1. NAME OF THE MEDICINAL PRODUCT

Synarel ® 2mg/ml Nasal Spray

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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, solution.
Clear, colourless to slightly yellow, aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The hormonal management of endometriosis, including pain relief and reduction of endometriotic lesions.

Use in controlled ovarian stimulation programmes prior to in-vitro fertilisation, under the supervision of an infertility specialist.

4.2 Posology and method of administration

Adult: Synarel is for administration by the intranasal route only.

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

Endometriosis: In the use of Synarel in endometriosis, the aim is to induce chronic pituitary desensitisation, which gives a menopause-like state maintained over many months.

The recommended daily dose of Synarel is 200 mcg taken twice daily as one spray (200 mcg of nafarelin) to one nostril in the morning and one spray into the other nostril in the evening (400 mcg/day). Treatment should be started between days 2 and 4 of the menstrual cycle. The recommended duration of therapy is six months; only one 6-month course is advised. In clinical studies the majority of women have only received up to six-months treatment with Synarel.

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 Synarel is 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 400 mcg taken twice daily as one spray to each nostril in the morning, and one spray to each nostril in the evening (800 mcg/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.

Important Tips about using Synarel

- The pump should produce a fine mist, which can only happen by a quick and firm pumping action. It is normal to see some larger droplets of liquid within the fine mist. However, if Synarel comes out of the pump as a thin stream of liquid instead of a fine mist, Synarel may not work as well, and the patient should talk to a pharmacist.
- Be sure to clean the Spray Tip after priming (at the time of the first use). The spray tip should then be cleaned before and after every use. Failure to do this may result in a clogged tip that may cause the patient not to get the right amount of medicine that is prescribed for them. Always replace the safety clip and the plastic dust cap on the nasal piece after use to help prevent the tip becoming clogged.
- The pump is made to deliver only a set amount of medicine, no matter how hard you pump it.
- Do not try to make the tiny hole in the spray tip larger. If the hole is made larger the pump will deliver a wrong dose of Synarel.

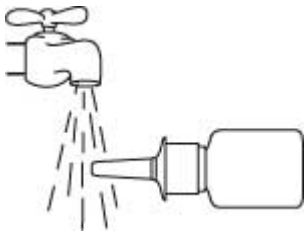
Priming the Spray Pump: Before the patient uses a bottle of Synarel for the first time, they have to prime the spray pump. This only needs to be done once, before they use the first dose.

1. Remove and save the safety clip and the plastic dust cap to uncover the nasal piece. Hold the bottle with in an upright position away from you with two fingers on the 'shoulders' and your thumb on the bottom of the bottle.

2. Prime the pump by pressing the bottle upwards several times firmly and quickly until the air is expelled and a fine spray appears. This usually requires about 5 - 7 presses. It is not necessary to prime the pump again during subsequent use. You will waste your medicine if you prime the pump every time you use it.

3. Clean the Spray Tip after Priming:

Hold the bottle in a horizontal position and rinse the spray tip with warm water, while wiping the tip with your finger or a clean soft cloth for 15 seconds.



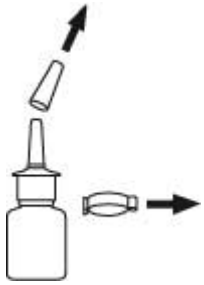
Do not clean the spray tip with a pointed object. This could cause an improper dose of the spray to be delivered. Do not remove the pump from the bottle, as this will release the priming pressure.

Wipe the tip dry with a clean soft cloth or tissue.

Using the Spray Pump

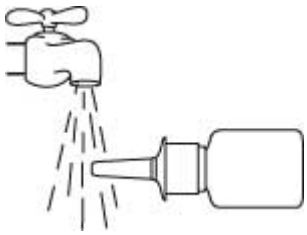
1. Gently blow the nose to clear the nostrils.

2. Remove the safety clip and the plastic cap to uncover the nasal piece. Hold the bottle as shown previously.



3. Clean the tip of pump.

Hold the bottle in a horizontal position and rinse the spray tip with warm water, while wiping the tip with your finger or a clean soft cloth for 15 seconds.



Do not clean the spray tip with a pointed object. This could cause an improper dose of the spray to be delivered. Do not remove the pump from the bottle, as this will release the priming pressure.

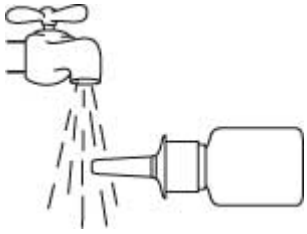
Wipe the tip dry with a clean soft cloth or tissue.

4. Bend head forward slightly. Close one nostril and put the spray tip into the other, aiming towards the **back** and **outer side** of the nose.

5. Press the bottle firmly up between thumb and fingers **once only** whilst gently breathing in through the nostril. For patients using 4 sprays per day, Synarel should now be sprayed into the other nostril.

6. Remove the sprayer from the nostril. Bend head backwards for a few seconds to let the spray spread over back of the nose.

7. Clean the tip of pump. Hold the bottle in a horizontal position and rinse the spray tip with warm water, while wiping the tip with your finger or a clean soft cloth for 15 seconds.

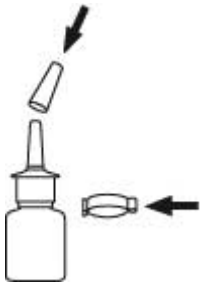


Do not clean the spray tip with a pointed object. This could cause an improper dose of the spray to be delivered. Do not remove the pump from the bottle, as this will release the priming pressure.

Wipe the tip dry with a clean soft cloth or tissue.

Cleaning the spray tip before and after use is important to prevent clogging of the tip that may cause you to get the wrong dose of medicine.

8. Replace the safety clip and the plastic dust cap on the nasal piece. This is important as it helps to prevent the spray tip becoming clogged.



4.3 Contraindications

A small loss of trabecula bone mineral content occurs during 6 months treatment with nafarelin. Although this is mostly reversible within 6 months of stopping treatment, there are no data on the effects of repeat courses on bone loss. Retreatment with Synarel or use for longer than 6 months is, therefore, not recommended. (See Special warnings and precautions for use on 'Changes in bone density').

Synarel should not be administered to patients who:

1. are hypersensitive to GnRH, GnRH agonist analogues or any of the excipients in Synarel;

2. have undiagnosed vaginal bleeding;

3. are pregnant or may become pregnant whilst taking Synarel (see 'use in pregnancy and lactation');

4. are breast-feeding.

4.4 Special warnings and precautions for use

When regularly used at the recommended dose, nafarelin inhibits ovulation. Patients should be advised to use non-hormonal, barrier methods of contraception. In the event of missed doses there may be breakthrough ovulation and a potential for conception. 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 fetal development and/or miscarriage. As there is a risk of miscarriage in the patient population, a causal association with nafarelin acetate is uncertain. NB Synarel treatment will be stopped at least 3 days before fertilised embryos are placed in the uterine cavity.

As with other drugs in this class ovarian cysts have been reported to occur 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 pretreatment levels.

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 regress spontaneously 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 ovulation induction regimens 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 ovulation induction regimes.
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 up to 8 weeks after discontinuation of nafarelin therapy may therefore be misleading.

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

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

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.

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

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), 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

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 of 400mcg per day), 4/80 fetuses in the highest dose group had major fetal abnormalities that were not seen in a repeat study in rats. Moreover, studies in mice and rabbits failed to demonstrate an increase in fetal abnormalities. In rats, there was a dose-related increase in fetal mortality, and a decrease in fetal weight with the highest dose. These effects on rat fetal mortality are logical consequences of the alterations in hormonal levels brought about by nafarelin in this species.

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 fetal development. (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. Barrier methods of contraception should be employed whilst Synarel is being taken.

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

Not applicable.

4.8 Undesirable effects

Initial treatment with nafarelin acetate may cause transient exacerbation of endometriosis and 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
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, increased levels of SGOT/SGPT and serum alkaline phosphatase have been reported but the frequencies are not known.

Reporting of suspected adverse reactions

Reporting 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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In animals, subcutaneous administration of up to 60 times the recommended human dose (expressed on a mcg/kg basis) had 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.

Based on studies in monkeys, nafarelin is not absorbed after oral administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: H01CA02

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 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%).

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. Experience in humans is limited but 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol, benzalkonium chloride, glacial acetic acid and water.
Sodium hydroxide or hydrochloric acid (for pH adjustment).

6.2 Incompatibilities

None stated.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store upright below 25ºC. Avoid heat above 30ºC. Protect from light and freezing.

6.5 Nature and contents of container

White, high density polyethylene bottles with a 0.1ml metered spray pump, containing 6.5ml or 10ml.

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 4ml or 8ml.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

In order to ensure that the correct dose of medicine is administered, it is important that the spray tip is cleaned after priming (at the time of the first use). The spray tip should then be cleaned before and after every use to avoid the tip becoming clogged (see section 4.2).

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/1052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 August 2003

10 DATE OF REVISION OF THE TEXT

14/11/2022