SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SYNAREL®

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nafarelin acetate is indicated for:

Use in controlled ovarian stimulation programmes prior to in-vitro fertilisation
Hormonal management of endometriosis, including pain relief and reduction of endometrial lesions.
Uterine fibroids

4.2 Posology and method of administration

Synarel® is for administration by the intranasal route only.
The 60 dose unit bottle is sufficient for 30 days' treatment at 400 mcg (2 sprays) per day, and 15 days' treatment at 800 mcg (4 sprays) per day.
Patients should be advised that the use of the contents of the container beyond the abovementioned treatment-days may result in delivery of an insufficient amount of nafarelin acetate.

Controlled Ovarian Stimulation prior to *in-vitro* Fertilisation
400 mcg or 800 mcg daily administered as follows:

400 mcg: one spray (200mcg) to one nostril in the morning and one spray (200 mcg) to the other nostril in the evening.

800 mcg: one spray to each nostril (2x200 mcg) in the morning, and one spray to each nostril (2x200 mcg) in the evening.

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. However, in the use of Synarel® associated with controlled ovarian stimulation prior to *in-vitro* fertilisation, the aims of the treatment protocols are different, as follows:

In the "long protocol" administration, 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 estradiol ≤50pg/ml and serum progesterone ≤1ng/ml , and the majority of patients down-regulate within 4 weeks.

Therapy should be continued until down regulation is achieved; if this does not occur within 12 weeks nafarelin acetate should be discontinued.

Once down-regulation is achieved, controlled ovarian stimulation with gonadotrophines, e.g. hMG, is commenced, and the Synarel® dosage maintained until an appropriate stage of follicular development, when both are withdrawn and chorionic gonadatropin is given to induce ovulation
The "short protocol" employs the flare effect as part of the gonadotrophin stimulation process, which is supplemented by concurrent administration of exogenous gonadotrophins. This usually takes 10-15 days, at which time, hCG is administered.

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

Clinical trials using the long protocol have shown that achievement of down-regulation is more predictable when using a Synarel® dosage of 800 mcg per day.

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

The recommended daily dose of nafarelin acetate is one spray (200 mcg of nafarelin free base) into one nostril in the morning and one spray into the other nostril in the evening (total of 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. Retreatment is not recommended.

The 400 mcg daily dose may not produce amenorrhea in all patients. For these patients, if the symptoms of endometriosis persist, the dose may be increased to 800 mcg daily. The 800 mcg dose is administered as one spray into each nostril in the morning (a total of two sprays) and again in the evening. This high dose should be maintained for 6 weeks and then reduced to 2 x 200 mcg/day.

Retreatment cannot be recommended since safety data beyond 6 months are not available.

Uterine Fibroids
The recommended dose of nafarelin acetate for uterine fibroid patients is one spray (200 mcg of nafarelin free base) to one nostril in the morning and one spray into the other nostril in the evening (400 mcg/day). The duration therapy should not exceed 3 months. Efficacy beyond 3 months has not been established.

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 section 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; 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)

Nafarelin acetate contains the preservative benzalkonium chloride, which may cause contractions of the respiratory passage. The preservative (benzalkonium chloride) in nafarelin

acetate may cause oedemas in the nasal mucosa, especially on long term use. 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. 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 by using an online form

(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic @moh.health.gov.il)

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

Synarel® contains:

Sorbitol, glacial acetic acid, benzalkonium chloride and purified water.
Sodium hydroxide or hydrochloric acid to adjust pH.

6.2 Incompatibilities

None stated.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials
After first opening: can be used for 4 weeks.

6.4 Special precautions for storage

Store upright below 25°C.
Protect from light and freezing.

6.5 Nature and contents of container

Bottle of 60 dose units. Each bottle contains nafarelin acetate solution (2 mg/mL) as nafarelin base.

6.6 Instructions for use and handling

After first opening: can be used for 4 weeks.

7. Manufacturer

PHARMACIA & UPJOHN COMPANY, KALAMAZOO, USA

License holder:
Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St, Hertzliya Pituach 46725

This leaflet format has been determined by the Ministry of Health and the content has been checked and approved in January 2018