HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUPANETA PACK safely and effectively. See full prescribing information for LUPANETA PACK.

LUPANETA PACK (leuprolide acetate for depot suspension, for injection; norethindrone acetate tablets), co-packaged for intramuscular use and for oral use, respectively

Initial U.S. Approval: 2012

RECENT MAJOR CHANGES

Warnings and Precautions, Embryofetal Toxicity (5.2)	08/2023
Warnings and Precautions, Hypersensitivity Reactions (5.3)	08/2023
Warnings and Precautions, Clinical Depression (5.7)	12/2022

INDICATIONS AND USAGE

LUPANETA PACK contains leuprolide acetate, a gonadotropin-releasing hormone (GnRH) agonist and norethindrone acetate, a progestin, and is indicated for:

- Initial management of the painful symptoms of endometriosis (1)
- Management of recurrence of symptoms (1)

Limitations of Use:

- The total duration of therapy with LUPANETA PACK should not exceed 12 months due to concerns about adverse impact on bone mineral density (BMD). (1, 2.1, 5.1)

DOSAGE AND ADMINISTRATION

- Do not administer leuprolide acetate for depot suspension in the LUPANETA PACK alone if the patient is not taking norethindrone acetate. (2.1)
- Do not administer leuprolide acetate for depot suspension 3.75 mg more frequently than once a month. (2.1)
- Do not substitute the leuprolide acetate for depot suspension 3.75 mg (one month of therapy) component for the leuprolide acetate for depot suspension 11.25 mg (3 months of therapy) component of the LUPANETA PACK; they are not equivalent due to the different release characteristics. (2.1)
- The recommended dosage is leuprolide acetate for depot suspension 3.75 mg for 1-month administration given by a healthcare provider as a single intramuscular (IM) injection every (1) month for up to six injections (6 months of therapy) co-administered with norethindrone acetate 5 mg tablets taken orally once daily by the patient for up to 6 months. If endometriosis symptoms recur after initial course of therapy, consider retreatment for up to another six months. (2.2)
- Reconstitute leuprolide acetate prior to use. See the full prescribing information for preparation and administration instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

- For injection: Leuprolide acetate for depot suspension: 3.75 mg lyophilized powder for reconstitution in a dual-chamber syringe (3)
- Tablets: Norethindrone acetate 5 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to GnRH, GnRH agonist or any of the excipients in leuprolide acetate for depot suspension or norethindrone acetate (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4, 8.1)
- Known, suspected or history of breast or other hormone-sensitive cancer (4)
- Thrombotic or thromboembolic disorders (4)
- Liver tumors or liver disease (4)

WARNINGS AND PRECAUTIONS

- Loss of bone mineral density (BMD): Duration of treatment is limited by risk of bone mineral density loss. When using LUPANETA PACK for the management of endometriosis, the norethindrone acetate component of the LUPANETA PACK reduces the BMD loss. Do not retreat with leuprolide acetate for depot suspension alone. Assess BMD after 6 months of treatment before retreatment. Do not use for more than 12 months due to concerns about adverse impact on BMD. (5.1)
- Embryo-Fetal Toxicity: May cause fetal harm. Exclude pregnancy before initiating treatment if clinically indicated and discontinue use if pregnancy occurs. Use non-hormonal methods of contraception only. (5.2)
- Hypersensitivity Reactions: Reactions, including anaphylaxis, have been reported. (5.3)
- Cardiovascular and Metabolic Disorders: Assess and manage risk factors before starting LUPANETA PACK. (5.4)
- Clinical Depression: Carefully observe women for depression and refer to a mental health professional, as appropriate. (5.7)
- Visual Abnormalities: Discontinue norethindrone acetate in case of sudden loss of vision or onset of proptosis, diplopia, or migraine pending visual examination. Discontinue LUPANETA PACK if examination reveals papilledema or retinal vascular lesions. (5.8)

ADVERSE REACTIONS

Leuprolide acetate for depot suspension co-administered with norethindrone acetate: Most common related adverse reactions (>10%) were hot flashes/sweats, headache/migraine, nausea/vomiting, pain, depression/emotional lability, asthenia, constipation/diarrhea, vaginitis, insomnia/sleep disorder, breast changes/pain/tenderness, weight gain, dizziness/vertigo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUPANETA PACK is indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms.

Limitations of Use

The total duration of therapy with LUPANETA PACK should not exceed 12 months due to concerns about adverse impact on bone mineral density *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

LUPANETA PACK is a co-packaged product containing leuprolide acetate for depot suspension 3.75 mg for intramuscular use and norethindrone acetate 5 mg tablets for oral use.

- Do not administer leuprolide acetate for depot suspension 3.75 mg in the LUPANETA PACK alone if the patient is not taking norethindrone acetate.
- Do not administer leuprolide acetate for depot suspension 3.75 mg more frequently than every once a month.
- Do not substitute the leuprolide acetate for depot suspension 3.75 mg (one month of therapy) component for the leuprolide acetate for depot suspension 11.25 mg (3 months of therapy) component of the LUPANETA PACK; they are not equivalent due to the different release characteristics.

2.2 Recommended Dosage and Administration

The recommended initial and retreatment dosage regimens for LUPANETA PACK for the management of women with endometriosis are outlined in Table 1.

Table 1. LUPANETA PACK. Management of Endometriosis

Treatment Phase	LUPANETA PACK 3.75 mg Dosing	Maximum Treatment Duration
Initial Treatment	Leuprolide acetate for depot suspension 3.75 mg IM every month Norethindrone acetate 5 mg orally once daily	6 months
Retreatment	Leuprolide acetate for depot suspension 3.75 mg IM every month Norethindrone acetate 5 mg orally once daily	6 months
Total Treatment Duration		12 Months

Assess bone mineral density (BMD) prior to retreatment with LUPANETA PACK *[see Warnings and Precautions (5.1)]*.

Total treatment duration with LUPANETA PACK should not exceed 12 months due to concerns about the adverse impact on bone mineral density.

2.3 Reconstitution and Administration Instructions for Leuprolide Acetate Injection

- Reconstitute and administer the lyophilized microspheres as a single IM injection as directed below. Visually inspect the drug product for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Inject the leuprorelin acetate for deport suspension 3.75 mg immediately or discard if not used within two hours as the suspension does not contain a preservative.

1. Visually inspect the leuprolide acetate for depot suspension powder. **Do not use** the syringe if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal prior to mixing with the diluent. The diluent should appear clear.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn (see Figure 1 and Figure 2).

Figure 1:

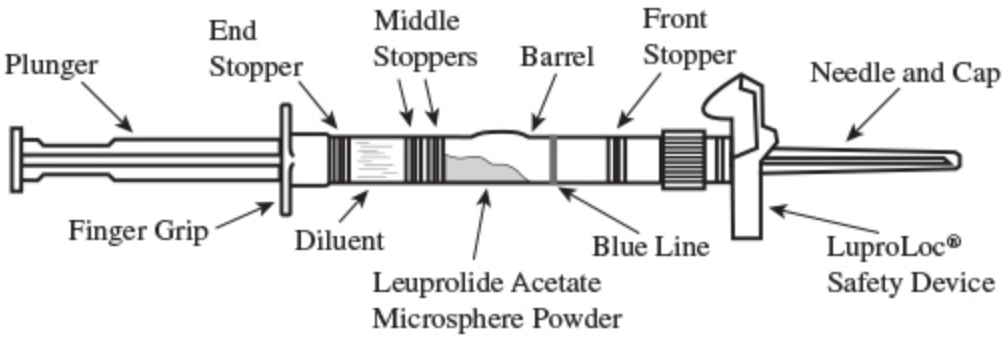
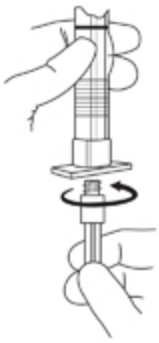
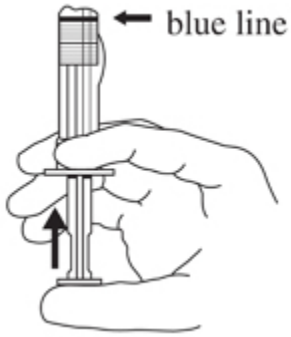


Figure 2:



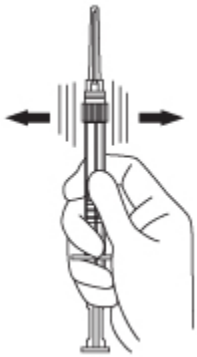
3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING the plunger for 6 to 8 seconds until the first middle stopper is **at the blue line** in the middle of the barrel (see Figure 3).

Figure 3:



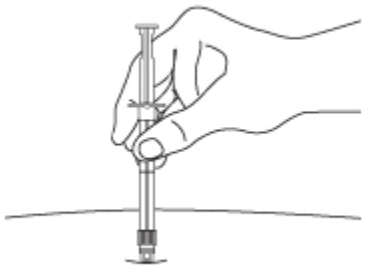
4. Keep the syringe **upright**. Mix the microsphere powder thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. **Do not use** if any of the powder has not gone into suspension (see Figure 4).

Figure 4:



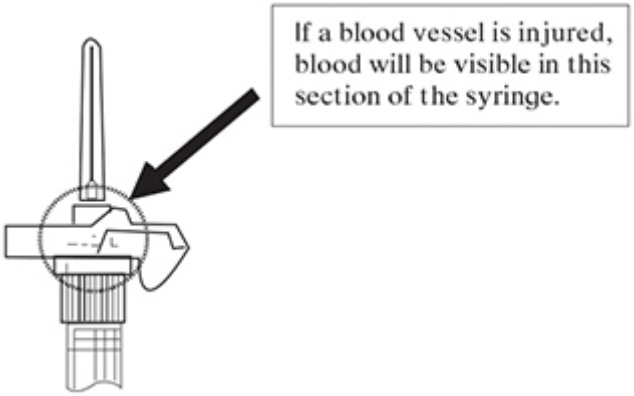
5. Keep the syringe **upright**. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe **upright**. Advance the plunger to expel the air from the syringe. Now the syringe is ready for injection.
7. After cleaning the injection site with an alcohol swab, administer the IM injection by inserting the needle at a 90-degree angle into the gluteal area, anterior thigh, or deltoid (see Figure 5). Injection sites should be alternated (see Figure 5).

Figure 5:



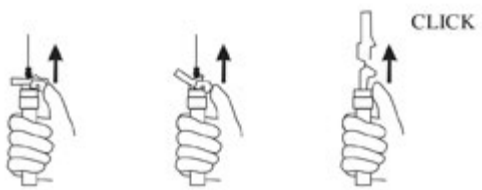
Note: If a blood vessel is accidentally penetrated, aspirated blood will be visible just below the luer lock (see Figure 6) and can be seen through the transparent LuproLoc safety device. If blood is present, remove the needle immediately. Do not inject the medication.

Figure 6:



8. Inject the entire contents of the syringe intramuscularly.
9. Withdraw the needle. Once the syringe has been withdrawn, immediately activate the LuproLoc® safety device by pushing the arrow on the lock upward towards the needle tip with the thumb or finger, as illustrated, until the needle cover of the safety device over the needle is fully extended and a **click** is heard or felt (see Figure 7).

Figure 7:



10. Dispose of the syringe according to local regulations/procedures.

3 DOSAGE FORMS AND STRENGTHS

LUPANETA PACK 1-month co-packaged kit contains two separate components:

- For Injection: Leuprolide acetate for depot suspension 3.75 mg as a white lyophilized microsphere powder for reconstitution in a single dose prefilled dual chamber syringe, with one chamber containing the lyophilized powder and the other chamber containing the clear diluent.
- Tablets: Norethindrone acetate 5 mg tablets as white to off-white oval, flat-faced beveled edged, uncoated, debossed with 'G' with a break line on one side and '304' on the other side

4 CONTRAINDICATIONS

LUPANETA PACK is contraindicated in women with the following:

- Hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs, any of the excipients in leuprolide acetate for depot suspension, or norethindrone acetate
- Undiagnosed abnormal uterine bleeding
- Pregnancy *[see Warnings and Precautions (5.2)* and *Use in Specific Populations (8.1)]*
- Known, suspected or history of breast cancer or other hormone-sensitive cancer
- Current or history of thrombotic or thromboembolic disorder
- Liver tumors or liver disease

5 WARNINGS AND PRECAUTIONS

5.1 Loss of Bone Mineral Density

Leuprolide acetate for depot suspension induces a hypoestrogenic state that results in loss of bone mineral density (BMD), some of which may not be reversible after stopping treatment. In women with major risk factors for decreased BMD such as chronic alcohol use (> 3 units per day), tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of LUPANETA PACK may pose an additional risk. Carefully weigh the risks and benefits of LUPANETA PACK use in these populations.

Total treatment duration with LUPANETA PACK should not exceed 12 months. The duration of LUPANETA PACK treatment is limited by the risk of loss of bone mineral density *[see Dosage and Administration (2.1)]*.

When using LUPANETA PACK for the management of endometriosis, the norethindrone acetate component of the LUPANETA PACK reduces the BMD loss that occurs with leuprolide acetate use alone *[see Clinical Studies (14)]*. Do not retreat with leuprolide acetate for depot suspension alone. Assess BMD after 6 months of treatment before retreatment.

5.2 Embryo-Fetal Toxicity

Based on animal reproduction studies and the drug's mechanism of action, leuprolide acetate for depot suspension may cause fetal harm if administered to a pregnant woman and is contraindicated in pregnant women. Exclude pregnancy prior to initiating treatment with

LUPANETA PACK if clinically indicated. Discontinue LUPANETA PACK if the woman becomes pregnant during treatment and inform the woman of potential risk to the fetus *[see Contraindications (4)* and *Use in Specific Populations (8.1)]*. Advise women to notify their healthcare provider if they believe they may be pregnant.

When used at the recommended dose and dosing interval, leuprolide acetate for depot suspension usually inhibits ovulation and stops menstruation. Contraception, however, is not ensured by taking leuprolide acetate for depot suspension. If contraception is indicated, advise women to use nonhormonal methods of contraception while on treatment with LUPANETA PACK.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, have been reported with LUPANETA PACK use. LUPANETA PACK is contraindicated in women with a history of hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs, or norethindrone acetate *[see Adverse Reactions (6.2)]*.

In clinical trials for LUPANETA PACK, adverse events of asthma were reported in women with pre-existing histories of asthma, sinusitis and environmental or drug allergies. Symptoms consistent with an anaphylactoid or asthmatic process have been reported postmarketing.

5.4 Cardiovascular and Metabolic Disorders

Assess and manage risk factors for cardiovascular disease before starting LUPANETA PACK. Closely monitor women on norethindrone acetate who have risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., family history of VTE, obesity, and smoking) when using LUPANETA PACK *[see Contraindications (4)]*.

5.5 Initial Flare of Symptoms

Following the first dose of leuprolide acetate component of LUPANETA PACK, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in symptoms may be observed during the initial days of therapy, but these should dissipate with continued therapy.

5.6 Convulsions

There have been postmarketing reports of convulsions in women taking GnRH agonists such as the leuprolide acetate component of LUPANETA PACK. These included women with and without concurrent medications and comorbid conditions.

5.7 Clinical Depression

Depression may occur or worsen during treatment with GnRH agonists including LUPANETA PACK *[see Adverse Reactions (6.1)]*. Carefully observe women for depression, especially those with a history of depression and consider whether the risks of continuing LUPANETA PACK

outweigh the benefits. Women with new or worsening depression should be referred to a mental health professional, as appropriate.

5.8 Visual Abnormalities

Discontinue norethindrone acetate tablets in the LUPANETA PACK pending examination if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine. Discontinue LUPANETA PACK if examination reveals papilledema or retinal vascular lesions.

5.9 Fluid Retention

Because norethindrone acetate, a component of LUPANETA PACK, may cause some degree of fluid retention, carefully observe women with conditions that might be influenced by this effect, such as epilepsy, migraine, cardiac or renal dysfunctions.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Loss of Bone Mineral Density *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Initial Flare of Symptoms *[see Warnings and Precautions (5.5)]*
- Convulsions *[see Warnings and Precautions (5.6)]*
- Clinical Depression *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of co-administering leuprolide acetate for depot suspension and norethindrone acetate was evaluated in two clinical studies in which a total of 242 women were treated for up to one year. Women were treated with monthly IM injections of leuprolide acetate 3.75 mg (13 injections) alone or monthly IM injections of leuprolide acetate 3.75 mg (13 injections) and norethindrone acetate 5 mg orally once daily. The population age range was 17-43 years old. The majority of women were Caucasian (87%).

In the first study, 106 women were randomized to one year of treatment with leuprolide acetate for depot suspension alone or with leuprolide acetate for depot suspension and norethindrone acetate. The second study was an open-label, single arm clinical study in 136 women who received one year of leuprolide acetate for depot suspension and norethindrone acetate; these women were followed for up to 12 months after completing treatment.

Adverse Reactions (>1%) Leading to Study Discontinuation:

In the controlled study, 18% of women treated monthly with leuprolide acetate for depot suspension 3.75 mg alone and 18% of women treated concomitantly monthly with leuprolide

acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg discontinued therapy due to adverse reactions. The most common adverse reactions leading to discontinuation were hot flashes (6%) and insomnia (4%) in the leuprolide acetate for depot suspension 3.75 mg alone group and hot flashes and emotional lability (4% each) in the leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg group.

In the open-label study, 13% of women treated monthly with leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg discontinued therapy due to adverse reactions, most commonly depression (4%) and acne (2%).

Common Adverse Reactions:

Table 2 lists the adverse reactions observed in at least 5% of women in any treatment group, during the first 6 months of treatment in the two clinical studies. The most common adverse reactions observed in these studies were hot flashes and headaches.

Table 2. Adverse Reactions Occurring in the First Six Months of Treatment in ≥ 5% of Women with Endometriosis

	Controlled Study		**Open Label Study**
	LA-Only*	**LA/N†**	**LA/N†**
	N=51	**N=55**	**N=136**
Adverse Reactions	**%**	**%**	**%**
Any Adverse Reaction	98	96	93
Hot flashes/Sweats	98	87	57
Headache/Migraine	65	51	46
Depression/Emotional Lability	31	27	34
Insomnia/Sleep Disorder	31	13	15
Nausea/Vomiting	25	29	13
Pain	24	29	21
Vaginitis	20	15	8
Asthenia	18	18	11
Dizziness/Vertigo	16	11	7
Altered Bowel Function (constipation, diarrhea)	14	15	10
Weight Gain	12	13	4
Decreased Libido	10	4	7
Nervousness/Anxiety	8	4	11
Breast Changes/Pain/Tenderness	6	13	8
Memory Disorder	6	2	4
Skin/Mucous Membrane Reaction	4	9	11
GI Disturbance (dyspepsia, flatulence)	4	7	4
Androgen-Like Effects (acne, alopecia)	4	5	18

Changes in Appetite	4	0	6
Injection Site Reaction	2	9	3
Neuromuscular Disorder (leg cramps, paresthesia)	2	9	3
Menstrual Disorders	2	0	5
Edema	0	9	7
* LA-Only = leuprolide acetate for depot suspension 3.75 mg † LA/N = leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg			

In the controlled clinical trial, 50 of 51 (98%) women in the leuprolide acetate for depot suspension and 48 of 55 (87%) women in the leuprolide acetate for depot suspension and norethindrone acetate arm reported experiencing hot flashes on one or more occasions during treatment.

Table 3 presents hot flash data in the sixth month of treatment.

Table 3. Hot Flashes in the Month Prior to the Assessment Visit (Controlled Study)

Assessment Visit	**Treatment Group**	**Number of Women Reporting Hot Flashes**		**Number of Days with Hot Flashes**		**Maximum Number of Hot Flashes in 24 Hours**	
		N	(%)	N[2]	Mean	N[2]	Mean
Week 24	LA-Only*	32/37	86	37	19	36	5.8
	LA/N†	22/38	58[1]	38	7[1]	38	1.9[1]

* LA-Only = leuprolide acetate for depot suspension 3.75 mg
† LA/N = leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg
[1]Statistically significantly less than the LA-Only group ($p<0.01$)
[2]Number of women assessed.

Serious Adverse Reactions:

Urinary tract infection (1.9%), renal calculus (0.7%), depression (0.7%)

Changes in Laboratory Values during Treatment:

Liver Enzymes

In the two clinical trials of women with endometriosis, 2% (4 of 191) women receiving leuprolide acetate for depot suspension and norethindrone acetate for up to 12 months developed an elevated (at least twice the upper limit of normal) serum glutamic pyruvic transaminase (SGPT) and 1% (2 of 136) developed an elevated gamma glutamyl transferase (GGT). Among these six women with increased liver tests, the increases in five were observed beyond 6 months of treatment. None were associated with an elevated bilirubin concentration.

Lipids

Percent changes from baseline for serum lipids and percentages of women with serum lipid values outside of the normal range in the two studies of leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg daily are summarized in Tables 4 and 5 below. The

major impact of adding norethindrone acetate to treatment with leuprolide acetate for depot suspension was a decrease in serum HDL cholesterol and an increase in the LDL/HDL ratio.

Table 4. Serum Lipids: Mean Percent Changes from Baseline Values at Treatment Week 24

	leuprolide acetate for depot suspension 3.75 mg		**leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg daily**			
	Controlled Study (n=39)		**Controlled Study (n=41)**		**Open Label Study (n=117)**	
	Baseline Value*	Week 24 % Change	Baseline Value*	Week 24 % Change	Baseline Value*	Week 24 % Change
Total Cholesterol	170.5	9.2%	179.3	0.2%	181.2	2.8%
HDL Cholesterol	52.4	7.4%	51.8	-18.8%	51.0	-14.6%
LDL Cholesterol	96.6	10.9%	101.5	14.1%	109.1	13.1%
LDL/HDL Ratio	2.0†	5.0%	2.1†	43.4%	2.3†	39.4%
Triglycerides	107.8	17.5%	130.2	9.5%	105.4	13.8%

* mg/dL
† ratio

Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from women with follow up data (105 of 158 women) returned to pretreatment values.

Table 5. Percent of Women with Serum Lipid Values Outside of the Normal Range

	leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study (n=41)		**Open Label Study (n=117)**	
	Week 0	Week 24*	Week 0	Week 24*
Total Cholesterol (>240 mg/dL)	15%	20%	6%	7%
HDL Cholesterol (<40 mg/dL)	15%	44%	15%	41%
LDL Cholesterol (>160 mg/dL)	5%	7%	9%	11%
LDL/HDL Ratio (>4.0)	2%	15%	7%	21%
Triglycerides (>200 mg/dL)	12%	10%	5%	9%

* Includes all women regardless of baseline value.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of leuprolide acetate for depot suspension or norethindrone acetate. Because these reactions are reported

voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

During postmarketing surveillance which includes other dosage forms and other populations, the following adverse reactions were reported:

- *Body as a whole:* Hypersensitivity reactions including anaphylaxis, localized reactions including induration and abscess at the site of injection
- *Nervous/Psychiatric System:* Mood swings, including depression; suicidal ideation and attempt; convulsion, peripheral neuropathy, paralysis
- *Hepato-biliary system:* Serious liver injury
- *Injury, poisoning and procedural complications:* Spinal fracture
- *Investigations:* Decreased white blood count
- *Musculoskeletal and connective tissue system:* Tenosynovitis-like symptoms
- *Vascular system:* Hypotension, hypertension, deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, transient ischemic attack
- *Respiratory system:* Symptoms consistent with an asthmatic process
- *Multi-system disorders:* Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath), individually and collectively.

Pituitary apoplexy

During post-marketing surveillance, cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of leuprolide acetate and other GnRH 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.

7 DRUG INTERACTIONS

Leuprolide Acetate for Depot Suspension

No drug-drug interaction studies have been conducted with leuprolide acetate for depot suspension. However, leuprolide acetate is a peptide that is not degraded by cytochrome P-450 enzymes; hence, drug interactions associated with cytochrome P-450 enzymes would not be expected to occur.

Norethindrone Acetate

No pharmacokinetic drug interaction studies investigating any drug-drug interactions with norethindrone acetate have been conducted. Drugs or herbal products that induce or inhibit certain enzymes, including CYP3A4, may decrease or increase the serum concentrations of norethindrone, respectively.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

LUPANETA PACK is contraindicated in pregnancy *[see Contraindications (4)]*.

Leuprolide acetate for depot suspension may cause fetal harm based on findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. There are limited human data on the use of LUPANETA PACK in pregnant women. Based on animal reproduction studies, leuprolide acetate for depot suspension may be associated with an increased risk of pregnancy complications, including early pregnancy loss and fetal harm. In animal reproduction studies, subcutaneous administration of leuprolide acetate to rabbits during the period of organogenesis caused embryo-fetal toxicity, decreased fetal weights and a dose-dependent increase in major fetal abnormalities in animals at doses less than the recommended human dose based on body surface area using an estimated daily dose. A similar rat study also showed increased fetal mortality and decreased fetal weights but no major fetal abnormalities at doses less than the recommended human dose based on body surface area using an estimated daily dose *[see Data]*.

Data

Animal Data

When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/300 to 1/3 of the human dose) to rabbits, leuprolide acetate produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of leuprolide acetate in rabbits and with the highest dose (0.024 mg/kg) in rats.

8.2 Lactation

Risk Summary

There are no data on the presence of leuprolide acetate for depot suspension in either animal or human milk, the effects on the breastfed infants, or the effects on milk production. Detectable amounts of progestins have been identified in the milk of mothers receiving them.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUPANETA PACK and any potential adverse effects on the breastfed infant from LUPANETA PACK or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Exclude pregnancy in women of reproductive potential prior to initiating LUPANETA PACK if clinically indicated *[see Warnings and Precautions (5.2)]*.

Contraception

Females
Based on animal reproduction studies and the drug's mechanism of action, the leuprolide acetate component of LUPANETA PACK may cause embryo-fetal harm when administered during pregnancy. LUPANETA PACK is not a contraceptive. If contraception is indicated, advise females of reproductive potential to use a non-hormonal method of contraception during treatment with LUPANETA PACK *[see Warnings and Precautions (5.2)]*.

Infertility

Based on its pharmacodynamic effects of decreasing secretion of gonadal steroids, fertility is expected to be decreased while on treatment with LUPANETA PACK. Clinical and pharmacologic studies in adults (>18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks *[see Clinical Pharmacology (12.1)]*.

There is no evidence that pregnancy rates are affected following discontinuation of LUPANETA PACK.

Animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery of fertility suppression.

8.4 Pediatric Use

Safety and effectiveness of LUPANETA PACK for management of endometriosis have been established in females of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older. The safety and effectiveness of LUPANETA PACK for these indications have not been established in premenarcheal pediatric patients.

8.5 Geriatric Use

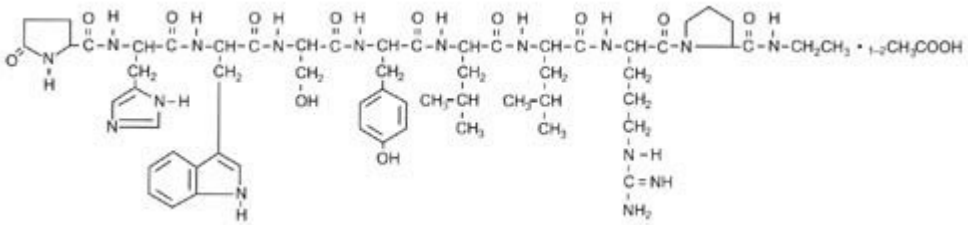
LUPANETA PACK is not indicated in postmenopausal women and has not been studied in women over 65 years of age.

11 DESCRIPTION

LUPANETA PACK (leuprolide acetate for depot suspension; norethindrone acetate tablets) 1-month co-packaged kit contains one dual chamber syringe with leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate tablets USP: 5 mg (bottle of 30 tablets).

Leuprolide Acetate for Depot Suspension

Leuprolide acetate is a synthetic nonapeptide analog of gonadotropin-releasing hormone [(GnRH) or luteinizing hormone releasing hormone (LH-RH)], a GnRH agonist. The chemical name is 5- oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



Leuprolide acetate for depot suspension 3.75 mg is available in a prefilled dual-chamber syringe containing sterile lyophilized microsphere powder which, when mixed with diluent, become a suspension intended as an IM injection.

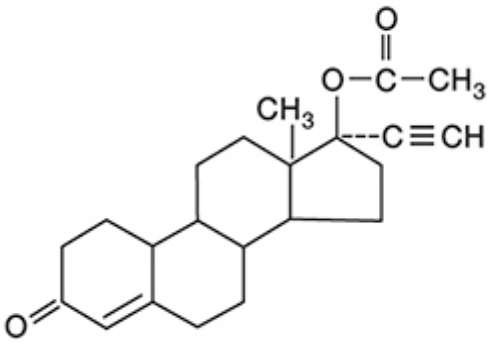
The front chamber of the leuprolide acetate for depot suspension 3.75 mg prefilled dual-chamber syringe contains leuprolide acetate for depot suspension (3.75 mg), gelatin (0.65 mg), DL-lactic and glycolic acids copolymer (33.1 mg), and D-mannitol (6.6 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacturing of leuprolide acetate for depot suspension, acetic acid is lost, leaving the peptide.

Norethindrone Acetate

Norethindrone acetate tablets USP - 5 mg oral tablets.

Norethindrone acetate USP, (17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate), a synthetic, orally active progestin, is the acetic acid ester of norethindrone. It is a white, or creamy white, crystalline powder.



Norethindrone acetate tablets USP, 5 mg contain the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leuprolide Acetate for Depot Suspension

Leuprolide acetate for depot suspension is a long-acting GnRH analog. A single injection of leuprolide acetate for depot suspension results in an initial elevation followed by a prolonged

suppression of pituitary gonadotropins. Repeated dosing at quarterly intervals results in decreased secretion of gonadal steroids; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible on discontinuation of drug therapy.

Leuprolide acetate is not active when given orally.

Norethindrone Acetate

Norethindrone acetate induces secretory changes in an estrogen-primed endometrium.

12.2 Pharmacodynamics

In a pharmacokinetic/pharmacodynamic study of leuprolide acetate for depot suspension 11.25 mg in healthy female subjects (N=20), the onset of estradiol suppression was observed for individual subjects between day 4 and week 4 after dosing. By the third week following the injection, the mean estradiol concentration (8 pg/mL) was in the menopausal range. Throughout the remainder of the dosing period, mean serum estradiol levels ranged from the menopausal to the early follicular range.

Serum estradiol was suppressed to ≤20 pg/mL in all subjects within four weeks and remained suppressed (≤40 pg/mL) in 80% of subjects until the end of the 12-week dosing interval, at which time two of these subjects had a value between 40 and 50 pg/mL. Four additional subjects had at least two consecutive elevations of estradiol (range 43-240 pg/mL) levels during the 12-week dosing interval, but there was no indication of luteal function for any of the subjects during this period.

Administration of leuprolide acetate for depot suspension 3.75 mg results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of leuprolide acetate for depot suspension 3.75 mg may be affected.

In a pharmacokinetic/pharmacodynamic study of endometriosis patients, intramuscular leuprolide acetate for depot suspension 11.25 mg (n=19) every 12 weeks or intramuscular leuprolide acetate for depot suspension 3.75 mg (n=15) every 4 weeks was administered for 24 weeks. There was no statistically significant difference in changes of serum estradiol concentration from baseline between the 2 treatment groups.

12.3 Pharmacokinetics

Absorption

Leuprolide Acetate for Depot Suspension

Following a single injection of the 3-month formulation of leuprolide acetate for depot suspension 11.25 mg in female subjects, a mean plasma leuprolide concentration of 36.3 ng/mL was observed at 4 hours. Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing and mean levels then declined gradually to near the lower limit of detection by 12 weeks. The mean (± standard deviation)

leuprolide concentration from 3 to 12 weeks was 0.23 ± 0.09 ng/mL. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

Norethindrone Acetate

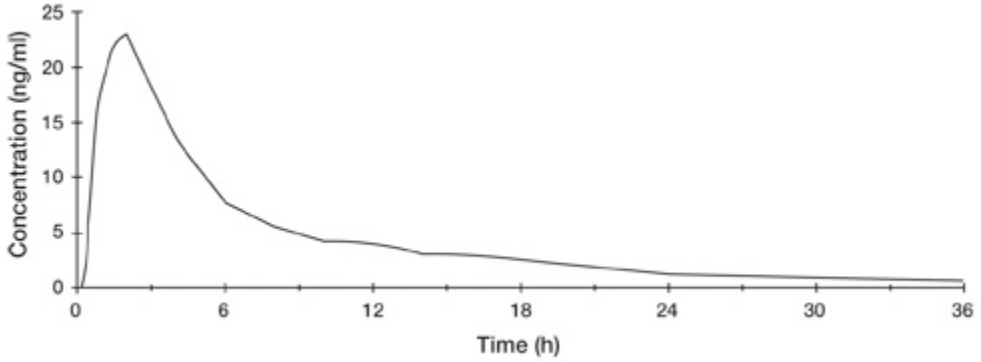
Norethindrone acetate is deacetylated to norethindrone after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate is absorbed from norethindrone acetate tablets, with maximum plasma concentration of norethindrone generally occurring at about 2 hours post-dose (see Figure 8). The pharmacokinetic parameters of norethindrone following single oral administration of norethindrone acetate 5 mg under fasting conditions in 29 healthy female volunteers are summarized in Table 6.

Table 6. Pharmacokinetic Parameters of Norethindrone after a Single Dose of Norethindrone Acetate 5 mg in Healthy Women (n=29)

Parameters	Arithmetic Mean ± SD
AUC (0-inf) (ng/ml*h)	166.90 ± 56.28
C_{max} (ng/ml)	26.19 ± 6.19
t_{max} (h)	1.83 ± 0.58
$t_{1/2}$ (h)	8.51 ± 2.19

AUC = area under the curve,
C_{max} = maximum plasma concentration,
t_{max} = time at maximum plasma concentration,
$t_{1/2}$ = half-life,
SD = standard deviation

Figure 8. Mean Norethindrone Plasma Concentration Profile after a Single Dose of Norethindrone Acetate 5 mg in Healthy Women (n=29) under Fasting Conditions



Distribution

Leuprolide Acetate for Depot Suspension

The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

Norethindrone Acetate

Norethindrone is 36% bound to sex hormone-binding globulin (SHBG) and 61% bound to albumin. Volume of distribution of norethindrone is about 4 L/kg.

Metabolism

Leuprolide Acetate for Depot Suspension

Leuprolide acetate is a peptide that is primarily degraded by peptidase. In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two-compartment model.

Metabolite I (M-I), a smaller inactive peptide, plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

Norethindrone Acetate

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. Norethindrone is also subject to oxidative metabolism catalyzed by CYP3A4. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.

Excretion

Leuprolide Acetate for Depot Suspension

Following administration of leuprolide acetate for depot suspension 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Norethindrone Acetate

Plasma clearance value for norethindrone is approximately 0.4 L/hr/kg. Norethindrone is excreted in both urine and feces, primarily as metabolites. The mean terminal elimination half-life of norethindrone following a single dose administration of norethindrone acetate is approximately 9 hours.

Use in Specific Populations

Hepatic Impairment

The effect of hepatic disease on the disposition of norethindrone after norethindrone acetate administration has not been evaluated. However, norethindrone acetate is contraindicated in markedly impaired liver function or liver disease *[see Contraindications (4)]*.

The pharmacokinetics of the leuprolide acetate for depot suspension in hepatically impaired patients has not been determined.

Renal Impairment

The effect of renal disease on the disposition of norethindrone after norethindrone acetate administration has not been evaluated. In pre-menopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma norethindrone concentration was unchanged compared to concentrations in pre-menopausal women with normal renal function.

The pharmacokinetics of the leuprolide acetate for depot suspension in renally impaired patients has not been determined.

Race

The effect of race on the disposition of norethindrone after norethindrone acetate administration has not been evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Leuprolide Acetate for Depot Suspension

A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

14 CLINICAL STUDIES

Two clinical studies with treatment duration of 12 months were conducted to evaluate the efficacy of LUPANETA PACK in relieving symptoms of endometriosis and the effect on the loss of bone mineral density (BMD). A total of 242 women were treated with monthly administration of leuprolide acetate for depot suspension 3.75 mg (13 injections) and 191 of them received co-administered norethindrone acetate 5 mg orally once daily. The population age range was 17-43 years old. The majority of women were Caucasian (87%). All women in these studies received calcium supplementation with 1000 mg elemental calcium.

The first study was a controlled, randomized, and double-blind study that included 51 women treated monthly with leuprolide acetate for depot suspension 3.75 mg alone and 55 women

treated monthly with leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg daily. Women in this trial were followed for up to 24 months after completing one year of treatment. The second study was an open-label, single-arm clinical study in 136 women treated with leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg daily for one year; these women had follow-up for up to 12 months after completing treatment. See Table 7.

In both clinical studies, the assessment of efficacy was based on the investigator's or the women's monthly assessment of five signs or symptoms of endometriosis (dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness and pelvic induration).

Table 7 below provides detailed efficacy data regarding relief of symptoms of endometriosis based on the two studies of coadministration of leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg daily.

Table 7. Percentages of Women with Symptoms of Endometriosis and Mean Clinical Severity Scores

			Percentage of Women with Symptom			Clinical Pain Severity Score		
			Baseline		Final	Baseline		Final
Variable	**Study**	**Group**	**N[1]**	**(%)[2]**	**(%)**	**N[1]**	**Value[3]**	**Change**
Dysmenorrhea	Controlled Study[4]	LA*	51	(100)	(4)	50	3.2	-2.0
		LA/N†	55	(100)	(4)	54	3.1	-2.0
	Open Label Study[5]	LA/N	136	(99)	(9)	134	3.3	-2.1
Pelvic Pain	Controlled Study[4]	LA	51	(100)	(66)	50	2.9	-1.1
		LA/N	55	(96)	(56)	54	3.1	-1.1
	Open Label Study[5]	LA/N	136	(99)	(63)	134	3.2	-1.2
Deep Dyspareunia	Controlled Study[4]	LA	42	(83)	(37)	25	2.4	-1.0
		LA/N	43	(84)	(45)	30	2.7	-0.8
	Open Label Study[5]	LA/N	102	(91)	(53)	94	2.7	-1.0
Pelvic Tenderness	Controlled Study[4]	LA	51	(94)	(34)	50	2.5	-1.0
		LA/N	54	(91)	(34)	52	2.6	-0.9
	Open Label Study[5]	LA/N	136	(99)	(39)	134	2.9	-1.4
Pelvic Induration	Controlled Study[4]	LA	51	(51)	(12)	50	1.9	-0.4
		LA/N	54	(46)	(17)	52	1.6	-0.4
	Open Label Study[5]	LA/N	136	(75)	(21)	134	2.2	-0.9

* LA = leuprolide acetate for depot suspension 3.75 mg assessment
† LA/N = leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg
[1] Number of women included in the analysis

[2] Percentage of women with the symptom/sign
[3] Value description: 1=none; 2= mild; 3= moderate; 4= severe
[4] 12-month treatment followed by up to 24 months of follow up
[5] 12-month treatment followed by up to 12 months of follow up

Suppression of menses (menses was defined as three or more consecutive days of menstrual bleeding) was maintained throughout treatment in 84% and 73% of women receiving leuprolide acetate and norethindrone acetate, in the controlled study and open label study, respectively. The median time for menses resumption after treatment with leuprolide acetate and norethindrone acetate was 8 weeks.

Changes in Bone Density

The effect of leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg on bone mineral density was evaluated by dual energy x-ray absorptiometry (DXA) scan in the two clinical trials. For the open-label study, success in mitigating BMD loss was defined as the lower bound of the 95% confidence interval around the change from baseline at one year of treatment not to exceed -2.2%. The bone mineral density data of the lumbar spine from these two studies are presented in Table 8.

Table 8. Mean Percent Change from Baseline in BMD of Lumbar Spine

	Controlled Study				Open Label Study	
	LA-Only		LA/N		LA/N	
Study Week	N	% Change (Mean, 95% CI)	N	% Change (Mean, 95% CI)	N	% Change (Mean, 95% CI)
Week 24*	41	-3.2 (-3.8, -2.6)	42	-0.3 (-0.8, 0.3)	115	-0.2 (-0.6, 0.2)
Week 52†	29	-6.3 (-7.1, -5.4)	32	-1.0 (-1.9, -0.1)	84	-1.1 (-1.6, -0.5)

* Includes on-treatment measurements that fell within 2-252 days after the first day of treatment.
† Includes on-treatment measurements >252 days after the first day of treatment.
95% CI: 95% Confidence Interval
LA-Only = leuprolide acetate for depot suspension 3.75 mg
LA/N = leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg

The change in BMD following discontinuation of treatment is shown in Table 9.

Table 9. Mean Percent Change from Baseline in BMD of Lumbar Spine in the Post-Treatment Follow-up Period

	Controlled Study				Open Label Study	
	LA-Only		LA/N		LA/N	
Post Treatment Follow up Month	N[1]	% Change (Mean, 95% CI[2])	N	% Change (Mean, 95% CI)	N	% Change (Mean, 95% CI)
Month 8	19	-3.3 (-4.9, -1.8)	23	-0.9 (-2.1, 0.4)	89	-0.6 (-1.2, 0.0)

Month 12	16	-2.2 (-3.3, -1.1)	12	-0.7 (-2.1, 0.6)	65	0.1 (-0.6, 0.7)

[1] Women with post treatment measurements
[2] 95% CI = 95% Confidence Interval (2-sided) of percent change in BMD values from baseline
Abbreviations: LA-Only = leuprolide acetate for depot suspension 3.75 mg,
LA/N = leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg

These clinical studies demonstrated that coadministration of leuprolide acetate 3.75 mg and norethindrone acetate 5 mg daily is effective in reducing the loss of bone mineral density that occurs with leuprolide acetate for depot suspension treatment, and in relieving symptoms of endometriosis.

16 HOW SUPPLIED/STORAGE AND HANDLING

LUPANETA PACK for 1-month co-packaged kit (NDC 0074-1052-05) is available in

cartons containing:

leuprolide acetate for depot suspension 3.75 mg for 1-month administration Kit (NDC 0074-3641-04)

- one prefilled dual-chamber syringe
- one plunger
- two alcohol swabs

norethindrone acetate 5 mg tablets; 30 count bottle (NDC 0074-1049-02)

1. Each leuprolide acetate for depot suspension 3.75 mg for 1-month administration kit contains a single-dose dual chamber syringe. The syringe contains sterile white lyophilized microsphere powder of leuprolide acetate incorporated in a biodegradable polymer in one chamber and a colorless diluent (1 mL) in the other chamber. When mixed with diluent, leuprolide acetate for depot suspension 3.75 mg for injection is administered as a single IM injection.
2. Norethindrone acetate 5 mg 30-count bottle
   White to off-white oval, flat faced beveled edged, uncoated tablets debossed with ‘G with break line’ on one side and 304 on the other side.

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Loss of Bone Density

Advise patients about the risk of loss of bone mineral density and that treatment duration is limited *[see Dosage and Administration (2.1)]*. Advise patients about other factors that can increase and decrease their risk of bone mineral density loss *[see Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the possible risk to a fetus. Advise patients to inform healthcare provider if they believe they may be pregnant *[see Warnings and Precautions (5.2) and Use in Special Populations (8.1)]*.
- If contraception is indicated, advise females of reproductive potential to use non-hormonal contraception during treatment with LUPANETA PACK *[see Use in Special Populations (8.3)]*.

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions, including anaphylaxis, have been reported with LUPANETA PACK. Advise patients to seek appropriate medical care if symptoms of hypersensitivity reactions occur *[see Warnings and Precautions (5.3) and Adverse Reactions (6.2)]*.

Cardiovascular and Metabolic Disorders

Advise patients of the need for close monitoring if they have cardiovascular risk factors, or conditions like epilepsy, migraine, or renal dysfunction *[see Warnings and Precautions (5.4)]*.

Initial Flare of Symptoms

Advise patients that they may experience an increase in symptoms during the initial days of therapy. Advise patients that these symptoms should dissipate with continued therapy *[see Warnings and Precautions (5.5)]*. Advise patients to notify their healthcare provider if they develop new or worsened symptoms after beginning treatment.

Convulsions

Inform patients that convulsions have been reported in patients who have received LUPANETA PACK. Advise patients to seek medical attention in the event of a convulsion *[see Warnings and Precautions (5.6)]*.

Clinical Depression

Inform patients that depression may occur or worsen during treatment with GnRH agonists, including LUPANETA PACK, especially in patients with a history of depression. Advise patients to immediately report thoughts and behaviors of concern to healthcare providers *[see Warnings and Precautions (5.7)]*.

Visual Abnormalities

Advise patients to discontinue norethindrone acetate and seek medical attention if they develop sudden loss of vision, double vision or sudden migraine *[see Warnings and Precautions (5.8)]*.

Leuprolide Acetate for Depot Suspension 3.75 mg:
Manufactured for
AbbVie Inc.
North Chicago, IL 60064

by Takeda Pharmaceutical Company Limited
Osaka, Japan 540–8645

Norethindrone acetate
Manufactured for
AbbVie Inc.
North Chicago, IL 60064

Manufactured by
Glenmark Pharmaceuticals Ltd.
Colvale-Bardez, Goa
403 513, India

LUPANETA PACK
Packaged by:
AbbVie Inc.
North Chicago, IL 60064

Revised: 08/2023

PATIENT INFORMATION
LUPANETA PACK® (loo-pan-e-tə pæk)
(leuprolide acetate for depot suspension and norethindrone acetate tablets)

Read this Patient Information before you start taking LUPANETA PACK and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is LUPANETA PACK?

LUPANETA PACK contains 2 different prescription medicines:

- **leuprolide acetate for depot suspension** is a medicine injected into your muscle and used to treat pain due to endometriosis.
- **norethindrone acetate tablets** is a medicine taken by mouth and used to help lower the side effect of bone thinning that is caused by leuprolide acetate for depot suspension.

LUPANETA PACK should not be used longer than 6 months at a time after you first start treatment for your endometriosis symptoms. LUPANETA PACK should not be used for more than a total of 12 months during your treatment.

It is not known if LUPANETA PACK is safe and effective in children who have not started their menstrual period.

Who should not take LUPANETA PACK?

Do not take LUPANETA PACK if you:

- have had an allergic reaction to gonadotropin-releasing hormone (GnRH), GnRH agonist medicines, or any ingredients in ~~like~~ leuprolide acetate for depot suspension or norethindrone acetate tablets. See the end of this leaflet for a complete list of ingredients in LUPANETA PACK.
- have uterine bleeding for which a cause has not been found
  - are pregnant or may be pregnant. LUPANETA PACK may harm your unborn baby. If you become pregnant while taking LUPANETA PACK, stop taking the norethindrone acetate tablets and call your doctor right away.
- have or have had breast cancer or other cancers that are sensitive to hormones
- have or have had problems with blood clots, including a stroke, or a heart attack.
- have liver problems

What should I tell my doctor before taking LUPANETA PACK?
Before you take LUPANETA PACK, tell your doctor if you:

- drink alcohol
- smoke
- have a family history of bone loss (osteoporosis)
- have depression
- have high cholesterol
- have had blood clots, a stroke, or a heart attack
- have migraine headaches
- have diabetes
- have epilepsy
- have kidney problems
- are breastfeeding or plan to breastfeed. It is not known if LUPANETA PACK passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while receiving LUPANETA PACK.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take anticonvulsant (seizure) or corticosteroid medicines.

Ask your doctor for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take LUPANETA PACK?

- **Leuprolide acetate for depot suspension** for 1month administration is injected into your muscle 1 time every month by a healthcare professional in your doctor's office.
- **Take norethindrone acetate tablets** exactly as your doctor tells you to take them. Take 1 norethindrone acetate tablet by mouth every day for 1 month after you receive your injection.
- Talk to your doctor about the birth control method that is right for you before you start taking LUPANETA PACK. You will need to use a form of birth control that does not contain hormones, such as:
  - a diaphragm with spermicide
  - condoms with spermicide
  - a copper IUD
- If you become pregnant while taking LUPANETA PACK, stop taking the norethindrone acetate tablets and call your doctor right away.

What are the possible side effects of LUPANETA PACK?

LUPANETA PACK may cause serious side effects, including:

- **bone thinning (decreased bone mineral density)**
- **harm to your unborn baby**

- **allergic reactions.** Get medical help right away if you have any of these symptoms of a serious allergic reaction:

  - swelling of your face, lips, mouth, or tongue
  - wheezing
  - skin rash, redness, or swelling
  - fast heartbeat or pounding in your chest (tachycardia)
  - trouble breathing
  - severe itching
  - dizziness or fainting
  - sweating

- **heart issues in people who already have high blood pressure, diabetes, high blood sugar, or kidney problems. Monitor these conditions closely with your doctor.**
- **worsening endometriosis symptoms when you start taking LUPANETA PACK**
- **seizures (convulsions).** Some people taking GnRH agonists like LUPANETA PACK have had seizures. Call you doctor with away if you have a seizure while taking LUPANETA PACK.
- **depression or worsening depression**
- **vision problems.** Call your doctor right away if you have sudden loss of vision, double vision, bulging eyes, or migraine headaches.
- **swelling (fluid retention)**

The most common side effects of LUPANETA PACK include:

  - hot flashes and sweats
  - depression and mood swings
  - nausea and vomiting
  - weakness
  - dizziness and spinning feeling
  - weight gain
  - headaches or migraine ~~headaches~~
  - problems sleeping
  - pain
  - vaginal infection or inflammation
  - constipation or diarrhea
  - breast tenderness or pain

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of LUPANETA PACK. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store norethindrone acetate tablets in the LUPANETA PACK?

- Store norethindrone acetate tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep LUPANETA PACK and all medicines out of the reach of children.

General information about the safe and effective use of LUPANETA PACK.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LUPANETA PACK for a condition for which it was not

prescribed. Do not give LUPANETA PACK to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about LUPANETA PACK that is written for health professionals.

What are the ingredients in LUPANETA PACK?

leuprolide acetate for depot suspension:
Active Ingredients: leuprolide acetate for depot suspension
Inactive Ingredients: gelatin, DL-lactic and glycolic acids copolymer, D-mannitol, carboxymethylcellulose sodium, polysorbate 80, water for injection, USP, and glacial acetic acid, USP to control pH.

norethindrone acetate tablets:
Active ingredients: norethindrone acetate USP
Inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose and talc.

Leuprolide Acetate for Depot Suspension:
Manufactured for
AbbVie Inc.
North Chicago, IL 60064

By Takeda Pharmaceutical Company Limited
Osaka, Japan 540-8645

Norethindrone acetate:
Manufactured for
AbbVie Inc.
North Chicago, IL 60064

By Glenmark Pharmaceuticals Ltd.
Colvale-Bardez, Goa
403 513, India

For more information, go to www.lupanetapack.com or call 1-800-633-9110.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: August/2023

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUPANETA PACK safely and effectively. See full prescribing information for LUPANETA PACK.

LUPANETA PACK (leuprolide acetate for depot suspension, for injection; norethindrone acetate tablets), co-packaged for intramuscular use and for oral use, respectively
Initial U.S. Approval: 2012

RECENT MAJOR CHANGES

Warnings and Precautions, Embryofetal Toxicity (5.2)	08/2023
Warnings and Precautions, Hypersensitivity Reactions (5.3)	08/2023
Warnings and Precautions, Clinical Depression (5.7)	12/2022

INDICATIONS AND USAGE

LUPANETA PACK contains leuprolide acetate, a gonadotropin-releasing hormone (GnRH) agonist and norethindrone acetate, a progestin, and is indicated for:

- Initial management of the painful symptoms of endometriosis (1)
- Management of recurrence of symptoms (1)

Limitations of Use:

- The total duration of therapy with LUPANETA PACK should not exceed 12 months due to concerns about the adverse impact on bone mineral density (BMD).(1, 2.1, 5.1)

DOSAGE AND ADMINISTRATION

- Do not administer leuprolide acetate for depot suspension in the LUPANETA PACK alone if the patient is not taking norethindrone acetate. (2.1)
- Do not administer leuprolide acetate for depot suspension 11.25 mg more frequently than every 3 months. (2.1)
- Do not administer a fractional dose of leuprolide acetate for depot suspension 11.25 mg. Do not substitute the leuprolide acetate for depot suspension 11.25 mg (3 months of therapy) component for the leuprolide acetate for depot suspension 3.75 mg (one month of therapy) component of the LUPANETA PACK; they are not equivalent due to the different release characteristics. (2.1)
- The recommended dosage is leuprolide acetate for depot suspension 11.25 mg for 3-month administration given by a healthcare provider as a single intramuscular (IM) injection every 3 months for up to two injections (6 months of therapy) co-administered with norethindrone acetate 5 mg tablets taken orally once daily by the patient for up to 6 months. If endometriosis symptoms recur after initial course of therapy, consider retreatment for up to another six months. (2.2)
- Reconstitute leuprolide acetate prior to use. See the full prescribing information for preparation and administration instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

- For injection: Leuprolide acetate for depot suspension 11.25 mg lyophilized powder for reconstitution in a dual-chamber syringe (3)
- Tablets: Norethindrone acetate 5 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to GnRH, GnRH agonist or any of the excipients in leuprolide acetate for depot suspension or norethindrone acetate (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4, 8.1)
- Known, suspected or history of breast or other hormone-sensitive cancer (4)
- Thrombotic or thromboembolic disorders (4)
- Liver tumors or liver disease (4)

WARNINGS AND PRECAUTIONS

- Loss of bone mineral density (BMD): Duration of treatment is limited by risk of bone mineral density loss. When using LUPANETA PACK for the management of endometriosis, the norethindrone acetate component of the LUPANETA PACK reduces the BMD loss. Do not retreat with leuprolide acetate for depot suspension alone. Assess BMD after 6 months of treatment before retreatment. Do not use for more than 12 months due to concerns about adverse impact on BMD. (5.1)
- Embryo-Fetal Toxicity: May cause fetal harm. Exclude pregnancy before initiating treatment if clinically indicated and discontinue use if pregnancy occurs. Use non-hormonal methods of contraception only. (5.2)
- Hypersensitivity Reactions: Reactions, including anaphylaxis, have been reported. (5.3)
- Cardiovascular and Metabolic Disorders: Assess and manage risk factors before starting LUPANETA PACK. (5.4)
- Clinical Depression: Carefully observe women for depression and refer to a mental health professional, as appropriate. (5.7)
- Visual Abnormalities: Discontinue norethindrone acetate in case of sudden loss of vision or onset of proptosis, diplopia, or migraine pending visual examination. Discontinue LUPANETA PACK if examination reveals papilledema or retinal vascular lesions. (5.8)

ADVERSE REACTIONS

Leuprolide acetate for depot suspension co-administered with norethindrone acetate: Most common related adverse reactions (>10%) were hot flashes/sweats, headache/migraine, nausea/vomiting, pain, depression/emotional lability, asthenia, constipation/diarrhea, vaginitis, insomnia/sleep disorder, breast changes/pain/tenderness, weight gain, dizziness/vertigo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUPANETA PACK is indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms.

Limitations of Use

The total duration of therapy with LUPANETA PACK should not exceed 12 months due to concerns about the adverse impact on bone mineral density *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

LUPANETA PACK is a co-packaged product containing leuprolide acetate for depot suspension 11.25 mg for intramuscular use and norethindrone acetate 5 mg tablets for oral use.

- Do not administer leuprolide acetate for depot suspension 11.25 mg in the LUPANETA PACK alone if the patient is not taking norethindrone acetate.
- Do not administer leuprolide acetate for depot suspension 11.25 mg more frequently than every 3 months.
- Do not administer a fractional dose of leuprolide acetate for depot suspension 11.25 mg.
- Do not substitute the leuprolide acetate for depot suspension 11.25 mg (3 months of therapy) component for the leuprolide acetate for depot suspension 3.75 mg (one month of therapy) component of the LUPANETA PACK; they are not equivalent due to the different release characteristics.

2.2 Recommended Dosage and Administration

The recommended initial and retreatment dosage regimens for LUPANETA PACK for the management of women with endometriosis are outlined in Table 1.

Table 1. LUPANETA PACK. Management of Endometriosis

Treatment Phase	LUPANETA PACK 11.25 mg Dosing	Maximum Treatment Duration
Initial Treatment	Leuprolide acetate for depot suspension 11.25 mg IM every 3 months Norethindrone acetate 5 mg orally once daily	6 months
Retreatment	Leuprolide acetate for depot suspension 11.25 mg IM every 3 months Norethindrone acetate 5 mg orally once daily	6 months
Total Treatment Duration		12 Months

Assess bone mineral density (BMD) prior to retreatment with LUPANETA PACK *[see Warnings and Precautions (5.1)]*.

Total treatment duration with LUPANETA PACK should not exceed 12 months due to concerns about the adverse impact on bone mineral density.

2.3 Reconstitution and Administration Instructions for Leuprolide Acetate Injection

- Reconstitute and administer the lyophilized microspheres as a single IM injection as directed below. Visually inspect the drug product for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Inject the leuprolide acetate for depot suspension 11.25 mg immediately or discard if not used within two hours as the suspension does not contain a preservative.

1. Visually inspect the leuprolide acetate for depot suspension powder. **Do not use** the syringe if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal prior to mixing with the diluent. The diluent should appear clear.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn (see Figure 1 and Figure 2).

Figure 1:

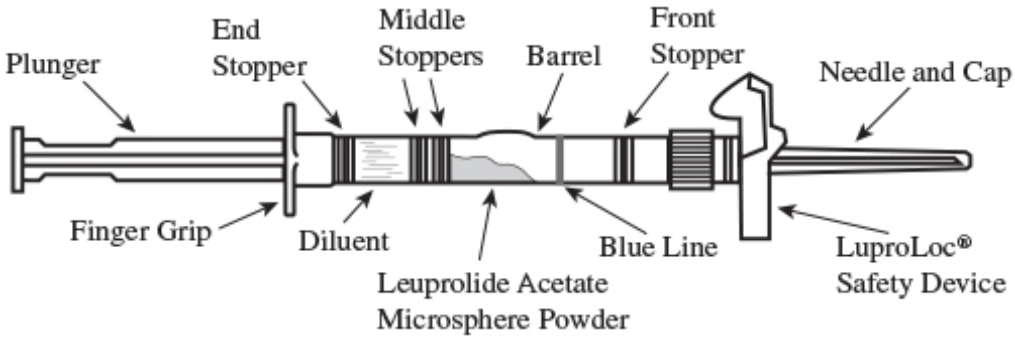
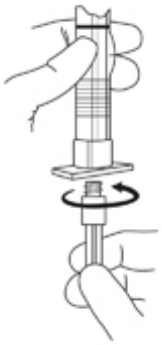
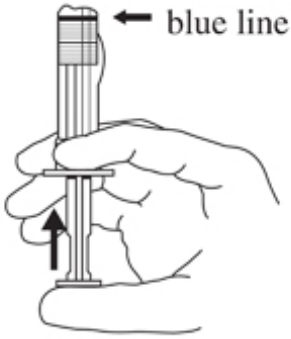


Figure 2:



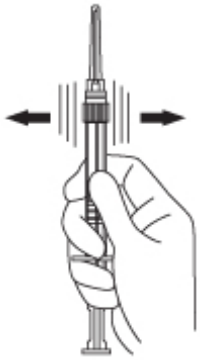
3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING the plunger for 6 to 8 seconds until the first middle stopper is **at the blue line** in the middle of the barrel (see Figure 3).

Figure 3:



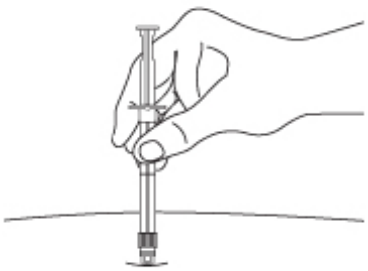
4. Keep the syringe **upright**. Mix the microsphere powder thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. **Do not use** if any of the powder has not gone into suspension (see Figure 4).

Figure 4:



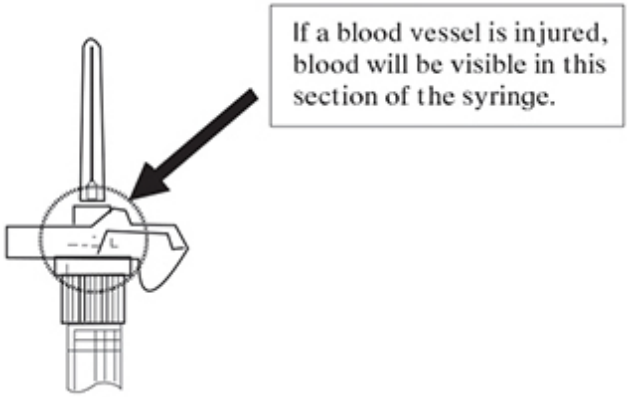
5. Keep the syringe **upright**. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe **upright**. Advance the plunger to expel the air from the syringe. Now the syringe is ready for injection.
7. After cleaning the injection site with an alcohol swab, administer the IM injection by inserting the needle at a 90 degree angle into the gluteal area, anterior thigh, or deltoid (see Figure 5). Injection sites should be alternated (see Figure 5).

Figure 5:



Note: If a blood vessel is accidentally penetrated, aspirated blood will be visible just below the luer lock (see Figure 6) and can be seen through the transparent LuproLoc safety device. If blood is present, remove the needle immediately. Do not inject the medication.

Figure 6:



8. Inject the entire contents of the syringe intramuscularly.
9. Withdraw the needle. Once the syringe has been withdrawn, immediately activate the LuproLoc® safety device by pushing the arrow on the lock upward towards the needle tip with the thumb or finger, as illustrated, until the needle cover of the safety device over the needle is fully extended and a **click** is heard or felt (see Figure 7).

   Figure 7:

10. Dispose of the syringe according to local regulations/procedures.

3 DOSAGE FORMS AND STRENGTHS

LUPANETA PACK 3-month co-packaged kit contains two separate components:

- For Injection: Leuprolide acetate for depot suspension 11.25 mg as a white lyophilized microsphere powder for reconstitution in a single-dose prefilled dual chamber syringe, with one chamber containing the lyophilized powder and the other chamber containing the clear diluent.
- Tablets: Norethindrone acetate 5 mg tablets as white to off-white oval, flat-faced beveled edged, uncoated, debossed with ‘G’ with a break line on one side and ‘304’ on the other side

4 CONTRAINDICATIONS

LUPANETA PACK is contraindicated in women with the following:

- Hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs, any of the excipients in leuprolide acetate for depot suspension, or norethindrone acetate
- Undiagnosed abnormal uterine bleeding
- Pregnancy *[see Warnings and Precautions (5.2)* and *Use in Specific Populations (8.1)]*
- Known, suspected or history of breast cancer or other hormone-sensitive cancer
- Current or history of thrombotic or thromboembolic disorder
- Liver tumors or liver disease

5 WARNINGS AND PRECAUTIONS

5.1 Loss of Bone Mineral Density

Leuprolide acetate for depot suspension induces a hypoestrogenic state that results in loss of bone mineral density (BMD), some of which may not be reversible after stopping treatment. In women with major risk factors for decreased BMD such as chronic alcohol use (> 3 units per day), tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of LUPANETA PACK may pose an additional risk. Carefully weigh the risks and benefits of LUPANETA PACK use in these populations.

Total treatment duration with LUPANETA PACK should not exceed 12 months. The duration of LUPANETA PACK treatment is limited by the risk of loss of bone mineral density *[see Dosage and Administration (2.1)]*.

When using LUPANETA PACK for the management of endometriosis, the norethindrone acetate component of the LUPANETA PACK reduces the BMD loss that occurs with leuprolide acetate use alone *[see Clinical Studies (14)]*. Do not retreat with leuprolide acetate for depot suspension alone. Assess BMD after 6 months of treatment before retreatment.

5.2 Embryo-Fetal Toxicity

Based on animal reproduction studies and the drug's mechanism of action, leuprolide acetate for depot suspension may cause fetal harm if administered to a pregnant woman and is contraindicated in pregnant women. Exclude pregnancy prior to initiating treatment with LUPANETA PACK if clinically indicated. Discontinue LUPANETA PACK if the woman becomes pregnant during treatment and inform the woman of potential risk to the fetus *[see Contraindications (4)* and *Use in Specific Populations (8.1)]*. Advise women to notify their healthcare provider if they believe they may be pregnant.

When used at the recommended dose and dosing interval, leuprolide acetate for depot suspension usually inhibits ovulation and stops menstruation. Contraception, however, is not ensured by taking leuprolide acetate for depot suspension. If contraception is indicated, advise women to use nonhormonal methods of contraception while on treatment with LUPANETA PACK.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, have been reported with LUPANETA PACK use. LUPANETA PACK is contraindicated in women with a history of hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs, or norethindrone acetate *[see Adverse Reactions (6.2)]*.

In clinical trials for LUPANETA PACK, adverse events of asthma were reported in women with pre-existing histories of asthma, sinusitis and environmental or drug allergies. Symptoms consistent with an anaphylactoid or asthmatic process have been reported postmarketing.

5.4 Cardiovascular and Metabolic Disorders

Assess and manage risk factors for cardiovascular disease before starting LUPANETA PACK. Closely monitor women on norethindrone acetate who have risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., family history of VTE, obesity, and smoking) when using LUPANETA PACK *[see Contraindications (4)]*.

5.5 Initial Flare of Symptoms

Following the first dose of leuprolide acetate component of LUPANETA PACK, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in symptoms may be observed during the initial days of therapy, but these should dissipate with continued therapy.

5.6 Convulsions

There have been postmarketing reports of convulsions in women taking GnRH agonists such as the leuprolide acetate component of LUPANETA PACK. These included women with and without concurrent medications and comorbid conditions.

5.7 Clinical Depression

Depression may occur or worsen during treatment with GnRH agonists including LUPANETA PACK *[see Adverse Reactions (6.1)]*. Carefully observe women for depression, especially those with a history of depression and consider whether the risks of continuing LUPANETA PACK outweigh the benefits. Women with new or worsening depression should be referred to a mental health professional, as appropriate.

5.8 Visual Abnormalities

Discontinue norethindrone acetate tablets in the LUPANETA PACK pending examination if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine. Discontinue LUPANETA PACK if examination reveals papilledema or retinal vascular lesions.

5.9 Fluid Retention

Because norethindrone acetate, a component of LUPANETA PACK, may cause some degree of fluid retention, carefully observe women with conditions that might be influenced by this effect, such as epilepsy, migraine, cardiac or renal dysfunctions.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Loss of Bone Mineral Density *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Initial Flare of Symptoms *[see Warnings and Precautions (5.5)]*
- Convulsions *[see Warnings and Precautions (5.6)]*
- Clinical Depression *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of co-administering leuprolide acetate for depot suspension and norethindrone acetate was evaluated in two clinical studies in which a total of 242 women were treated for up to one year. Women were treated with monthly IM injections of leuprolide acetate 3.75 mg (13 injections) alone or monthly IM injections of leuprolide acetate 3.75 mg (13 injections) and norethindrone acetate 5 mg orally once daily. The population age range was 17-43 years old. The majority of women were Caucasian (87%).

In the first study, 106 women were randomized to one year of treatment with leuprolide acetate for depot suspension alone or with leuprolide acetate for depot suspension and norethindrone acetate. The second study was an open-label, single arm clinical study in 136 women who received one year of leuprolide acetate for depot suspension and norethindrone acetate; these women were followed for up to 12 months after completing treatment.

Adverse Reactions (>1%) Leading to Study Discontinuation:

In the controlled study, 18% of women treated monthly with leuprolide acetate for depot suspension 3.75 mg alone and 18% of women treated concomitantly monthly with leuprolide acetate for depot suspension 3.75 mg

and norethindrone acetate 5 mg discontinued therapy due to adverse reactions. The most common adverse reactions leading to discontinuation were hot flashes (6%) and insomnia (4%) in the leuprolide acetate for depot suspension 3.75 mg alone group and hot flashes and emotional lability (4% each) in the leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg group.

In the open-label study, 13% of women treated monthly with leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg discontinued therapy due to adverse reactions, most commonly depression (4%) and acne (2%).

Common Adverse Reactions:

Table 2 lists the adverse reactions observed in at least 5% of women in any treatment group, during the first 6 months of treatment in the two clinical studies. The most common adverse reactions observed in these studies were hot flashes and headaches.

Table 2. Adverse Reactions Occurring in the First Six Months of Treatment in ≥ 5% of Women with Endometriosis

	Controlled Study		Open Label Study
	LA-Only*	LA/N†	LA/N†
	N=51	N=55	N=136
Adverse Reactions	%	%	%
Any Adverse Reaction	98	96	93
Hot flashes/Sweats	98	87	57
Headache/Migraine	65	51	46
Depression/Emotional Lability	31	27	34
Insomnia/Sleep Disorder	31	13	15
Nausea/Vomiting	25	29	13
Pain	24	29	21
Vaginitis	20	15	8
Asthenia	18	18	11
Dizziness/Vertigo	16	11	7
Altered Bowel Function (constipation, diarrhea)	14	15	10
Weight Gain	12	13	4
Decreased Libido	10	4	7
Nervousness/Anxiety	8	4	11
Breast Changes/Pain/Tenderness	6	13	8
Memory Disorder	6	2	4
Skin/Mucous Membrane Reaction	4	9	11
GI Disturbance (dyspepsia, flatulence)	4	7	4
Androgen-Like Effects (acne, alopecia)	4	5	18
Changes in Appetite	4	0	6
Injection Site Reaction	2	9	3
Neuromuscular Disorder (leg cramps, paresthesia)	2	9	3
Menstrual Disorders	2	0	5
Edema	0	9	7

* LA-Only = leuprolide acetate for depot suspension 3.75 mg
† LA/N = leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg

In the controlled clinical trial, 50 of 51 (98%) women in the leuprolide acetate for depot suspension and 48 of 55 (87%) women in the leuprolide acetate for depot suspension and norethindrone acetate arm reported experiencing hot flashes on one or more occasions during treatment.

Table 3 presents hot flash data in the sixth month of treatment.

Table 3. Hot Flashes in the Month Prior to the Assessment Visit (Controlled Study)

Assessment Visit	Treatment Group	Number of Women Reporting Hot Flashes		Number of Days with Hot Flashes		Maximum Number of Hot Flashes in 24 Hours	
		N	(%)	N[2]	Mean	N[2]	Mean
Week 24	LA-Only*	32/37	86	37	19	36	5.8
	LA/N†	22/38	58[1]	38	7[1]	38	1.9[1]

* LA-Only = leuprolide acetate for depot suspension 3.75 mg
† LA/N = leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg
[1]Statistically significantly less than the LA-Only group ($p<0.01$)
[2]Number of women assessed.

Serious Adverse Reactions:

Urinary tract infection (1.9%), renal calculus (0.7%), depression (0.7%)

Changes in Laboratory Values during Treatment:

Liver Enzymes

In the two clinical trials of women with endometriosis, 2% (4 of 191) women receiving leuprolide acetate for depot suspension and norethindrone acetate for up to 12 months developed an elevated (at least twice the upper limit of normal) serum glutamic pyruvic transaminase (SGPT) and 1% (2 of 136) developed an elevated gamma glutamyl transferase (GGT). Among these six women with increased liver tests, the increases in five were observed beyond 6 months of treatment. None were associated with an elevated bilirubin concentration.

Lipids

Percent changes from baseline for serum lipids and percentages of women with serum lipid values outside of the normal range in the two studies of leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg daily are summarized in Tables 4 and 5 below. The major impact of adding norethindrone acetate to treatment with leuprolide acetate for depot suspension was a decrease in serum HDL cholesterol and an increase in the LDL/HDL ratio.

Table 4. Serum Lipids: Mean Percent Changes from Baseline Values at Treatment Week 24

	leuprolide acetate for depot suspension 3.75 mg		leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg daily			
	Controlled Study (n=39)		Controlled Study (n=41)		Open Label Study (n=117)	
	Baseline Value*	Week 24 % Change	Baseline Value*	Week 24 % Change	Baseline Value*	Week 24 % Change
Total Cholesterol	170.5	9.2%	179.3	0.2%	181.2	2.8%
HDL Cholesterol	52.4	7.4%	51.8	-18.8%	51.0	-14.6%
LDL Cholesterol	96.6	10.9%	101.5	14.1%	109.1	13.1%
LDL/HDL Ratio	2.0†	5.0%	2.1†	43.4%	2.3†	39.4%
Triglycerides	107.8	17.5%	130.2	9.5%	105.4	13.8%

* mg/dL
† ratio

Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from women with follow up data (105 of 158 women) returned to pretreatment values.

Table 5. Percent of Women with Serum Lipid Values Outside of the Normal Range

	leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study (n=41)		Open Label Study (n=117)	
	Week 0	Week 24*	Week 0	Week 24*
Total Cholesterol (>240 mg/dL)	15%	20%	6%	7%
HDL Cholesterol (<40 mg/dL)	15%	44%	15%	41%
LDL Cholesterol (>160 mg/dL)	5%	7%	9%	11%
LDL/HDL Ratio (>4.0)	2%	15%	7%	21%
Triglycerides (>200 mg/dL)	12%	10%	5%	9%

* Includes all women regardless of baseline value.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of leuprolide acetate for depot suspension or norethindrone acetate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

During postmarketing surveillance which includes other dosage forms and other populations, the following adverse reactions were reported:

- *Body as a whole:* Hypersensitivity reactions including anaphylaxis, localized reactions including induration and abscess at the site of injection
- *Nervous/Psychiatric System:* Mood swings, including depression; suicidal ideation and attempt; convulsion, peripheral neuropathy, paralysis
- *Hepato-biliary system:* Serious liver injury
- *Injury, poisoning and procedural complications*: Spinal fracture
- *Investigations*: Decreased white blood count
- *Musculoskeletal and connective tissue system*: Tenosynovitis-like symptoms
- *Vascular system:* Hypotension, hypertension, deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, transient ischemic attack
- *Respiratory system:* Symptoms consistent with an asthmatic process
- *Multi-system disorders:* Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath), individually and collectively.

Pituitary apoplexy

During post-marketing surveillance, cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of leuprolide acetate and other GnRH 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.

7 DRUG INTERACTIONS

Leuprolide Acetate for Depot Suspension

No drug-drug interaction studies have been conducted with leuprolide acetate for depot suspension 11.25 mg. However, leuprolide acetate is a peptide that is not degraded by cytochrome P-450 enzymes; hence, drug interactions associated with cytochrome P-450 enzymes would not be expected to occur.

Norethindrone Acetate

No pharmacokinetic drug interaction studies investigating any drug-drug interactions with norethindrone acetate have been conducted. Drugs or herbal products that induce or inhibit certain enzymes, including CYP3A4, may decrease or increase the serum concentrations of norethindrone, respectively.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

LUPANETA PACK is contraindicated in pregnancy *[see Contraindications (4)]*.

Leuprolide acetate for depot suspension may cause fetal harm based on findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. There are limited human data on the use of LUPANETA PACK in pregnant women. Based on animal reproduction studies, leuprolide acetate for depot suspension may be associated with an increased risk of pregnancy complications, including early pregnancy loss and fetal harm. In animal reproduction studies, subcutaneous administration of leuprolide acetate to rabbits during the period of organogenesis caused embryo-fetal toxicity, decreased fetal weights and a dose-dependent increase in major fetal abnormalities in animals at doses less than the recommended human dose based on body surface area using an estimated daily dose. A similar rat study also showed increased fetal mortality and decreased fetal weights but no major fetal abnormalities at doses less than the recommended human dose based on body surface area using an estimated daily dose *[see Data]*.

Data

Animal Data

When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/300 to 1/3 of the human dose) to rabbits, leuprolide acetate produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of leuprolide acetate in rabbits and with the highest dose (0.024 mg/kg) in rats.

8.2 Lactation

Risk Summary

There are no data on the presence of leuprolide acetate for depot suspension in either animal or human milk, the effects on the breastfed infants, or the effects on milk production. Detectable amounts of progestins have been identified in the milk of mothers receiving them.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUPANETA PACK and any potential adverse effects on the breastfed infant from LUPANETA PACK or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Exclude pregnancy in women of reproductive potential prior to initiating LUPANETA PACK if clinically indicated *[see Warnings and Precautions (5.2)]*.

Contraception

Females

Based on animal reproduction studies and the drug's mechanism of action, the leuprolide acetate component of LUPANETA PACK may cause embryo-fetal harm when administered during pregnancy. LUPANETA PACK is not a contraceptive. If contraception is indicated, advise females of reproductive potential to use a non-hormonal method of contraception during treatment with LUPANETA PACK *[see Warnings and Precautions (5.2)]*.

Infertility

Based on its pharmacodynamic effects of decreasing secretion of gonadal steroids, fertility is expected to be decreased while on treatment with LUPANETA PACK. Clinical and pharmacologic studies in adults (>18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks *[see Clinical Pharmacology (12.1)]*.

There is no evidence that pregnancy rates are affected following discontinuation of LUPANETA PACK.

Animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery of fertility suppression.

8.4 Pediatric Use

Safety and effectiveness of LUPANETA PACK for management of endometriosis have been established in females of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older. The safety and effectiveness of LUPANETA PACK for these indications have not been established in premenarcheal pediatric patients.

8.5 Geriatric Use

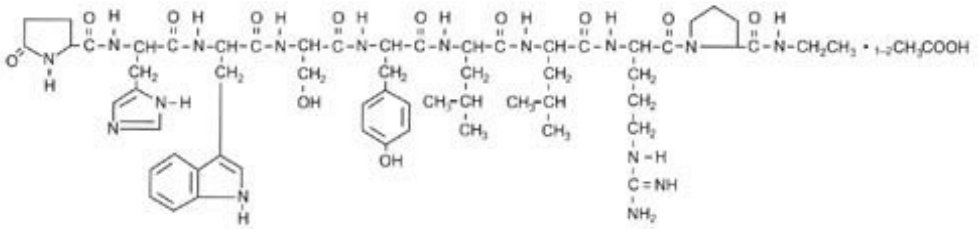
LUPANETA PACK is not indicated in postmenopausal women and has not been studied in women over 65 years of age.

11 DESCRIPTION

LUPANETA PACK (leuprolide acetate for depot suspension; norethindrone acetate tablets) 3-month co-packaged kit contains one dual chamber syringe with leuprolide acetate for depot suspension 11.25 mg and norethindrone acetate tablets USP: 5 mg (bottle of 90 tablets).

Leuprolide Acetate for Depot Suspension

Leuprolide acetate is a synthetic nonapeptide analog of gonadotropin-releasing hormone [(GnRH) or luteinizing hormone releasing hormone (LH-RH)], a GnRH agonist. The chemical name is 5- oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



Leuprolide acetate for depot suspension 11.25 mg is available in a prefilled dual-chamber syringe containing sterile lyophilized microsphere powder which, when mixed with diluent, become a suspension intended as an IM injection.

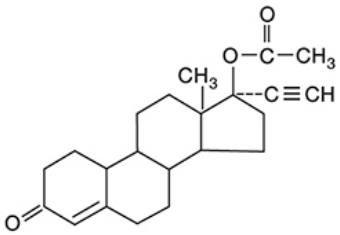
The front chamber of the leuprolide acetate for depot suspension 11.25 mg prefilled dual-chamber syringe contains leuprolide acetate for depot suspension (11.25 mg), polylactic acid (99.3 mg) and D-mannitol (19.45 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacturing of leuprolide acetate for depot suspension, acetic acid is lost, leaving the peptide.

Norethindrone Acetate

Norethindrone acetate tablets USP - 5 mg oral tablets.

Norethindrone acetate USP, (17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate), a synthetic, orally active progestin, is the acetic acid ester of norethindrone. It is a white, or creamy white, crystalline powder.



Norethindrone acetate tablets USP, 5 mg contain the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leuprolide Acetate for Depot Suspension

Leuprolide acetate for depot suspension is a long-acting GnRH analog. A single injection of leuprolide acetate for depot suspension results in an initial elevation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing at quarterly intervals results in decreased secretion of gonadal steroids; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible on discontinuation of drug therapy.

Leuprolide acetate is not active when given orally.

Norethindrone Acetate

Norethindrone acetate induces secretory changes in an estrogen-primed endometrium.

12.2 Pharmacodynamics

In a pharmacokinetic/pharmacodynamic study of leuprolide acetate for depot suspension 11.25 mg in healthy female subjects (N=20), the onset of estradiol suppression was observed for individual subjects between day 4

and week 4 after dosing. By the third week following the injection, the mean estradiol concentration (8 pg/mL) was in the menopausal range. Throughout the remainder of the dosing period, mean serum estradiol levels ranged from the menopausal to the early follicular range.

Serum estradiol was suppressed to ≤20 pg/mL in all subjects within four weeks and remained suppressed (≤40 pg/mL) in 80% of subjects until the end of the 12-week dosing interval, at which time two of these subjects had a value between 40 and 50 pg/mL. Four additional subjects had at least two consecutive elevations of estradiol (range 43-240 pg/mL) levels during the 12-week dosing interval, but there was no indication of luteal function for any of the subjects during this period.

Administration of leuprolide acetate for depot suspension 11.25 mg results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of leuprolide acetate for depot suspension 11.25 mg may be affected.

In a pharmacokinetic/pharmacodynamic study of endometriosis patients, intramuscular leuprolide acetate for depot suspension 11.25 mg (n=19) every 12 weeks or intramuscular leuprolide acetate for depot suspension 3.75 mg (n=15) every 4 weeks was administered for 24 weeks. There was no statistically significant difference in changes of serum estradiol concentration from baseline between the 2 treatment groups.

12.3 Pharmacokinetics

Absorption

Leuprolide Acetate for Depot Suspension

Following a single injection of the 3-month formulation of leuprolide acetate for depot suspension 11.25 mg in female subjects, a mean plasma leuprolide concentration of 36.3 ng/mL was observed at 4 hours. Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing and mean levels then declined gradually to near the lower limit of detection by 12 weeks. The mean (± standard deviation) leuprolide concentration from 3 to 12 weeks was 0.23 ± 0.09 ng/mL. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

Norethindrone Acetate

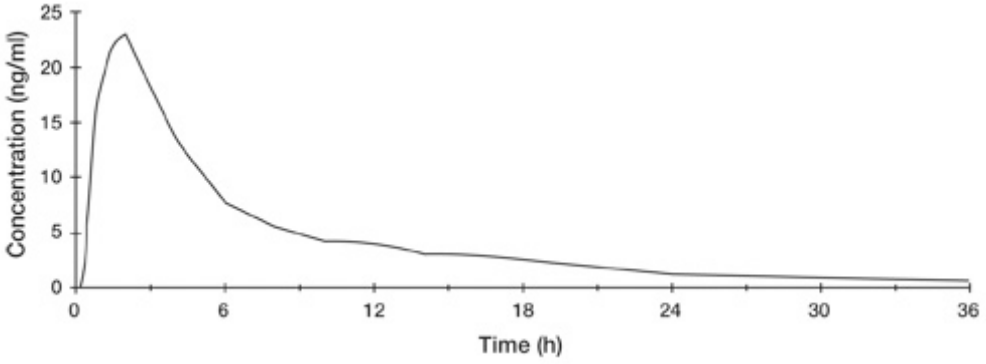
Norethindrone acetate is deacetylated to norethindrone after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate is absorbed from norethindrone acetate tablets, with maximum plasma concentration of norethindrone generally occurring at about 2 hours post-dose (see Figure 8). The pharmacokinetic parameters of norethindrone following single oral administration of norethindrone acetate 5 mg under fasting conditions in 29 healthy female volunteers are summarized in Table 6.

Table 6. Pharmacokinetic Parameters of Norethindrone after a Single Dose of Norethindrone Acetate 5 mg in Healthy Women (n=29)

Parameters	Arithmetic Mean ± SD
AUC (0-inf) (ng/ml*h)	166.90 ± 56.28
C_{max} (ng/ml)	26.19 ± 6.19
t_{max} (h)	1.83 ± 0.58
$t_{1/2}$ (h)	8.51 ± 2.19

AUC = area under the curve, C_{max} = maximum plasma concentration, t_{max} = time at maximum plasma concentration, $t_{1/2}$ = half-life, SD = standard deviation

Figure 8. Mean Norethindrone Plasma Concentration Profile after a Single Dose of Norethindrone Acetate 5 mg in Healthy Women (n=29) under Fasting Conditions



Distribution

Leuprolide Acetate for Depot Suspension

The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

Norethindrone Acetate

Norethindrone is 36% bound to sex hormone-binding globulin (SHBG) and 61% bound to albumin. Volume of distribution of norethindrone is about 4 L/kg.

Metabolism

Leuprolide Acetate for Depot Suspension

Leuprolide acetate is a peptide that is primarily degraded by peptidase. In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two-compartment model.

Metabolite I (M-I), a smaller inactive peptide, plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

Norethindrone Acetate

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. Norethindrone is also subject to oxidative metabolism catalyzed by CYP3A4. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.

Excretion

Leuprolide Acetate for Depot Suspension

Following administration of leuprolide acetate for depot suspension 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Norethindrone Acetate

Plasma clearance value for norethindrone is approximately 0.4 L/hr/kg. Norethindrone is excreted in both urine and feces, primarily as metabolites. The mean terminal elimination half-life of norethindrone following a single dose administration of norethindrone acetate is approximately 9 hours.

Use in Specific Populations

Hepatic Impairment

The effect of hepatic disease on the disposition of norethindrone after norethindrone acetate administration has not been evaluated. However, norethindrone acetate is contraindicated in markedly impaired liver function or liver disease *[see Contraindications (4)]*.

The pharmacokinetics of the leuprolide acetate for depot suspension in hepatically impaired patients has not been determined.

Renal Impairment

The effect of renal disease on the disposition of norethindrone after norethindrone acetate administration has not been evaluated. In pre-menopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma norethindrone concentration was unchanged compared to concentrations in pre-menopausal women with normal renal function.

The pharmacokinetics of the leuprolide acetate for depot suspension in renally impaired patients has not been determined.

Race

The effect of race on the disposition of norethindrone after norethindrone acetate administration has not been evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Leuprolide Acetate for Depot Suspension

A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

14 CLINICAL STUDIES

Two clinical studies with treatment duration of 12 months were conducted to evaluate the efficacy of LUPANETA PACK in relieving symptoms of endometriosis and the effect on the loss of bone mineral density (BMD). A total of 242 women were treated with monthly administration of leuprolide acetate for depot suspension 3.75 mg (13 injections) and 191 of them received co-administered norethindrone acetate 5 mg orally once daily. The population age range was 17-43 years old. The majority of women were Caucasian (87%). All women in these studies received calcium supplementation with 1000 mg elemental calcium.

The first study was a controlled, randomized, and double-blind study that included 51 women treated monthly with leuprolide acetate for depot suspension 3.75 mg alone and 55 women treated monthly with leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg daily. Women in this trial were followed for up to 24 months after completing one year of treatment. The second study was an open-label, single-arm clinical study in 136 women treated with leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg daily for one year; these women had follow-up for up to 12 months after completing treatment. See Table 7.

In both clinical studies, the assessment of efficacy was based on the investigator's or the women's monthly assessment of five signs or symptoms of endometriosis (dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness and pelvic induration).

Table 7 below provides detailed efficacy data regarding relief of symptoms of endometriosis based on the two studies of coadministration of leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg daily.

Table 7. Percentages of Women with Symptoms of Endometriosis and Mean Clinical Severity Scores

			Percentage of Women with Symptom			Clinical Pain Severity Score		
			Baseline		Final	Baseline		Final
Variable	**Study**	**Group**	**N[1]**	**(%)[2]**	**(%)**	**N[1]**	**Value[3]**	**Change**
Dysmenorrhea	Controlled Study[4]	LA*	51	(100)	(4)	50	3.2	-2.0
		LA/N†	55	(100)	(4)	54	3.1	-2.0
	Open Label Study[5]	LA/N	136	(99)	(9)	134	3.3	-2.1
Pelvic Pain	Controlled Study[4]	LA	51	(100)	(66)	50	2.9	-1.1
		LA/N	55	(96)	(56)	54	3.1	-1.1
	Open Label Study[5]	LA/N	136	(99)	(63)	134	3.2	-1.2
Deep Dyspareunia	Controlled Study[4]	LA	42	(83)	(37)	25	2.4	-1.0
		LA/N	43	(84)	(45)	30	2.7	-0.8
	Open Label Study[5]	LA/N	102	(91)	(53)	94	2.7	-1.0
Pelvic Tenderness	Controlled Study[4]	LA	51	(94)	(34)	50	2.5	-1.0
		LA/N	54	(91)	(34)	52	2.6	-0.9
	Open Label Study[5]	LA/N	136	(99)	(39)	134	2.9	-1.4
Pelvic Induration	Controlled Study[4]	LA	51	(51)	(12)	50	1.9	-0.4
		LA/N	54	(46)	(17)	52	1.6	-0.4
	Open Label Study[5]	LA/N	136	(75)	(21)	134	2.2	-0.9

* LA = leuprolide acetate for depot suspension 3.75 mg assessment
† LA/N = leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg
[1] Number of women included in the analysis
[2] Percentage of women with the symptom/sign
[3] Value description: 1=none; 2= mild; 3= moderate; 4= severe
[4] 12-month treatment followed by up to 24 months of follow up
[5] 12-month treatment followed by up to 12 months of follow up

Suppression of menses (menses was defined as three or more consecutive days of menstrual bleeding) was maintained throughout treatment in 84% and 73% of women receiving leuprolide acetate and norethindrone acetate, in the controlled study and open label study, respectively. The median time for menses resumption after treatment with leuprolide acetate and norethindrone acetate was 8 weeks.

Changes in Bone Density

The effect of leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg on bone mineral density was evaluated by dual energy x-ray absorptiometry (DXA) scan in the two clinical trials. For the open-label study, success in mitigating BMD loss was defined as the lower bound of the 95% confidence interval around the change from baseline at one year of treatment not to exceed -2.2%. The bone mineral density data of the lumbar spine from these two studies are presented in Table 8.

Table 8. Mean Percent Change from Baseline in BMD of Lumbar Spine

	Controlled Study				Open Label Study	
	LA-Only		LA/N		LA/N	
Study Week	N	% Change (Mean, 95% CI)	N	% Change (Mean, 95% CI)	N	% Change (Mean, 95% CI)
Week 24*	41	-3.2 (-3.8, -2.6)	42	-0.3 (-0.8, 0.3)	115	-0.2 (-0.6, 0.2)
Week 52†	29	-6.3 (-7.1, -5.4)	32	-1.0 (-1.9, -0.1)	84	-1.1 (-1.6, -0.5)

* Includes on-treatment measurements that fell within 2-252 days after the first day of treatment.
† Includes on-treatment measurements >252 days after the first day of treatment.
Abbreviations:
CI = confidence interval; LA-Only = leuprolide acetate for depot suspension 3.75 mg;
LA/N = leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg

The change in BMD following discontinuation of treatment is shown in Table 9.

Table 9. Mean Percent Change from Baseline in BMD of Lumbar Spine in the Post-Treatment Follow-up Period

	Controlled Study				Open-Label Study	
	LA-Only		LA/N		LA/N	
Post-Treatment Follow up Month	N[1]	% Change (Mean, 95% CI[2])	N	% Change (Mean, 95% CI)	N	% Change (Mean, 95% CI)
Month 8	19	-3.3 (-4.9, -1.8)	23	-0.9 (-2.1, 0.4)	89	-0.6 (-1.2, 0.0)
Month 12	16	-2.2 (-3.3, -1.1)	12	-0.7 (-2.1, 0.6)	65	0.1 (-0.6, 0.7)

[1] Women with post treatment measurements
[2] 95% CI (2-sided) of percent change in BMD values from baseline
Abbreviations:
CI = confidence interval; LA-Only = leuprolide acetate for depot suspension 3.75 mg;
LA/N = leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate 5 mg

These clinical studies demonstrated that coadministration of leuprolide acetate 3.75 mg and norethindrone acetate 5 mg daily is effective in reducing the loss of bone mineral density that occurs with leuprolide acetate for depot suspension treatment, and in relieving symptoms of endometriosis.

16 HOW SUPPLIED/STORAGE AND HANDLING

LUPANETA PACK for 3-month co-packaged kit (NDC 0074-1053-05) is available in cartons containing:

leuprolide acetate for depot suspension 11.25 mg for 3-month administration Kit (NDC 0074-3663-04)

- one prefilled dual-chamber syringe
- one plunger
- two alcohol swabs

norethindrone acetate 5 mg tablets; 90-count bottle (NDC 0074-1049-04)

1. Each leuprolide acetate for depot suspension 11.25 mg for 3-month administration kit contains a single-dose dual chamber syringe. The syringe contains sterile white lyophilized microsphere powder of leuprolide acetate incorporated in a biodegradable polymer in one chamber and a colorless diluent (1.5 mL) in the other chamber. When mixed with diluent, leuprolide acetate for depot suspension 11.25 mg for injection is administered as a single IM injection.
2. Norethindrone acetate 5 mg 90-count bottle
   White to off-white oval, flat faced beveled edged, uncoated tablets debossed with 'G with break line on one side and 304 on the other side.

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Loss of Bone Density

Advise patients about the risk of loss of bone mineral density and that treatment duration is limited *[see Dosage and Administration (2.1)]*. Advise patients about other factors that can increase and decrease their risk of bone mineral density loss *[see Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the possible risk to a fetus. Advise patients to inform healthcare provider if they believe they may be pregnant *[see Warnings and Precautions (5.2) and Use in Special Populations (8.1)]*.
- If contraception is indicated, advise females of reproductive potential to use non-hormonal contraception during treatment with LUPANETA PACK *[see Use in Special Populations (8.3)]*.

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions, including anaphylaxis, have been reported with LUPANETA PACK. Advise patients to seek appropriate medical care if symptoms of hypersensitivity reactions occur *[see Warnings and Precautions (5.3) and Adverse Reactions (6.2)]*.

Cardiovascular and Metabolic Disorders

Advise patients of the need for close monitoring if they have cardiovascular risk factors, or conditions like epilepsy, migraine, or renal dysfunction *[see Warnings and Precautions (5.4)]*.

Initial Flare of Symptoms

Advise patients that they may experience an increase in symptoms during the initial days of therapy. Advise patients that these symptoms should dissipate with continued therapy *[see Warnings and Precautions (5.5)]*. Advise patients to notify their healthcare provider if they develop new or worsened symptoms after beginning treatment.

Convulsions

Inform patients that convulsions have been reported in patients who have received LUPANETA PACK. Advise patients to seek medical attention in the event of a convulsion *[see Warnings and Precautions (5.6)]*.

Clinical Depression

Inform patients that depression may occur or worsen during treatment with GnRH agonists, including LUPANETA PACK, especially in patients with a history of depression. Advise patients to immediately report thoughts and behaviors of concern to healthcare providers *[see Warnings and Precautions (5.7)]*.

Visual Abnormalities

Advise patients to discontinue norethindrone acetate and seek medical attention if they develop sudden loss of vision, double vision or sudden migraine *[see Warnings and Precautions (5.8)]*.

Leuprolide Acetate for Depot Suspension 11.25 mg:
Manufactured for
AbbVie Inc.
North Chicago, IL 60064
by Takeda Pharmaceutical Company Limited
Osaka, Japan 540–8645

Norethindrone acetate
Manufactured for
AbbVie Inc.
North Chicago, IL 60064

Manufactured by
Glenmark Pharmaceuticals Ltd.
Colvale-Bardez, Goa
403 513, India

LUPANETA PACK
Packaged by:
AbbVie Inc.
North Chicago, IL 60064

Revised: 08/2023

PATIENT INFORMATION
LUPANETA PACK® (loo-pan-e-tə pæk)
(leuprolide acetate for depot suspension and norethindrone acetate tablets)

Read this Patient Information before you start taking LUPANETA PACK and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is LUPANETA PACK?

LUPANETA PACK contains 2 different prescription medicines:

- **leuprolide acetate for depot suspension** is a medicine injected into your muscle and used to treat pain due to endometriosis.
- **norethindrone acetate tablets** is a medicine taken by mouth and used to help lower the side effect of bone thinning that is caused by leuprolide acetate for depot suspension.

LUPANETA PACK should not be used longer than 6 months at a time after you first start treatment for your endometriosis symptoms. LUPANETA PACK should not be used for more than a total of 12 months during your treatment.

It is not known if LUPANETA PACK is safe and effective in children who have not started their menstrual period.

Who should not take LUPANETA PACK?
Do not take LUPANETA PACK if you:

- have had an allergic reaction to gonadotropin-releasing hormone (GnRh), GnRh agonist medicines, or any ingredients in leuprolide acetate for depot suspension or norethindrone acetate tablets. See the end of this leaflet for a complete list of ingredients in LUPANETA PACK.
- have uterine bleeding for which a cause has not been found
- are pregnant or may be pregnant. LUPANETA PACK may harm your unborn baby. If you become pregnant while taking LUPANETA PACK, stop taking the norethindrone acetate tablets and call your doctor right away.
- have or have had breast cancer or other cancers that are sensitive to hormones
- have or have had problems with blood clots, a stroke or a heart attack.
- have liver problems

What should I tell my doctor before taking LUPANETA PACK?
Before you take LUPANETA PACK, tell your doctor if you:

- drink alcohol.
- smoke.
- have a family history of bone loss (osteoporosis).
- have diabetes.
- have high cholesterol.
- have had blood clots, a stroke, or a heart attack.
- have epilepsy.
- have depression.
- have migraine headaches.
- have kidney problems.
- are breastfeeding or plan to breastfeed. It is not known if LUPANETA PACK passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while receiving LUPANETA PACK.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.
Especially tell your doctor if you take anticonvulsant (seizure) or corticosteroid medicines.
Ask your doctor for a list of these medicines if you are not sure. Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take LUPANETA PACK?

- **Leuprolide acetate for depot suspension** for 3- month administration is injected into your muscle 1 time every month by a healthcare professional in your doctor's office.
- **Take norethindrone acetate tablets** exactly as your doctor tells you to take them. Take 1 norethindrone acetate tablet by mouth every day for 3 months after you receive your injection.
- Talk to your doctor about the birth control method that is right for you before you start taking LUPANETA PACK. You will need to use a form of birth control that does not contain hormones, such as:
  - a diaphragm with spermicide

- condoms with spermicide
- a copper IUD

- If you become pregnant while taking LUPANETA PACK, stop taking the norethindrone acetate tablets and call your doctor right away.

What are the possible side effects of LUPANETA PACK?

LUPANETA PACK may cause serious side effects, including:

- **bone thinning (decreased bone mineral density)**
- **harm to your unborn baby**
- **allergic reactions.** Get medical help right away if you have any of these symptoms of a serious allergic reaction:
  - swelling of your face, lips, mouth, or tongue
  - trouble breathing
  - wheezing
  - severe itching
  - skin rash, redness, or swelling
  - dizziness or fainting
  - fast heartbeat or pounding in your chest (tachycardia)
  - sweating
- **heart issues in people who already have high blood pressure, diabetes, high blood sugar, or kidney problems. Monitor these conditions closely with the doctor.**
- **worsening endometriosis symptoms when you start taking LUPANETA PACK**
- **seizures (convulsions).** Some people taking GnRH agonists like LUPANETA PACK have had seizures. Call your doctor right away if you have a seizure while taking LUPANETA PACK.
- **depression or worsening depression**
- **vision problems.** Call your doctor right away if you have sudden loss of vision, double vision, bulging eyes, or migraine headaches.
- **swelling (fluid retention)**

The most common side effects of LUPANETA PACK include:

- hot flashes and sweats
- headaches or migraines
- depression and mood swings
- problems sleeping
- nausea and vomiting
- pain
- vaginal infection or inflammation
- weakness
- dizziness or spinning feeling
- constipation or diarrhea
- weight gain
- breast tenderness or pain

Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of LUPANETA PACK. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store norethindrone acetate tablets in the LUPANETA PACK?

- Store norethindrone acetate tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep LUPANETA PACK and all medicines out of the reach of children.

General information about the safe and effective use of LUPANETA PACK.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LUPANETA PACK for a condition for which it was not prescribed. Do not give LUPANETA PACK to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about LUPANETA PACK that is written for health professionals.

What are the ingredients in LUPANETA PACK?

leuprolide acetate for depot suspension:
Active ingredients: leuprolide acetate for depot suspension
Inactive ingredients: polylactic acid, D-mannitol, carboxymethylcellulose sodium, polysorbate 80, water for injection, USP, and glacial acetic acid, USP to control pH.

norethindrone acetate tablets:
Active ingredients: norethindrone acetate USP
Inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose and talc.

Leuprolide Acetate for Depot Suspension:
Manufactured for
AbbVie Inc.
North Chicago, IL 60064

By Takeda Pharmaceutical Company Limited
Osaka, Japan 540-8645

Norethindrone acetate:
Manufactured for
AbbVie Inc.
North Chicago, IL 60064

By Glenmark Pharmaceuticals Ltd.
Colvale-Bardez, Goa
403 513, India

For more information, go to www.lupanetapack.com or call 1-800-633-9110.

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: August/2023