in combination with gonadotropin. Patients being treated for controlled ovarian stimulation prior to in vitro fertilisation should be monitored carefully. If signs of OHSS develop, treatment should be discontinued (see section 4.8).

Transient ovarian cyst formation is a recognised complication of GnRH agonist use. These cysts tend to spontaneously regress over a number of weeks and are more common when GnRH agonists are commenced in the follicular phase of the cycle.

There are no clinical data available on the use of Synarel in controlled ovarian stimulation regimes involving patients with polycystic ovarian syndrome. Caution is advised in this patient group as they are at greater risk of excessive follicular recruitment when undergoing controlled ovarian stimulation regimes.

Synarel contains the preservative benzalkonium chloride. Long-term use may cause oedema of the nasal mucosa. If a persistent oedema in the nasal mucosa is suspected, a medicinal product for nasal use without preservative should be chosen, if possible. If such products for nasal use are not available, the use of other formulations of the medicinal product should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic-based drug-drug interaction studies have been conducted with nafarelin acetate. Nafarelin would not be expected to participate in pharmacokinetic-based drug-drug interactions because degradation of the compound is primarily by the action of peptidases not cytochrome P-450 enzymes. Additionally, because nafarelin is only about 80% bound to plasma proteins (albumin) at 4°C, drug interactions at the protein-binding level would not be expected to occur.

Rhinitis does not impair nasal absorption of nafarelin. Nasal decongestants used 30 minutes before nafarelin administration decrease absorption.
The use of the decongestant oxymetazoline hydrochloride by subjects with perennial rhinitis 30 minutes prior to nafarelin acetate administration significantly reduced the extent of nasal absorption of nafarelin acetate (39% decrease in AUC0-8h; 49% decrease in Cmax) compared to the absorption attained in subjects with normal nasal mucosa. The concomitant use of decongestants should be discouraged in patients receiving nafarelin acetate (see Section 4.4.)

4.6 Fertility, pregnancy and lactation

Use of nafarelin in human pregnancy has not been studied.

Synarel should not therefore be used during pregnancy or suspected pregnancy. Before starting treatment with Synarel pregnancy must be excluded. If a patient becomes pregnant during treatment, administration of the drug must be discontinued and the patient must be informed of a potential risk to foetal development.

Reproductive studies of nafarelin acetate in rats have shown foetal toxicity at 10 times the intranasal human dose. No such toxicity was noted in mice or rabbits (see Section 5.3). Nafarelin acetate may cause foetal harm when administered to a pregnant woman (see section 5.3). Thus nafarelin acetate is contra-indicated for use during pregnancy (see Section 4.3).

Controlled ovarian stimulation prior to in vitro fertilisation:

Pregnancy should be excluded before starting treatment with Synarel, and the medication should be stopped on the day of administration of hCG.

It is not known whether or to what extent nafarelin is excreted into human breast milk. The effects, if any on the breast-fed child have not been determined and therefore Synarel should not be used by breast-feeding women, (see Section 4.3).

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Initial treatment with nafarelin acetate may cause transient exacerbation of endometriosis and other symptoms of oestrogen imbalance; chronic treatment may induce a menopausal state. The following undesirable effects have been observed and reported during treatment of 282 adult patients with nafarelin acetate with the following frequencies: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Not known: Cannot be estimated from the available data.

Adult population

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Immune system disorders	***Common***	Drug hypersensitivity (Chest pain, Dyspnoea, Pruritus, Rash, Urticaria)
Endocrine disorders	***Common***	Oestrogen deficiency
Metabolism and nutrition disorders	***Very common***	Weight increased
	Common	Weight decreased
Psychiatric disorders	***Very common***	Affect lability, Libido decreased
	Common	Depression, Insomnia, Libido increased, mood changes
Nervous system disorders	***Very common***	Headache
	Common	Paraesthesia
Vascular disorders	***Very common***	Hot flush
	Common	Hypertension, Hypotension
Respiratory, thoracic and mediastinal disorders	***Very common***	Rhinitis
Skin and subcutaneous tissue disorders	***Very common***	Acne, Seborrhoea
	Common	Hirsutism
	Uncommon	Alopecia
Musculoskeletal and connective tissue disorders	***Very common***	Myalgia
	Uncommon	Arthralgia
Reproductive system and breast disorders	***Very common***	Breast atrophy, Vulvovaginal dryness
	Common	Artificial menopause, Uterine haemorrhage
	Uncommon	Breast enlargement, Ovarian cyst
	Not known	Ovarian hyperstimulation syndrome
General disorders and administration site conditions	***Very common***	Oedema
Investigations	***Common***	Bone density decreased

In addition to the above mentioned undesirable affects, migraine, blurred vision, palpitations, shortness of breath, androgenic, arthritic symptoms, interstitial pneumonitis, pulmonary fibrosis, increased levels of SGOT/SGPT and serum alkaline phosphatase have been reported but the frequencies are not known.

Changes in bone density:
After six months of Synarel treatment there was very little, if any, decrease in the mineral content of compact bone of the distal radius and second metacarpal. There was a reduction in vertebral trabecular bone density and total vertebral mass averaging 8.7% and 4.3%, respectively. Substantial recovery of bone occurred during the post-treatment period. Total vertebral bone mass, measured by dual photon absorptiometry (DPA), decreased by a mean of 5.9% at the end of treatment. Mean total vertebral mass, re-examined by DPA six months after completion of treatment, was 1.4% below pre-treatment levels. These changes are similar to those which occur during treatment with other GnRH agonists.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of themedicinal product is important. It allows continued monitoring of thebenefit/risk balance of the medicinal product. Healthcare professionals areasked to report any suspected adverse reactions via HPRA Pharmacovigilance.Website: www.hpra.ie.

4.9 Overdose

In animals, subcutaneous administration of up to 60 times the recommended human dose (expressed on a mcg/kg basis) has no adverse effects. Orally administered nafarelin is subject to enzymatic degradation in the gastro-intestinal tract and is therefore inactive. At present there is no clinical experience with overdosage of nafarelin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03X
Nafarelin is a potent agonistic analogue of gonadotrophin releasing hormone (GnRH). Given as a single dose, nafarelin stimulates release of the pituitary gonadotrophins, LH and FSH, with consequent increase of ovarian and testicular steroidogenesis. During repeated dosing this response to stimulation gradually diminishes. Within three to four weeks, daily administration leads to decreased pituitary gonadotrophin secretion and/or the secretion of gonadotrophins with lowered biological activity. There is a consequent suppression of gonadal steroidogenesis and inhibition of functions in tissues that depend on gonadal steroids for their maintenance

5.2 Pharmacokinetic properties

Nafarelin is rapidly absorbed into the circulation after intranasal administration. Maximum plasma concentration is achieved 20 minutes after dosing and the plasma half-life is approximately 4 hours. Bioavailability of the intranasal dose averages 2.8% (range 1.2-5.6%).

Twice daily administration of 200 or 400mcg of nafarelin in 18 healthy women for 22 days did not lead to significant accumulation of the drug.

When nasal decongestants were used 30 minutes before nafarelin administration, nafarelin absorption was decreased.

In vitro studies using adult human plasma showed 78% to 84% of nafarelin is bound to plasma protein, primarily the albumin fraction.

In three subjects given ^{14}C-Nafarelin subcutaneously, 44% to 56% and 19% to 44% of radioactivity was recovered in the urine and faeces, respectively. Approximately 3% of the dose appears as unchanged nafarelin in urine. The total recovery of the administered dose averaged 83%. Six metabolites have been identified; however, their biological activities have not been determined.

5.3 Preclinical safety data

Carcinogenesis/mutagenesis:
As seen with other GnRH agonists, nafarelin given parenterally in high doses to laboratory rodents for prolonged periods induced hyperplasia and neoplasia of endocrine organs, including the anterior pituitary (adenoma/carcinoma) of both mice and rats; tumours of the pancreatic islets, adrenal medulla, testes and ovaries occurred only in long-term studies in rats. No metastases of these tumours were observed.

Monkeys treated with high doses of nafarelin for one year did not develop any tumours or proliferative changes. There is no evidence for tumorigenesis of GnRH analogues in human beings.

In vitro studies conducted in bacterial and mammalian systems provided no indication of a mutagenic potential for nafarelin.

Impairment of fertility:

Reproduction studies in rats of both sexes have shown full reversibility of fertility suppression when drug treatment was discontinued after continuous administration for up to six months.

When administered intramuscularly to rats on days 6-15 of pregnancy at doses of 0.4, 1.6 and 6.4 mcg/kg/day (0.6, 2.5 and 10.0 times the intranasal human dose), 4/80 foetuses in the highest dose group had major foetal abnormalities that were not seen in a repeat study in rats.
Moreover, studies in mice and rabbits failed to demonstrate an increase in foetal abnormalities.
In rats, there was a dose-related increase in foetal mortality, and a decrease in foetal weight with the highest dose.

These effects on rat foetal mortality are logical consequences of the alterations in hormonal levels brought about by Synarel in this species.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol
Benzalkonium chloride
Glacial acetic acid
Purified water
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. Store in upright position. Store in the original container.

6.5 Nature and contents of container

White, high density polyethylene bottles with a 0.1 ml metered spray pump, containing 6.5 ml (30 sprays) or 10 ml (60 sprays).

PVC-coated glass bottles with an internal conical reservoir in the base and a valois pump, with either an aluminium crimp-on cap or a polypropylene snap-on cap, containing 4 ml (30 sprays) or 8 ml (60 sprays).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The bottle should not be used after 30 or 60 sprays, depending on the bottle size.

7 MARKETING AUTHORISATION HOLDER

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The Watermarque Building
Ringsend Road
Dublin 4
D04 K7N3
Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 7th March 2007

10 DATE OF REVISION OF THE TEXT

December 2024