

Synarel[®]

(nafarelin acetate)
nasal solution

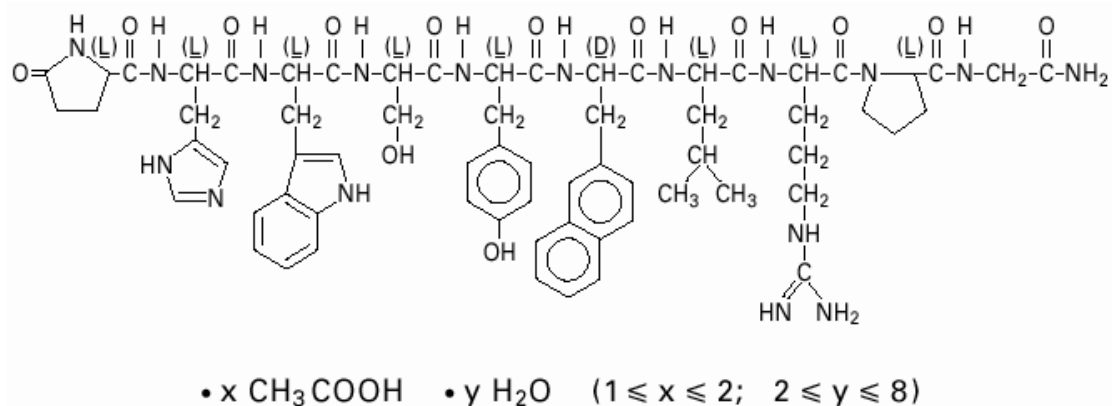
CENTRAL PRECOCIOUS PUBERTY (FOR ENDOMETRIOSIS, SEE REVERSE SIDE)

PHYSICIAN LABELING

DESCRIPTION

SYNAREL (nafarelin acetate) Nasal Solution is intended for administration as a spray to the nasal mucosa. Nafarelin acetate, the active component of SYNAREL Nasal Solution, 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-prolyl-glycinamide acetate. Nafarelin acetate is a synthetic analog of the naturally occurring gonadotropin-releasing hormone (GnRH).

Nafarelin acetate has the following chemical structure:



SYNAREL Nasal Solution contains nafarelin acetate (2 mg/mL, content expressed as nafarelin base) in a solution of benzalkonium chloride, glacial acetic acid, sodium hydroxide or hydrochloric acid (to adjust pH), sorbitol, and purified water.

After priming the pump unit for SYNAREL, each actuation of the unit delivers approximately 100 µL of the spray containing approximately 200 µg nafarelin base. The contents of one spray bottle are intended to deliver at least 60 sprays.

CLINICAL PHARMACOLOGY

Nafarelin acetate is a potent agonistic analog of gonadotropin-releasing hormone (GnRH). At the onset of administration, nafarelin stimulates the release of the pituitary gonadotropins, LH and FSH, resulting in a temporary increase of gonadal steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary gland. Twice daily administration leads to decreased secretion of gonadal steroids by about 4 weeks; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.

In **children**, nafarelin acetate was rapidly absorbed into the systemic circulation after intranasal administration. Maximum serum concentrations (measured by RIA) were achieved between 10 and 45 minutes. Following a single dose of 400 µg base, the observed peak concentration was 2.2 ng/mL, whereas following a single dose of 600 µg base, the observed peak concentration was 6.6 ng/mL. The average serum half-life of nafarelin following intranasal administration of a 400 µg dose was approximately 2.5 hours. It is not known and cannot be predicted what the pharmacokinetics of nafarelin will be in children given a dose above 600 µg.

In **adult women**, nafarelin acetate was rapidly absorbed into the systemic circulation after intranasal administration. Maximum serum concentrations (measured by RIA) were achieved between 10 and 40 minutes. Following a single dose of 200 µg base, the observed average peak concentration was 0.6 ng/mL (range 0.2 to 1.4 ng/mL), whereas following a single dose of 400 µg base, the observed average peak concentration was 1.8 ng/mL (range 0.5 to 5.3 ng/mL). Bioavailability from a 400 µg dose averaged 2.8% (range 1.2 to 5.6%). The average serum half-life of nafarelin following intranasal administration was approximately 3 hours. About 80% of nafarelin acetate was bound to plasma proteins at 4°C. Twice daily intranasal administration of 200 or 400 µg of SYNAREL in 18 healthy women for 22 days did not lead to significant accumulation of the drug. Based on the mean C_{\min} levels on Days 15 and 22, there appeared to be dose proportionality across the two dose levels.

After subcutaneous administration of ^{14}C -nafarelin acetate to men, 44–55% of the dose was recovered in urine and 18.5–44.2% was recovered in feces. Approximately 3% of the administered dose appeared as unchanged nafarelin in urine. The ^{14}C serum half-life of the metabolites was about 85.5 hours. Six metabolites of nafarelin have been identified of which the major metabolite is Tyr-D(2)-Nal-Leu-Arg-Pro-Gly-NH₂(5-10). The activity of the metabolites, the metabolism of nafarelin by nasal mucosa, and the pharmacokinetics of the drug in hepatically- and renally- impaired patients have not been determined.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be

used until at least 2 hours following dosing with SYNAREL.

When used regularly in girls and boys with **central precocious puberty (CPP)** at the recommended dose, SYNAREL suppresses LH and sex steroid hormone levels to prepubertal levels, affects a corresponding arrest of secondary sexual development, and slows linear growth and skeletal maturation. In some cases, initial estrogen withdrawal bleeding may occur, generally within 6 weeks after initiation of therapy. Thereafter, menstruation should cease.

In clinical studies the peak response of LH to GnRH stimulation was reduced from a pubertal response to a prepubertal response (< 15 mIU/mL) within one month of treatment.

Linear growth velocity, which is commonly pubertal in children with CPP, is reduced in most children within the first year of treatment to values of 5 to 6 cm/year or less. Children with CPP are frequently taller than their chronological age peers; height for chronological age approaches normal in most children during the second or third year of treatment with SYNAREL. Skeletal maturation rate (bone age velocity—change in bone age divided by change in chronological age) is usually abnormal (greater than 1) in children with CPP; in most children, bone age velocity approaches normal (1) during the first year of treatment. This results in a narrowing of the gap between bone age and chronological age, usually by the second or third year of treatment. The mean predicted adult height increases.

In clinical trials, breast development was arrested or regressed in 82% of girls, and genital development was arrested or regressed in 100% of boys. Because pubic hair growth is largely controlled by adrenal androgens, which are unaffected by nafarelin, pubic hair development was arrested or regressed only in 54% of girls and boys.

Reversal of the suppressive effects of SYNAREL has been demonstrated to occur in all children with CPP for whom one-year posttreatment follow-up is available (n=69). This demonstration consisted of the appearance or return of menses, the return of pubertal gonadotropin and gonadal sex steroid levels, and/or the advancement of secondary sexual development. Semen analysis was normal in the two ejaculated specimens obtained thus far from boys who have been taken off therapy to resume puberty. Fertility has not been documented by pregnancies and the effect of long-term use of the drug on fertility is not known.

INDICATIONS AND USAGE FOR CENTRAL PRECOCIOUS PUBERTY

(For Endometriosis, *See Reverse Side*)

SYNAREL is indicated for treatment of **central precocious puberty (CPP)** (gonadotropin-dependent precocious puberty) in children of both sexes.

The diagnosis of **central precocious puberty (CPP)** is suspected when premature development of secondary sexual characteristics occurs at or before the age of 8 years in girls and 9 years in boys, and is accompanied by significant advancement of bone age and/or a poor adult height prediction. The diagnosis should be confirmed by pubertal gonadal sex steroid levels and a pubertal LH response to stimulation by native GnRH. Pelvic ultrasound assessment in girls usually reveals enlarged uterus and ovaries, the latter often with multiple cystic formations. Magnetic resonance imaging or CT-scanning of the brain is recommended to detect hypothalamic or pituitary tumors, or anatomical changes associated with increased intracranial pressure. Other causes of sexual precocity, such as congenital adrenal hyperplasia, testotoxicosis, testicular tumors and/or other autonomous feminizing or masculinizing disorders must be excluded by proper clinical hormonal and diagnostic imaging examinations.

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in SYNAREL;
2. Undiagnosed abnormal vaginal bleeding;
3. Use in pregnancy or in women who may become pregnant while receiving the drug. SYNAREL may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rats, but not in mice or rabbits after administration of SYNAREL during the period of organogenesis. There was a dose-related increase in fetal mortality and a decrease in fetal weight in rats (see *Pregnancy* Section). The effects on rat fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus;
4. Use in women who are breast-feeding (see *Nursing Mothers* Section).

WARNINGS

The diagnosis of central precocious puberty (CPP) must be established before treatment is initiated. Regular monitoring of CPP patients is needed to assess both patient response as well as compliance. This is particularly important during the first 6 to 8 weeks of treatment to assure that suppression of pituitary-gonadal function is rapid. Testing may include LH response to GnRH stimulation and circulating gonadal sex steroid levels. Assessment of growth velocity and bone age velocity should begin within 3 to 6 months of treatment initiation.

Some patients may not show suppression of the pituitary-gonadal axis by clinical and/or biochemical parameters. This may be due to lack of compliance with the recommended

treatment regimen and may be rectified by recommending that the dosing be done by caregivers. If compliance problems are excluded, the possibility of gonadotropin independent sexual precocity should be reconsidered and appropriate examinations should be conducted. If compliance problems are excluded and if gonadotropin independent sexual precocity is not present, the dose of SYNAREL may be increased to 1800 µg/day administered as 600 µg tid.

PRECAUTIONS

General

As with other drugs that stimulate the release of gonadotropins or that induce ovulation, in adult women with endometriosis 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 women 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. The relevance, if any, of such events in children is unknown.

Information for Patients, Patients' Parents or Guardians

An information pamphlet for patients is included with the product. Patients and their caregivers should be aware of the following information:

1. Reversibility of the suppressive effects of nafarelin has been demonstrated by the appearance or return of menses, by the return of pubertal gonadotropin and gonadal sex steroid levels, and/or by advancement of secondary sexual development. Semen analysis was normal in the two ejaculated specimens obtained thus far from boys who have been taken off therapy to resume puberty. Fertility has not been documented by pregnancies and the effect of long-term use of the drug on fertility is not known.
2. Patients and their caregivers should be adequately counseled to assure full compliance; irregular or incomplete daily doses may result in stimulation of the pituitary-gonadal axis.
3. During the first month of treatment with SYNAREL, some signs of puberty, e.g., vaginal bleeding or breast enlargement, may occur. This is the expected initial effect of the drug. Such changes should resolve soon after the first month. If such resolution does not occur within the first two months of treatment, this may be due to lack of compliance or the presence of gonadotropin independent sexual precocity. If both possibilities are definitively excluded, the dose of SYNAREL may be increased to 1800 µg/day administered as 600 µg tid.
4. Patients with intercurrent rhinitis should consult their physician for the use of a topical nasal decongestant. If the use of a topical nasal decongestant is required during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following

dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with SYNAREL. However, because nafarelin acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes, and the drug is only about 80% bound to plasma proteins at 4°C, drug interactions would not be expected to occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies of nafarelin were conducted in rats (24 months) at doses up to 100 µg/kg/day and mice (18 months) at doses up to 500 µg/kg/day using intramuscular doses (up to 110 times and 560 times the maximum recommended human intranasal dose, respectively). These multiples of the human dose are based on the relative bioavailability of the drug by the two routes of administration. As seen with other GnRH agonists, nafarelin acetate given to laboratory rodents at high doses for prolonged periods induced proliferative responses (hyperplasia and/or neoplasia) of endocrine organs. At 24 months, there was an increase in the incidence of pituitary tumors (adenoma/carcinoma) in high-dose female rats and a dose-related increase in male rats. There was an increase in pancreatic islet cell adenomas in both sexes, and in benign testicular and ovarian tumors in the treated groups. There was a dose-related increase in benign adrenal medullary tumors in treated female rats. In mice, there was a dose-related increase in Harderian gland tumors in males and an increase in pituitary adenomas in high-dose females. No metastases of these tumors were observed. It is known that tumorigenicity in rodents is particularly sensitive to hormonal stimulation.

Mutagenicity studies were performed with nafarelin acetate using bacterial, yeast, and mammalian systems. These studies provided no evidence of mutagenic potential.

Reproduction studies in male and female rats have shown full reversibility of fertility suppression when drug treatment was discontinued after continuous administration for up to 6 months. The effect of treatment of prepubertal rats on the subsequent reproductive performance of mature animals has not been investigated.

Pregnancy, Teratogenic Effects

Pregnancy Category X. See '**CONTRAINDICATIONS.**' Intramuscular SYNAREL was administered to rats during the period of organogenesis at 0.4, 1.6, and 6.4 µg/kg/day (about 0.5, 2, and 7 times the maximum recommended human intranasal dose based on the relative bioavailability by the two routes of administration). An increase in major fetal abnormalities was observed in 4/80 fetuses at the highest dose. A similar, repeat study at

the same doses in rats and studies in mice and rabbits at doses up to 600 µg/kg/day and 0.18 µg/kg/day, respectively, failed to demonstrate an increase in fetal abnormalities after administration during the period of organogenesis. In rats and rabbits, there was a dose-related increase in fetal mortality and a decrease in fetal weight with the highest dose.

Nursing Mothers

It is not known whether SYNAREL is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of SYNAREL on lactation and/or the breastfed child have not been determined, SYNAREL should not be used by nursing mothers.

ADVERSE REACTIONS

In clinical trials of 155 pediatric patients, 2.6% reported symptoms suggestive of drug sensitivity, such as shortness of breath, chest pain, urticaria, rash, and pruritus.

In these 155 patients treated for an average of 41 months and as long as 80 months (6.7 years), adverse events most frequently reported (>3% of patients) consisted largely of episodes occurring during the first 6 weeks of treatment as a result of the transient stimulatory action of nafarelin upon the pituitary-gonadal axis:

- acne (10%)
- transient breast enlargement (8%)
- vaginal bleeding (8%)
- emotional lability (6%)
- transient increase in pubic hair (5%)
- body odor (4%)
- seborrhea (3%)

Hot flashes, common in adult women treated for endometriosis, occurred in only 3% of treated children and were transient. Other adverse events thought to be drug-related, and occurring in > 3% of patients were rhinitis (5%) and white or brownish vaginal discharge (3%). Approximately 3% of patients withdrew from clinical trials due to adverse events.

In one male patient with concomitant congenital adrenal hyperplasia, and who had discontinued treatment 8 months previously to resume puberty, adrenal rest tumors were found in the left testis. Relationship to SYNAREL is unlikely.

Regular examinations of the pituitary gland by magnetic resonance imaging (MRI) or computer assisted tomography (CT) of children during long-term nafarelin therapy as well as during the post-treatment period has occasionally revealed changes in the shape and size of the pituitary gland. These changes include asymmetry and enlargement of the pituitary gland, and a pituitary microadenoma has been suspected in a few children. The

relationship of these findings to SYNAREL is not known.

Post-Marketing

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

OVERDOSAGE

In experimental animals, a single subcutaneous administration of up to 60 times the recommended human dose (on a $\mu\text{g}/\text{kg}$ basis, not adjusted for bioavailability) had no adverse effects. At present, there is no clinical evidence of adverse effects following overdosage of GnRH analogs.

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

DOSAGE AND ADMINISTRATION

For the treatment of central precocious puberty (CPP), the recommended daily dose of SYNAREL is 1600 μg . The dose can be increased to 1800 μg daily if adequate suppression cannot be achieved at 1600 $\mu\text{g}/\text{day}$.

The 1600 μg dose is achieved by two sprays (400 μg) into each nostril in the morning (4 sprays) and two sprays into each nostril in the evening (4 sprays), a total of 8 sprays per day. The 1800 μg dose is achieved by 3 sprays (600 μg) into alternating nostrils three times a day, a total of 9 sprays per day. The patient's head should be tilted back slightly, and 30 seconds should elapse between sprays.

If the prescribed therapy has been well tolerated by the patient, treatment of CPP with SYNAREL should continue until resumption of puberty is desired.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

At 1600 µg/day, a bottle of SYNAREL provides about a 7-day supply (about 56 sprays). If the daily dose is increased, increase the supply to the patient to ensure uninterrupted treatment for the duration of therapy.

HOW SUPPLIED

Each 0.5 ounce bottle (NDC 0025-0166-08) contains 8 mL SYNAREL (nafarelin acetate) Nasal Solution 2 mg/mL (as nafarelin base), and is supplied with a metered spray pump that delivers 200 µg of nafarelin per spray. A dust cover and a leaflet of patient instructions are also included.

Store upright at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

Rx only

Revised: July 2005



Synarel[®]

(nafarelin acetate)
nasal solution

ENDOMETRIOSIS
(FOR CENTRAL PRECOCIOUS PUBERTY,
SEE REVERSE SIDE)

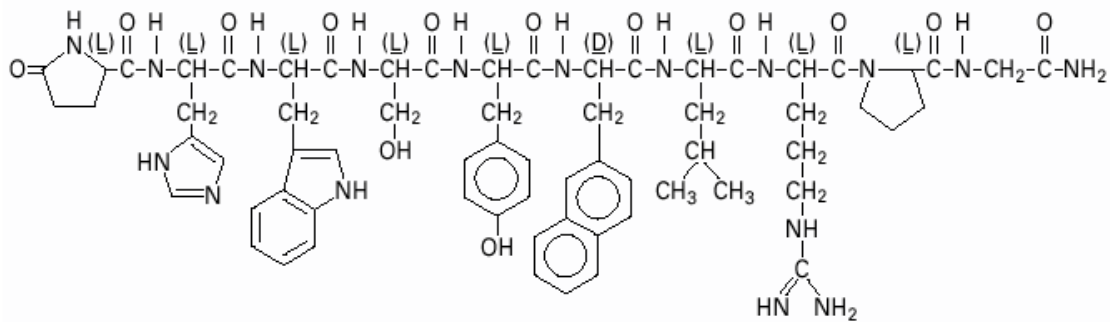
PHYSICIAN LABELING

DESCRIPTION

SYNAREL (nafarelin acetate) Nasal Solution is intended for administration as a spray to the nasal mucosa. Nafarelin acetate, the active component of SYNAREL Nasal Solution, 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-prolyl-glycinamide acetate.

Nafarelin acetate is a synthetic analog of the naturally occurring gonadotropin-releasing hormone (GnRH).

Nafarelin acetate has the following chemical structure:



SYNAREL Nasal Solution contains nafarelin acetate (2 mg/mL, content expressed as nafarelin base) in a solution of benzalkonium chloride, glacial acetic acid, sodium hydroxide or hydrochloric acid (to adjust pH), sorbitol, and purified water.

After priming the pump unit for SYNAREL, each actuation of the unit delivers approximately 100 μL of the spray containing approximately 200 μg nafarelin base. The contents of one spray bottle are intended to deliver at least 60 sprays.

CLINICAL PHARMACOLOGY

Nafarelin acetate is a potent agonistic analog of gonadotropin-releasing hormone (GnRH). At the onset of administration, nafarelin stimulates the release of the pituitary gonadotropins, LH and FSH, resulting in a temporary increase of ovarian steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary gland. Twice daily administration leads to decreased secretion of gonadal steroids by about 4 weeks;

consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.

Nafarelin acetate is rapidly absorbed into the systemic circulation after intranasal administration. Maximum serum concentrations (measured by RIA) were achieved between 10 and 40 minutes. Following a single dose of 200 µg base, the observed average peak concentration was 0.6 ng/mL (range 0.2 to 1.4 ng/mL), whereas following a single dose of 400 µg base, the observed average peak concentration was 1.8 ng/mL (range 0.5 to 5.3 ng/mL). Bioavailability from a 400 µg dose averaged 2.8% (range 1.2 to 5.6%). The average serum half-life of nafarelin following intranasal administration is approximately 3 hours. About 80% of nafarelin acetate is bound to plasma proteins at 4°C. Twice daily intranasal administration of 200 or 400 µg of SYNAREL in 18 healthy women for 22 days did not lead to significant accumulation of the drug. Based on the mean C_{\min} levels on Days 15 and 22, there appeared to be dose proportionality across the two dose levels.

After subcutaneous administration of ^{14}C -nafarelin acetate to men, 44–55% of the dose was recovered in urine and 18.5–44.2% was recovered in feces. Approximately 3% of the administered dose appeared as unchanged nafarelin in urine. The ^{14}C serum half-life of the metabolites was about 85.5 hours. Six metabolites of nafarelin have been identified of which the major metabolite is Tyr-D(2)-Nal-Leu-Arg-Pro-Gly-NH₂(5-10). The activity of the metabolites, the metabolism of nafarelin by nasal mucosa, and the pharmacokinetics of the drug in hepatically- and renally-impaired patients have not been determined.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing of SYNAREL.

In controlled clinical studies, SYNAREL at doses of 400 and 800 µg/day for 6 months was shown to be comparable to danazol, 800 mg/day, in relieving the clinical symptoms of endometriosis (pelvic pain, dysmenorrhea, and dyspareunia) and in reducing the size of endometrial implants as determined by laparoscopy. The clinical significance of a decrease in endometriotic lesions is not known at this time and, in addition, laparoscopic staging of endometriosis does not necessarily correlate with severity of symptoms.

In a single controlled clinical trial, intranasal SYNAREL (nafarelin acetate) at a dose of 400 µg per day was shown to be clinically comparable to intramuscular leuprolide depot, 3.75 mg monthly, for the treatment of the symptoms (dysmenorrhea, dyspareunia and pelvic pain) associated with endometriosis.

SYNAREL 400 µg daily induced amenorrhea in approximately 65%, 80%, and 90% of the patients after 60, 90, and 120 days, respectively. 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.

At the end of treatment, 60% of patients who received SYNAREL, 400 µg/day, were

symptom free, 32% had mild symptoms, 7% had moderate symptoms, and 1% had severe symptoms. Of the 60% of patients who had complete relief of symptoms at the end of treatment, 17% had moderate symptoms 6 months after treatment was discontinued, 33% had mild symptoms, 50% remained symptom free, and no patient had severe symptoms.

During the first two months use of SYNAREL, some women experience vaginal bleeding of variable duration and intensity. In all likelihood, this bleeding represents estrogen withdrawal bleeding and is expected to stop spontaneously. If vaginal bleeding continues, the possibility of lack of compliance with the dosing regimen should be considered. If the patient is complying carefully with the regimen, an increase in dose to 400 µg twice a day should be considered.

There is no evidence that pregnancy rates are enhanced or adversely affected by the use of SYNAREL.

INDICATIONS AND USAGE FOR ENDOMETRIOSIS

(For Central Precocious Puberty, See *Reverse Side*)

SYNAREL is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Experience with SYNAREL for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months.

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in SYNAREL;
2. Undiagnosed abnormal vaginal bleeding;
3. Use in pregnancy or in women who may become pregnant while receiving the drug. SYNAREL may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rats, but not in mice or rabbits after administration of SYNAREL during the period of organogenesis. There was a dose-related increase in fetal mortality and a decrease in fetal weight in rats (see *Pregnancy* Section). The effects on rat fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus;
4. Use in women who are breast-feeding (see *Nursing Mothers* Section).

WARNINGS

Safe use of nafarelin acetate in pregnancy has not been established clinically. Before starting treatment with SYNAREL, pregnancy must be excluded.

When used regularly at the recommended dose, SYNAREL usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking SYNAREL, particularly if patients miss successive doses. Therefore, patients should use nonhormonal methods of contraception. Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the fetus.

PRECAUTIONS

General

As with other drugs that stimulate the release of gonadotropins or that induce ovulation, 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.

Information for Patients

An information pamphlet for patients is included with the product. Patients should be aware of the following information:

1. Since menstruation should stop with effective doses of SYNAREL, the patient should notify her physician if regular menstruation persists. The cause of vaginal spotting, bleeding or menstruation could be noncompliance with the treatment regimen, or it could be that a higher dose of the drug is required to achieve amenorrhea. The patient should be questioned regarding her compliance. If she is careful and compliant, and menstruation persists to the second month, consideration should be given to doubling the dose of SYNAREL. If the patient has missed several doses, she should be counseled on the importance of taking SYNAREL regularly as prescribed.
2. Patients should not use SYNAREL if they are pregnant, breastfeeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of the ingredients in SYNAREL.
3. Safe use of the drug in pregnancy has not been established clinically. Therefore, a nonhormonal method of contraception should be used during treatment. Patients should be advised that if they miss successive doses of SYNAREL, breakthrough bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.
4. Those adverse events occurring most frequently in clinical studies with SYNAREL are associated with hypoestrogenism; the most frequently reported are hot flashes, headaches, emotional lability, decreased libido, vaginal dryness, acne, myalgia, and reduction in breast size. Estrogen levels returned to normal after treatment was discontinued. Nasal irritation occurred in about 10% of all patients who used intranasal nafarelin.
5. The induced hypoestrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible. During one six-month treatment period, this bone loss should not be important. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, therapy with SYNAREL may pose an additional risk. In these patients the risks and benefits must be weighed carefully before therapy with SYNAREL is instituted. Repeated courses of treatment with gonadotropin releasing

hormone analogs are not advisable in patients with major risk factors for loss of bone mineral content.

6. Patients with intercurrent rhinitis should consult their physician for the use of a topical nasal decongestant. If the use of a topical nasal decongestant is required during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

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

Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with SYNAREL. However, because nafarelin acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes, and the drug is only about 80% bound to plasma proteins at 4°C, drug interactions would not be expected to occur.

Drug/Laboratory Test Interactions

Administration of SYNAREL 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. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and up to 4 to 8 weeks after discontinuation of therapy with SYNAREL may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies of nafarelin were conducted in rats (24 months) at doses up to 100 µg/kg/day and mice (18 months) at doses up to 500 µg/kg/day using intramuscular doses (up to 110 times and 560 times the maximum recommended human intranasal dose, respectively). These multiples of the human dose are based on the relative bioavailability of the drug by the two routes of administration. As seen with other GnRH agonists, nafarelin acetate given to laboratory rodents at high doses for prolonged periods induced proliferative responses (hyperplasia and/or neoplasia) of endocrine organs. At 24 months, there was an increase in the incidence of pituitary tumors (adenoma/carcinoma) in high-dose female rats and a dose-related increase in male rats. There was an increase in pancreatic islet cell adenomas in both sexes, and in benign testicular and ovarian tumors in the treated groups. There was a dose-related increase in benign adrenal medullary tumors in treated female rats. In mice, there was a dose-related increase in Harderian gland tumors in males and an increase in pituitary adenomas in high-dose females. No metastases of these tumors were observed. It is known that tumorigenicity in rodents is particularly sensitive to hormonal stimulation.

Mutagenicity studies were performed with nafarelin acetate using bacterial, yeast, and mammalian systems. These studies provided no evidence of mutagenic potential.

Reproduction studies in male and female rats have shown full reversibility of fertility suppression when drug treatment was discontinued after continuous administration for up to 6 months. The effect of treatment of prepubertal rats on the subsequent reproductive performance of mature animals has not been investigated.

Pregnancy, Teratogenic Effects

Pregnancy Category X. See '**CONTRAINDICATIONS.**' Intramuscular SYNAREL was administered to rats during the period of organogenesis at 0.4, 1.6, and 6.4 $\mu\text{g}/\text{kg}/\text{day}$ (about 0.5, 2, and 7 times the maximum recommended human intranasal dose based on the relative bioavailability by the two routes of administration). An increase in major fetal abnormalities was observed in 4/80 fetuses at the highest dose. A similar, repeat study at the same doses in rats and studies in mice and rabbits at doses up to 600 $\mu\text{g}/\text{kg}/\text{day}$ and 0.18 $\mu\text{g}/\text{kg}/\text{day}$, respectively, failed to demonstrate an increase in fetal abnormalities after administration during the period of organogenesis. In rats and rabbits, there was a dose-related increase in fetal mortality and a decrease in fetal weight with the highest dose.

Nursing Mothers

It is not known whether SYNAREL is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of SYNAREL on lactation and/or the breastfed child have not been determined, SYNAREL should not be used by nursing mothers.

Pediatric Use

Safety and effectiveness of SYNAREL for endometriosis in patients younger than 18 years have not been established.

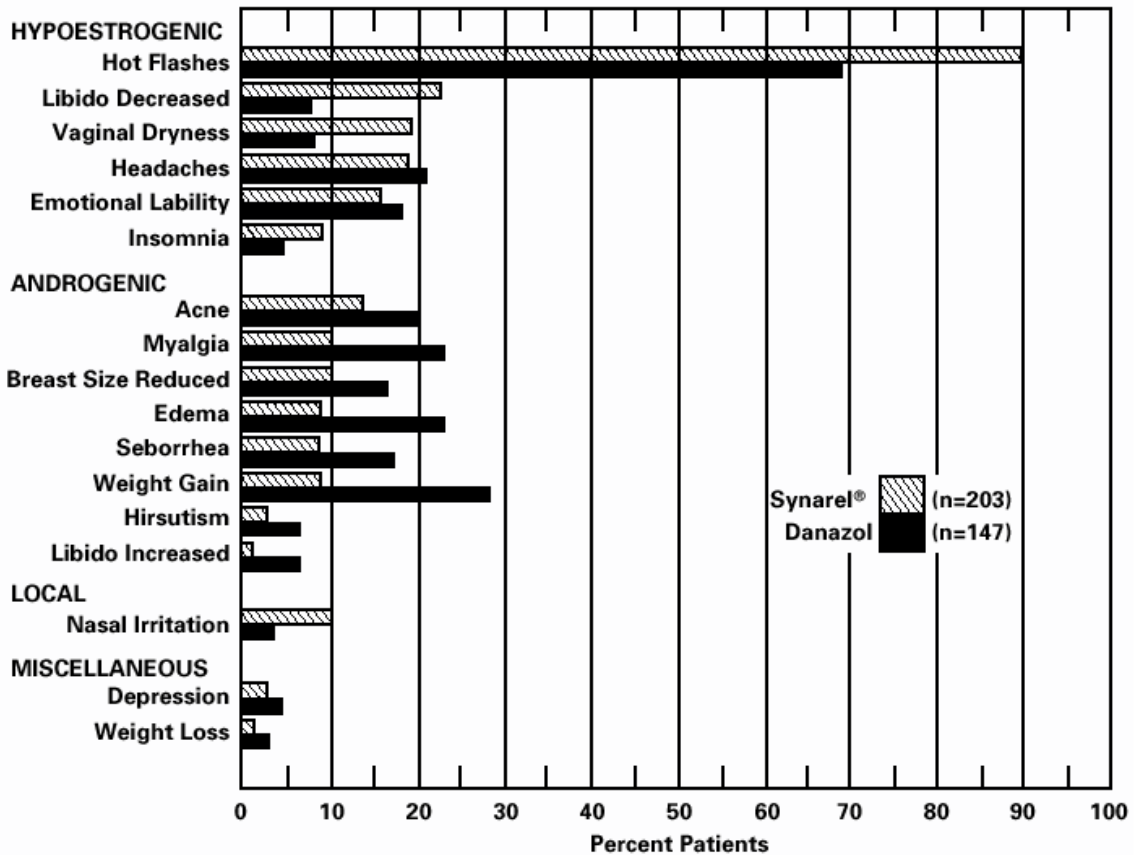
ADVERSE REACTIONS

In formal clinical trials of 1509 healthy adult patients, symptoms suggestive of drug sensitivity, such as shortness of breath, chest pain, urticaria, rash and pruritus occurred in 3 patients (approximately 0.2%).

As would be expected with a drug which lowers serum estradiol levels, the most frequently reported adverse reactions were those related to hypoestrogenism.

In controlled studies comparing SYNAREL (400 $\mu\text{g}/\text{day}$) and danazol (600 or 800 mg/day), adverse reactions most frequently reported and thought to be drug-related are shown in the figure below:

**ADVERSE EVENTS DURING 6 MONTHS TREATMENT
WITH SYNAREL® 400 µg/day vs
DANAZOL 600 OR 800 mg/day**



In addition, less than 1% of patients experienced paresthesia, palpitations, chloasma, maculopapular rash, eye pain, asthenia, lactation, breast engorgement, and arthralgia.

Post-Marketing

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

Changes in Bone Density

After six months of treatment with SYNAREL, 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.

After six months treatment with SYNAREL, bone mass as measured by dual x-ray bone densitometry (DEXA), decreased 3.2%. Mean total vertebral mass, re-examined by DEXA six months after completion of treatment, was 1.4% below pretreatment. 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 months or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss.

Changes in Laboratory Values During Treatment

Plasma enzymes. During clinical trials with SYNAREL, regular laboratory monitoring revealed that SGOT and SGPT levels were more than twice the upper limit of normal in only one patient each. There was no other clinical or laboratory evidence of abnormal liver function and levels returned to normal in both patients after treatment was stopped.

Lipids. At enrollment, 9% of the patients in the group taking SYNAREL 400 µg/day and 2% of the patients in the danazol group had total cholesterol values above 250 mg/dL. These patients also had cholesterol values above 250 mg/dL at the end of treatment.

Of those patients whose pretreatment cholesterol values were below 250 mg/dL, 6% in the group treated with SYNAREL and 18% in the danazol group, had post-treatment values above 250 mg/dL.

The mean (\pm SEM) pretreatment values for total cholesterol from all patients were 191.8 (4.3) mg/dL in the group treated with SYNAREL and 193.1 (4.6) mg/dL in the danazol group. At the end of treatment, the mean values for total cholesterol from all patients were 204.5 (4.8) mg/dL in the group treated with SYNAREL and 207.7 (5.1) mg/dL in the danazol group. These increases from the pretreatment values were statistically significant ($p < 0.05$) in both groups.

Triglycerides were increased above the upper limit of 150 mg/dL in 12% of the patients who received SYNAREL and in 7% of the patients who received danazol.

At the end of treatment, no patients receiving SYNAREL had abnormally low HDL cholesterol fractions (less than 30 mg/dL) compared with 43% of patients receiving danazol. None of the patients receiving SYNAREL had abnormally high LDL cholesterol fractions (greater than 190 mg/dL) compared with 15% of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving SYNAREL, but there was approximately a 2-fold increase in the LDL/HDL ratio in patients receiving danazol.

Other changes. In comparative studies, the following changes were seen in approximately 10% to 15% of patients. Treatment with SYNAREL was associated with elevations of plasma phosphorus and eosinophil counts, and decreases in serum calcium and WBC counts. Danazol therapy was associated with an increase of hematocrit and WBC.

OVERDOSAGE

In experimental animals, a single subcutaneous administration of up to 60 times the recommended human dose (on a $\mu\text{g}/\text{kg}$ basis, not adjusted for bioavailability) had no adverse effects. At present, there is no clinical evidence of adverse effects following overdosage of GnRH analogs.

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

DOSAGE AND ADMINISTRATION

For the management of endometriosis, the recommended daily dose of SYNAREL is 400 μg . This is achieved by one spray (200 μg) into one nostril in the morning and one spray into the other nostril in the evening. Treatment should be started between days 2 and 4 of the menstrual cycle.

In an occasional patient, the 400 μg daily dose may not produce amenorrhea. For these patients with persistent regular menstruation after 2 months of treatment, the dose of SYNAREL 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 administration 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 is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

At 400 $\mu\text{g}/\text{day}$, a bottle of SYNAREL provides a 30-day (about 60 sprays) supply. If the daily dose is increased, increase the supply to the patient to ensure uninterrupted treatment for the recommended duration of therapy.

HOW SUPPLIED

Each 0.5 ounce bottle (NDC 0025-0166-08) contains 8 mL SYNAREL (nafarelin acetate) Nasal Solution 2 mg/mL (as nafarelin base), and is supplied with a metered spray pump

that delivers 200 µg of nafarelin per spray. A dust cover and a leaflet of patient instructions are also included.

Store upright at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

Rx only

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