

PRODUCT INFORMATION

SYNAREL[®] NASAL SPRAY

NAME OF THE DRUG

Nafarelin Acetate

DESCRIPTION

Nafarelin acetate (SYNAREL[™]) is a decapeptide with the chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-3-(2-naphthyl)-D-alanyl-L-leucyl-L-arginyl-L-prolylglycinamide acetate.

Nafarelin acetate is a fine white to off-white amorphous powder. It is sparingly soluble in water and less soluble in methanol and ethanol. The molecular weight of the anhydrous free decapeptide is 1322.5.

SYNAREL NASAL SPRAY is supplied as a clear, colourless to slightly yellow solution containing 2 mg/mL of nafarelin base. SYNAREL also contains sorbitol, benzalkonium chloride, glacial acetic acid, hydrochloric acid, sodium hydroxide and purified water.

PHARMACOLOGY

Pharmacodynamics

Nafarelin is a potent agonistic analogue of the gonadotrophin releasing hormone (GnRH). Given as a single 250 µg to 1000 µg dose, nafarelin stimulates release of the pituitary gonadotrophins, LH and FSH, with consequent increase of ovarian and testicular steroidogenesis. Repeated intranasal 250 µg to 1000 µg dosing gradually abolishes the stimulatory effect on the pituitary gland. Within three to four weeks, daily administration leads to decreased pituitary gonadotrophin secretion and/or the secretion of gonadotrophins with lowered biological activity with consequent suppression of gonadal steroidogenesis and inhibition of functions and tissues that depend on gonadal steroids for their maintenance.

In controlled clinical studies in patients with endometriosis, SYNAREL was shown to relieve the clinical symptoms of endometriosis (pelvic pain, dyspareunia, dysmenorrhoea) and to reduce the size of endometrial implants as determined by laparoscopy.

In 73 patients, SYNAREL 400 µg daily induced amenorrhoea in approximately 65%, 80% and 90% of patients after 60, 90 and 120 days, respectively. Most of the remaining patients reported episodes of only light bleeding or spotting. In the first, second and third post-treatment months normal menstrual cycles resumed in 4%, 82% and 100%, respectively, of those patients who did not become pregnant.

The efficacy of SYNAREL in controlled ovarian stimulation prior to *in-vitro* fertilisation has been shown in several clinical studies. In 160 women who received nafarelin 200 µg bd or

400 µg bd (80 in each group) as part of a “long” protocol, 86% and 100% respectively achieved down regulation. The 200 µg bd dose did not produce ideal down regulation in all patients in the two pivotal trials, hence subsequent patients were allocated to either 400 µg bd or a comparator GnRH analogue. The time taken for 75% of the women in each group to down regulate was 38 and 24 days respectively. Clinical pregnancy was achieved in 23% and 31% respectively.

The purpose of down regulation is to provide a more controlled stimulation for subsequent stimulation and thereby minimise the occurrence of spontaneous ovulation and premature luteinisation. Limited data only, are available for the “short” protocol.

Pharmacokinetics

Nafarelin is rapidly absorbed into the systemic circulation after intranasal administration. The average time to maximum plasma concentration after dosing is 26 minutes (range 5 to 60 minutes). Bioavailability of the intranasal dose averages 2.8% (range 1.2 to 5.6%). Twice daily administration of 200 µg to 400 µg of nafarelin in 18 healthy women for 22 days did not lead to significant accumulation of the drug.

In vitro studies using human plasma showed 78 to 84% of nafarelin is bound to plasma proteins, primarily the albumin fraction. This contrasts with 22 to 25% binding for GnRH.

In rats given ¹⁴C-nafarelin, the highest concentrations of radioactivity were observed in kidneys, liver and intestines and lowest concentrations were in the brain. In pregnant rabbits dosed with ³H-nafarelin, less than 1% of the radioactivity was found in the uterus, placenta, foetuses and amniotic fluid. In 3 subjects given ¹⁴C-nafarelin subcutaneously, 44 to 56% and 19 to 44% of radioactivity was recovered in the urine and faeces, respectively. The total recovery of the administered dose averaged 83%. Major metabolites recovered in urine of humans have been identified and are thought to be inactive.

The pharmacokinetics of the drug in hepatically and renally-impaired patients have not been determined (Refer to “PRECAUTIONS – Use in hepatically and renally impaired patients”).

INDICATIONS

SYNAREL is indicated for the hormonal management of visually proven endometriosis, including pain relief and reduction of endometriotic lesions and for use in controlled ovarian stimulation programmes prior to *in-vitro* fertilisation, under the supervision of an infertility specialist.

CONTRAINDICATIONS

SYNAREL should not be administered to patients who are hypersensitive to GnRH, GnRH agonist analogues or any of the excipients in SYNAREL, have undiagnosed abnormal vaginal bleeding, are pregnant or who may become pregnant while using SYNAREL or are breast-feeding.

PRECAUTIONS

Effects on Bone Density

The effect of shorter intermittent courses employed for IVF programmes on bone mineral density has not been investigated.

Repeat Courses in Endometriosis

If the symptoms of endometriosis recur after a course of therapy, and further treatment with SYNAREL or another GnRH agonist is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. Current data suggests that at least two years are required between courses of treatment.

Use in Women at High Risk of Reduced Bone Mass

Since the full reversibility of the bone atrophy induced by nafarelin (Refer to “ADVERSE REACTIONS – Changes in bone density”) is currently not clear SYNAREL should be used cautiously in women with clinical conditions where there is a high risk of reduced bone mass. These include women with chronic anovulation/ menstrual disturbances due to weight loss, athletic or other forms of hypothalamic amenorrhoea, immobilisation, glucocorticoid usage or a strong family history of osteoporosis. In such women bone density should be measured prior to the first course of therapy.

General

Functional 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 within four to six weeks of therapy, but in some cases discontinuation of drug and/ or surgical intervention may be required. There are no clinical data available on the use of SYNAREL in ovulation induction 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 ovulation induction regimes.

Transient cyst formation that may accompany GnRH agonist use is more common when GnRH agonists are commenced in the follicular phase of the cycle (flare effect). Patients should be advised of the potential for clinical flare-up of endometriotic symptoms and lesions within the first few weeks of treatment due to the transient rise in oestradiol secretion. During this time the possibility exists of other oestrogen induced side effects occurring i.e. oestrogen-sensitive migraine, epilepsy.

Use in Pregnancy

PREGNANCY CATEGORISATION: D

Before starting treatment with SYNAREL, pregnancy must be excluded (refer “CONTRAINDICATIONS”). When used regularly at the recommended dosage, SYNAREL inhibits ovulation. In the event of missed doses, there may be breakthrough ovulation and a potential for conception. Therefore, patients should be advised to use non-hormonal methods of contraception throughout SYNAREL treatment. If a patient becomes pregnant during

treatment, administration of the drug must be discontinued, and the patient must be apprised of a potential risk to foetal development; NB when used as part of an ovarian stimulation programme, SYNAREL treatment should be stopped at least 3 days before fertilised embryos are placed in the uterine cavity.

In animal studies, intramuscular administration of nafarelin acetate to pregnant rats at doses of 0.4, 1.6 and 6.4 µg/kg/day during organogenesis resulted in a low incidence of foetal abnormalities at the highest dose. This finding was confirmed in a repeat study in rats, but studies in mice and rabbits showed no evidence of teratogenic activity at doses up to 600 µg/kg/day and 0.18 µg/kg/day, respectively.

Use During Lactation

It is not known whether or to what extent nafarelin is excreted into human breast milk. The effects, if any, on the breastfed child have not been determined and therefore SYNAREL should not be used in breastfeeding women.

Use in Women Under 18 Years

Clinical experience with SYNAREL for the treatment of endometriosis has been limited to women 18 years and over.

Use in Hepatically and Renally Impaired Patients

Experience with SYNAREL in patients with hepatic or renal diseases is not available but is believed not to entail any extra risks. Due to lack of data in these patient populations no specific recommendations for dosage adjustments can be made.

Use in Women with Intercurrent Rhinitis

Excessive intercurrent rhinitis either of allergic origin or due to upper respiratory tract infection may impair the absorption of nafarelin from the nasal mucosa. Patients with intercurrent rhinitis should be advised to consult their physician for use of a nasal decongestant. If the use of a nasal decongestant is required during SYNAREL treatment, the decongestant must be used at least 30 minutes after SYNAREL dosing to decrease the possibility of reducing drug absorption.

Drug Interactions

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. Since nafarelin is only 80% bound to plasma proteins (albumin), drug interactions at the protein binding level would not be expected to occur.

Interference with Laboratory Tests

Administration of nafarelin in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nafarelin acetate administered for prolonged periods to rats and mice, at intramuscular doses up to 100 and 500 µg/kg/day respectively, induced hyperplasia and neoplasia of various tissues, inclusive of the anterior pituitary in both species; tumours of pancreatic islet cells, adrenal medulla, testes and ovaries occurred only 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 tumourigenesis of gonadorelin analogues in humans.

Studies conducted in bacterial and mammalian systems provide no indication of a mutagenic potential for nafarelin.

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

ADVERSE REACTIONS

As would be expected with a drug which lowers serum oestradiol concentrations, the most frequently reported adverse reactions were those related to hypoestrogenism. Chronic treatment may induce a menopausal state.*

In controlled studies of nafarelin 400 µg/day, adverse reactions most frequently reported are listed in order of decreasing frequency:

- hot flushes
- change in libido
- vaginal dryness
- headaches
- emotional lability
- acne
- myalgia
- decreased breast size
- irritation of nasal mucosa

Other adverse reactions reported for the same dose of nafarelin include:

- insomnia*
- change in weight*
- oedema*

- hirsutism*
- seborrhoea*

In other clinical studies and during postmarketing surveillance, paraesthesia, depression, arthritic symptoms*, interstitial pneumonitis, pulmonary fibrosis and alopecia have been reported. Blood pressure changes can occur*. In approximately 0.2% of adult patients, symptoms suggestive of drug sensitivity, such as shortness of breath, chest pain, urticaria, rash and pruritus have occurred. In very rare instances, uterine haemorrhage can occur.

Ovarian Hyperstimulation and Multiple Pregnancies

Some degree of ovarian hyperstimulation occurs in all women who respond to gonadotrophins, but this must be distinguished from the Ovarian Hyperstimulation Syndrome (OHSS). This syndrome is conventionally classified as mild, moderate or severe and severe OHSS remains the most important cause of morbidity following controlled ovarian stimulation, often necessitating prolonged periods of hospitalisation. The syndrome is associated with an exaggerated follicular response to gonadotrophin stimulation and is triggered by the luteinising agent (ie. hCG administration or a spontaneous LH surge). Severe OHSS is manifested by hypovolaemia, oliguria, ascites, pleural effusions, haemoconcentration, electrolytic disturbances and hepatic dysfunction. Severe instances of moderate to severe OHSS were reported during IVF trials employing GnRH analogues including nafarelin acetate. The risks of OHSS can be reduced by strict monitoring of follicular size and number, and oestrogen output, thereby reducing the risk of spontaneous LH surge. If criteria for overstimulation are met, then pituitary desensitisation should continue and gonadotrophins withheld until the ovaries have recovered.

Changes in Bone Density

After six months of SYNAREL treatment, vertebral trabecular bone density and total vertebral bone mass, measured by quantitative computed tomography (QCT), decreased by an average of 8.7% and 4.3%, respectively, compared to pretreatment levels. There was partial recovery of bone density in the post-treatment period; the average trabecular bone density and total bone mass were 4.9% and 3.3% less than the pretreatment levels, respectively. 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. There was little, if any, decrease in the mineral content in compact bone of the distal radius and second metacarpal. Use of SYNAREL for longer than the recommended six month period or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss (Refer to “PRECAUTIONS – Use in Women at High Risk of Reduced Bone Mass”).

Changes in Laboratory Values

Plasma Enzymes

During clinical trials with SYNAREL regular laboratory monitoring revealed that one patient each had SGOT and SGPT levels which were more than twice the upper limit of normal. In neither of these patients did the other laboratory values indicate abnormal liver function.

Lipids

In patients treated with SYNAREL 400 µg/day for 6 months 9% (5/59), at enrolment, had total cholesterol values above 6.5 mmol/L which were still above 6.5 mmol/L at the end of treatment. Of those patients whose pretreatment cholesterol values were below 6.5 mmol/L, 6% (3/54) had post-treatment values above 6.5 mmol/L.

The mean (\pm SEM) pretreatment values for total cholesterol in all SYNAREL patients were 5.0 (0.1) mmol/L. At the end of the treatment period the mean values for total cholesterol were 5.3 (0.1) mmol/L. The increase from the pretreatment value was statistically significant ($p < 0.05$). At the end of the 6 month treatment period triglycerides were increased above the upper limit of 1.7 mmol/L in 12% of patients, however, no patient had abnormally low HDL cholesterol fractions (less than 0.8 mmol/L) and none had abnormally high LDL cholesterol fractions (greater than 4.9 mmol/L). There was no increase in the LDL/HDL ratio in patients. The above changes in plasma lipids are consistent with an oestrogen deficiency state.

DOSAGE AND ADMINISTRATION

Endometriosis

The recommended daily dose of SYNAREL in endometriosis patients is one spray (200 µg of nafarelin free base) to one nostril in the morning and one spray into the other nostril in the evening (400 µg/day). Treatment should be started between days 2 and 4 of the menstrual cycle. The 400 µg daily dose may not produce amenorrhoea in all endometriosis patients. For these patients, if the symptoms of endometriosis persist, the dose may be increased to 800 µg daily. The 800 µg dose is administered as one spray into each nostril in the morning (a total of two sprays) and again in the evening.

The recommended duration of therapy is six months. Retreatment cannot be recommended since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with SYNAREL or another GnRH agonist is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. Current data suggests that at least two years are required between courses of treatment. It is recommended that the risks and benefits of treatment with SYNAREL be considered for each individual patient and discussed between patient and prescriber (Refer to “PRECAUTIONS – Use in Women at High Risk of Reduced Bone Mass”).

Controlled Ovarian Stimulation Prior to In-Vitro Fertilisation

The patient should be informed to consult the physician if one or more doses have been missed, and a pregnancy test should subsequently be performed before treatment is to continue.

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 throughout a period of transient gonadotrophin stimulation lasting 10 to 15 days (the ‘flare effect’) through to pituitary desensitisation (down regulation). Down regulation may be defined as serum oestradiol < 50 pg/mL (184 pmol/L) and serum progesterone < 1 ng/mL (3.2 nmol/L); the majority of patients down regulate within 4 weeks.

The precise dosing schedule will depend on the experience of the particular IVF unit and individual patient response in a closely monitored situation. SYNAREL can be given at a dose of 400 µg twice daily administered as one spray in each nostril in the morning and one spray in each nostril at night. This provides a total daily dose of 800 µg of nafarelin. Treatment may begin in the early follicular phase (day 2), or the mid-luteal phase (usually day 21). Administration commencing in the early follicular phase however, probably increases the risk of cyst formation (see “PRECAUTIONS – General”).

Once down regulation is achieved, controlled ovarian stimulation with gonadotrophins, eg hMG, is then commenced, and the SYNAREL dosage is maintained until the administration of hCG at follicular maturity (usually a further 8 to 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.

General

Nasal decongestants should not be administered less than 30 minutes after administering nafarelin.

The 8 mL presentation of SYNAREL (60 x 200 µg actuations) is sufficient for 30 days of SYNAREL treatment at a dose of 400 µg/day and for 15 days treatment at a dose of 800 µg/day. Patients should be advised that the use of the product beyond these times will result in delivery of an insufficient amount of SYNAREL. Refer to the Consumer Product Information for instructions for use of the metered spray pump.

OVERDOSAGE

In animals subcutaneous administration of up to 60 times the recommended human dose (expressed on a µg/kg basis) had no adverse effects. Orally administered nafarelin is subject to enzymatic degradation in the gastrointestinal tract and is therefore inactive. Clinical adverse events reported following overdosage of nafarelin have included local (epistaxis, rhinitis, sinusitis and rash) and systemic (vaginal haemorrhage secondary to enlarged fibroids) effects.

PRESENTATION

SYNAREL NASAL SPRAY is supplied as an 8 mL solution containing nafarelin acetate equivalent to 2 mg/mL of nafarelin base. The spray is supplied with a metered spray pump unit, which, after priming, delivers 200 µg of nafarelin base per spray. The contents of one spray bottle are intended to deliver at least 60 sprays.

PHARMACEUTICAL PRECAUTIONS

Shelf life: 24 months when stored below 25⁰C. Protect from light. Do not freeze. Store container in an upright position.

SPONSOR

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* Please note changes in Product Information

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