Medicines & Healthcare products
Regulatory Agency

10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom
gov.uk/mhra

[redacted]

27 October 2023

Our ref: FOI 23/050

Dear [redacted]

Thank you for your letter, dated 23 December 2022, making a request for information under the Freedom of Information Act. We apologise for the long delay in this reply. You requested:

1. What is the current and past regulatory status of “Suprecur 150 micrograms Nasal Spray Solution” (Buserelin) and reasoning therefore?
2. As estimated date by which “Suprecur 150 micrograms Nasal Spray Solution” (Buserelin) will be re-approved / the regulatory issue preventing the sale thereof be resolved, and a summary of the regulatory issues standing in the way of this occurring.
3. The current regulatory status of the related medicine “Synarel 2mg/ml Nasal Spray” (Nafarelin)
4. In the event that “Synarel 2mg/ml Nasal Spray” is also not currently authorised for sale in the UK as of 23rd December 2022, I request details of current and past regulatory status, an estimated date by which regulatory issues will be resolved, and a summary of the issues standing in the way.

We confirm that we hold some of the information you have requested.

According to our records, Suprecur 150 micrograms Nasal Spray (product licence number PL 45043/0049) is a UK licensed medicine and has been so since 14 October 1998. A product licence will only be granted if an application is received, which is subject to our assessment, that demonstrates the product meets the required standards of safety, quality and efficacy. Further information about this product can be found in the Summary of Product Characteristics, a copy of which is enclosed.

We received a notification from the licence holder, Neon Healthcare Limited, on 01 February 2022, stating that the status of the product is ‘not marketed’. We have not yet received anything further to change the status to marketed.

In terms of the second product you asked us about, according to our records, Synarel 2 mg/ml Nasal Spray Solution (product licence number PL 00057/1052) is a UK licensed medicine and has been so since 13 August 2003. As we have said above, a product licence will only be granted if an application is received, which is subject to our assessment, that demonstrates the product meets the required standards of safety, quality and efficacy. Further information about this product can be found in the Summary of Product Characteristics, a copy of which is also enclosed.

We were notified by the licence holder, Pfizer Limited, in May 2023 that there would be a cessation in marketing of this product. However, we have since received a notification from Pfizer Limited, in August, confirming that the product would be marketed. That is the latest update we have received.

Whilst we are the regulatory body for medicines in the UK, we do not lead on supply issues. These are managed by a team at the Department of Health and Social Care (DHSC). If you need any information about supply issues affecting any medicines then please contact DHSC directly via:

Ministerial Correspondence and Public Enquiries Unit
Department of Health and Social Care
39 Victoria Street
London
SW1H 0EU

We apologise once more for the long delay in this reply, but we hope the information is useful to you.

If you are dissatisfied with the handling of your request, you have the right to ask for an internal review. Internal review requests should be submitted within two months of the date you receive this response and addressed to: info@mhra.gov.uk

Please remember to quote the reference number above in any future communications.

If you were to remain dissatisfied with the outcome of the internal review, you would have the right to apply directly to the Information Commissioner for a decision. Please bear in mind that the Information Commissioner will not normally review our handling of your request unless you have first contacted us to conduct an internal review. The Information Commissioner can be contacted at:

Information Commissioner’s Office
Wycliffe House
Water Lane
Wilmslow
Cheshire
SK9 5AF

Yours sincerely

MHRA Customer Experience Centre
Communications and engagement team
Medicines and Healthcare products Regulatory Agency
10 South Colonnade, Canary Wharf, London E14 4PU

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Suprecur 150 micrograms Nasal Spray Solution
Buserelin 150 micrograms Nasal Spray Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Suprecur/Buserelin nasal spray contains 150 micrograms buserelin, as buserelin acetate, in one spray dose.
150 micrograms buserelin is equivalent to 157.5 micrograms buserelin acetate.

Excipient(s) with known effect: benzalkonium chloride
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal Spray Solution

The preparation is a clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of endometriosis in cases that do not require surgery as primary therapy.

Pituitary desensitisation in preparation for ovulation induction regimens using gonadotrophins.

4.2 Posology and method of administration

Posology

Endometriosis:
The total daily dose is 900 micrograms buserelin, administered as one spray dose in each nostril in the morning, at mid-day and in the evening. The product may be used

before or after meals or at other times, provided that uniform intervals are maintained between doses.

The usual duration of treatment is six months and this should not be exceeded. Only a single course of treatment is recommended.

Repeated courses of treatment must only be administered after a careful review of the risk/benefit ratio by the attending physician since the possibility of additive effects on bone mass (reduction in bone mass) cannot be excluded (see also section 4.4).

Pituitary desensitisation prior to ovulation induction:
The total daily intranasal dose for this indication is 600 micrograms buserelin, given in four divided dosages of 150 micrograms (one application in one nostril) spread over the waking hours. Treatment should start in the early follicular phase (day 1) or, provided the existence of an early pregnancy has been excluded in the midluteal phase (day 21). It should continue at least until down-regulation is achieved e.g. serum oestradiol <50 ng/l and serum progesterone <1 microgram/l. This will usually take about 2-3 weeks. In some patients, dosages up to 4 x 300 micrograms may be required to achieve these levels. When down-regulation is achieved, stimulation with gonadotropin is commenced while the dosage of buserelin is maintained. At the appropriate stage of follicular development, gonadotropin and buserelin are stopped and hCG is given to induce ovulation.

Treatment monitoring, oocyte transfer and fertilisation techniques are performed according to the normal practice of the individual clinic.

Luteal support with hCG or progesterone should be given as appropriate.

If used correctly, reliable absorption of the active ingredient takes place via nasal mucous membranes. The drug is absorbed even if the patient has a cold; however, in such cases the nose should be blown thoroughly before administration.

If nasal decongestants are being used concurrently, they should be administered at least 30 minutes after the buserelin.

Children:
Suprecur/Buserelin is not suitable for use in children.

Elderly:
Suprecur/Buserelin is not suitable for use in post-menopausal women.

Method of administration
Nasal use only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or LHRH. Buserelin should not be used if the tumour is found to be insensitive to hormone manipulation, after surgical removal of the testes or in cases of undiagnosed vaginal bleeding. It should not be used during pregnancy or lactation (see section 4.6).

4.4 Special warnings and precautions for use

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

Patients known to suffer from depression should be carefully monitored and treated if necessary during treatment with Suprecur/Buserelin (risk of recurrence or worsening of depression).

In patients with hypertension, blood pressure must be checked regularly (risk of deterioration of blood pressure levels).

QT Prolongation
Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Suprecur/Buserelin.

The use of GnRH-agonists may be associated with decreased bone density and may lead to osteoporosis and an increased risk of bone fracture (see section 4.8). Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with anticonvulsants or corticosteroids or a family history of osteoporosis) it is recommended to periodically monitor bone mineral density (BMD) and use preventative measures during therapy to prevent osteopenia/osteoporosis.

In some patients treated with GnRH-agonists, change in glucose tolerance is observed (see section 4.8). In diabetic patients blood glucose levels must be checked regularly (risk of deterioration of metabolic control).

Endometriosis:
Patients should discontinue oral contraceptives before starting treatment. Where appropriate, alternative, non-hormonal methods of contraception should be used. If treatment is interrupted even for only a few days, ovulation may occur and there is a risk of pregnancy.

Suprecur/Buserelin treatment should be started on the first or second day of menstruation in order to exclude pre-existing pregnancy as far as possible. A pregnancy test is advisable if there is any doubt.

It is not expected that pregnancy will occur during the course of the treatment if the recommended doses are taken regularly. However, if treatment is interrupted for only a few days, ovulation and pregnancy may occur. If pregnancy does occur, treatment with buserelin must be discontinued immediately and a physician must me informed (see also section 4.6).

Repeated courses of treatment must only be administered after a careful review of the risk/benefit ratio by the attending physician since the possibility of additive effects on bone mass (reduction in bone mass) cannot be excluded (see also section 4.8). A course of treatment with buserelin lasting several months may lead to loss of bone mineral content. For this reason, the recommended **maximal** duration of treatment should be 6 months.

A menstruation-like bleed usually occurs during the first few weeks of treatment. Breakthrough bleeding may also occur during continuing courses of treatment in some patients. Recovery of pituitary-gonadal function usually occurs within 8 weeks of discontinuing treatment.

In the initial treatment with buserelin, ovarian cysts may develop.

Pituitary desensitisation prior to ovulation induction:
Before treatment is started, it is recommended that a pregnancy test be performed.

Induction of ovulation should be carried out under close medical supervision. Risks specific to IVF/ET and related assisted reproduction procedures such as increase in miscarriages, ectopic and multiple pregnancies are unaltered under adjunctive use of buserelin. In addition, follicle recruitment may be increased especially in patients with PCOD.

Combined use of buserelin with gonadotropins may bear a higher risk of ovarian hyperstimulation syndrome (OHSS) than the use of gonadotropins alone.

In patients with polycystic ovarian syndrome, caution is recommended, because there is an increased tendency towards ovarian hyperstimulation syndrome when combined with gondatropins.

Possible clinical signs of ovarian hyperstimulation syndrome (OHSS) include: abdominal pain, feeling of abdominal tension, increased abdominal girth, occurrence of ovarian cysts, nausea, vomiting, as well as massive enlargement of the ovaries, dyspnoea, diarrhoea, oliguria, haemoconcentration, hypercoagulability. Pedicle torsion or rupture of the ovary may lead to an acute abdomen. Severe thromboembolic events may also occur. Fatal outcome is possible.

The stimulation cycle should be monitored carefully to identify patients at risk of developing OHSS. hCG should be withheld if necessary.

Ovarian cysts have been observed in the initial phase of buserelin treatment. No impact on the stimulation cycle has been reported so far.

Treatment with Suprecur/Buserelin should be initiated only under the supervision of a specialist with experience of the indication.

Suprecur/Buserelin Nasal Spray contains benzalkonium chloride.
This medicine contains 0.1 mg benzalkonium chloride in each spray dose. Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time.

4.5 Interaction with other medicinal products and other forms of interaction

During treatment with buserelin, the effect of antidiabetic agents may be attenuated.
In concomitant treatment with sexual hormones ("add back"), the dosage is to be selected so as to ensure that the overall therapeutic effect is not affected.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Suprecur/Buserelin with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)

antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Suprecur/Buserelin is contraindicated in pregnancy and lactation. In rats, foetal malformations have been seen after very high doses.

Breast-feeding
Buserelin passes into breast milk in small amounts. Although negative effects on the infant have not been observed, it is recommended that breast-feeding be avoided during treatment with Suprecur/Buserelin in order to prevent the infant from ingesting small quantities of buserelin with breast milk.

In endometriosis:
It is unlikely that pregnancy will occur in the later stages of treatment if the recommended doses are taken regularly. However, if treatment is interrupted even for only a few days, ovulation may occur and the patient may become pregnant. In this event, Suprecur/Buserelin must be withdrawn immediately and a physician must be informed (see also section 4.4).

In pituitary desensitisation prior to ovulation induction:
Pregnancy should be excluded before starting Suprecur/Buserelin, and the medication should be stopped on the day of administration of hCG.

4.7 Effects on ability to drive and use machines

Certain adverse effects (e.g. dizziness) may impair the patients ability to concentrate and react, and therefore, constitute a risk in those situations where these abilities are of special importance (e.g. operating a vehicle or machinery).

4.8 Undesirable effects

The following CIOMS frequency rating is used: *Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10 000 to <1/1000); very rare (<1/10 000), not known (cannot be estimated from the available data).*

In isolated cases severe hypersensitivity reactions with shock can occur. These may become manifest as, e.g. reddening of the skin, itching, skin rashes (including urticaria) and allergic asthma with dyspnoea as well as, in isolated cases leading to anaphylactic/anaphylactoid shock.

The nasal spray may irritate the nasal mucosa, leading to nosebleeds and hoarseness as well as to disturbances of smell and taste.

Treatment with buserelin inhibits oestrogen production. As evidence of the biological response to hormone deprivation, patients may experience menopausal-like symptoms and withdrawal bleeding, which are directly related to the pharmacological

action of the drug. Symptoms such as hot flushes, increased sweating, dry vagina, dyspareunia, loss of libido generally occur some weeks after starting treatment and may be severe in some patients. Withdrawal bleeding may occur during the first few weeks of treatment. Breakthrough bleeding may occur during continuing treatment. After several months' treatment, a decrease in bone mass may occur.

Changes in bone density:
A decrease in bone mineral, the magnitude of which relates to the duration of therapy, occurs during treatment with buserelin alone. The evidence available indicates that six months' treatment is associated with a decrease in bone mineral density of the spine of 3.5%. These changes are similar to those seen with other agonists. Increased levels of serum alkaline phosphatase may occur. These are reversible on discontinuing treatment.

Buserelin treatment may also lead to:

Neoplasms benign and malignant – Very rare cases of pituitary adenomas were reported during treatment with GnRH agonists, including buserelin.

Blood disorders – Very rare cases of thrombocytopenia or leukopenia.

Metabolism and nutrition disorders – Frequent: increase or decrease in weight. Occasional: changes in appetite and increased thirst. Rarely: increase or decrease in blood lipid levels. Very rarely: reduction in glucose tolerance which may lead to the worsening of metabolic control in diabetics.

Psychiatric disorders – Frequent: nervousness, emotional instability. Occasional: anxiety, depression or worsening of existing depression.
Mood changes, depression. Frequency: long term use: common
short term use: uncommon

Nervous system disorders – Dizziness, headache (in women in rare cases migraine-like), sleep disturbances, tiredness, drowsiness. Occasional: paraesthesia (especially in the arms and legs), disturbances of memory and concentration.

Eye disorders – Occasional: dry eyes (possibly leading to eye irritations in people who wear contact lenses), impaired vision (e.g. blurred vision), feeling of pressure behind the eyes.

Ear and labyrinth disorders – Rare cases of tinnitus, hearing disorders found.

Cardiac disorders – Frequent: palpitations.
Frequency unknown: QT prolongation (see sections 4.4 and 4.5).

Vascular disorders – Occasional: oedema (of face and extremities) and hot flushes. Very rare cases of a deterioration of blood pressure levels in patients with hypertension.

Gastrointestinal disorders – Frequent: lower abdominal pain, stomach ache, nausea, vomiting, diarrhoea, constipation.

Hepatobiliary disorders – Occasional: increase in serum liver enzyme levels (e.g. transaminases), increase in serum bilirubin.

Skin and subcutaneous tissue disorders – Frequent: dry skin, acne, increase or decrease in scalp hair (alopecia, hirsutism). Occasional: increase or decrease in body hair, splitting nails.

Musculoskeletal and bone disorders – Frequent: musculoskeletal discomfort and pain (including shoulder pain/stiffness). The use of GnRH-agonists may be associated with decreased bone density and may lead to osteoporosis and an increased risk of bone fracture. The risk of skeletal fracture increases with the duration of therapy.

Reproductive system and breast disorders – Frequent: vaginal discharge, increase or decrease in breast size, breast tenderness. Occasional: lactation.

In the initial phase of treatment with buserelin, ovarian cysts may develop (see also section 4.4). For preparation of ovulation induction, however, no negative effect on the course of stimulation has been reported so far.

In-vitro fertilization/embryo transfer programmes and similar assisted reproduction procedures carry inherent risks, e.g. increased occurrence of ectopic pregnancies, miscarriages or multiple pregnancies; this also applies where buserelin is used as adjunctive therapy. The fact that follicle recruitment may be increased under buserelin treatment (especially in the case of polycystic ovaries) may, however, in some patients also represent a desirable effect.

Combined use of buserelin with gonadotropins may bear a higher risk of ovarian hyperstimulation syndrome (OHSS) than the use of gonadotropins alone (see also section 4.4).

Degeneration of uterine fibroids in women with uterine fibroids.

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 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

Overdose may lead to signs and symptoms such as asthenia, headache, nervousness, hot flushes, dizziness, nausea, abdominal pain, oedema of the lower extremities and mastodynia. Treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Hormones and Related Agents
ATC Code: L02AE01

Buserelin is a synthetic peptide. It is a superactive analogue of natural gonadotrophin releasing hormone (gonadorelin, LHRH or GNRH). After an initial stimulation of gonadotrophin release, it down-regulates the hypothalamic-pituitary-gonadal axis.

5.2 Pharmacokinetic properties

The intra-nasal absorption rate of buserelin is about 3%. Metabolic inactivation by peptides occurs in the liver and kidney. The drug is also inactivated by pituitary membrane enzymes. After intra-nasal administration to humans, buserelin is excreted for more than 8 hours in the urine. Virtually all the serum fraction, and half the urine fraction of buserelin, are present as the parent drug.

The bioavailability of buserelin after nasal administration is not adversely influenced by the presence of rhinitis.

5.3 Preclinical safety data

None of clinical relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The nasal spray also contains citric acid, sodium citrate, sodium chloride and benzalkonium chloride in aqueous solution.

6.2 Incompatibilities

None.

6.3 Shelf life

3 years (Unopened).
5 weeks after first opening.

6.4 Special precautions for storage

Store between 2 °C and 25 °C. Do not freeze.

6.5 Nature and contents of container

Cartons containing two bottles and two metered-dose pumps (nebulisers).
Each bottle
contains l0g solution.

6.6 Special precautions for disposal

How to use the spray bottle:

1. Remove screw cap from bottle.

2. Remove metered-dose nebulizer from transparent plastic container and take off both protective caps.

3. Screw nebulizer on to bottle.

4. Before first application only, pump 5-8 times, holding bottle vertical, until the solution has filled the system and a uniform spray is emitted. The preliminary pumping is for the purpose of filling the system and testing the spray. It must not be repeated after the first use, in order to avoid wasting the contents.

5. Keeping bottle vertical and bending head over it slightly, spray solution into nose. If necessary, the nose should be cleaned before applying the solution.

6. After use leave nebulizer on bottle. After replacing protective cap, spray bottle is best stored in its transparent container in an upright position.

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

7 MARKETING AUTHORISATION HOLDER

Neon Healthcare Limited
Mill Studio Business Centre
Crane Mead
Ware, Hertfordshire
SG12 9PY
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 45043/0049

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 23 April 2002
Date of latest Renewal: 20 January 2005

10 DATE OF REVISION OF THE TEXT

24/05/2022

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.

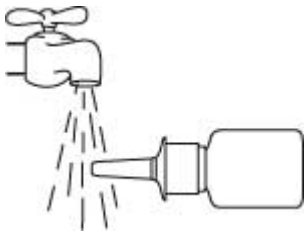
Priming the Spray Pump: Before the patient uses a bottle of Synarel for the first time, they have to prime the spray pump. This only needs to be done once, before they use the first dose.

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.



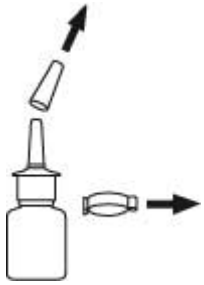
Do not clean the spray tip with a pointed object. This could cause an improper dose of the spray to be delivered. Do not remove the pump from the bottle, as this will release the priming pressure.

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

Using the Spray Pump

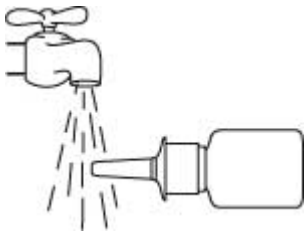
1. Gently blow the nose to clear the nostrils.

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.

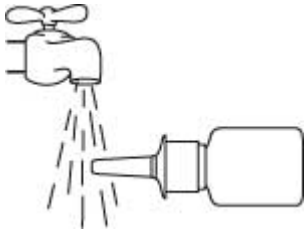
Wipe the tip dry with a clean soft cloth or tissue.

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.

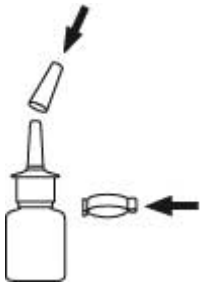


Do not clean the spray tip with a pointed object. This could cause an improper dose of the spray to be delivered. Do not remove the pump from the bottle, as this will release the priming pressure.

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