

Bon Secours Health System
Pharmacy and Therapeutics Committees
Lupron Depot Injection
5/2003

Recommendations: MEC approved

- Depot Lupron is recommended for outpatient use, as its action is time dependent and is indicated for treatment of chronic conditions that may be treated on an outpatient basis. Depot Lupron provides serum levels that plateau within two days after dosing and remain relatively stable for 4-5 weeks. Injection of Depot Lupron initially stimulates pituitary gonadotropins followed by prolonged suppression. Repeated dosing at monthly intervals results in decreased secretion of gonadal steroids; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. The biological effect is strictly time-dependent and not concentration-dependent.
- Pharmacy will not routinely stock Depot Lupron.
- Pharmacy will order and provide Lupron Depot 7.5 mg strength for patients who are hospitalized and who are not anticipated to be discharged within the next 5 days. Pharmacists will determine if the patient is nearing discharge before dispensing Lupron.
- Lupron will only be dispensed for FDA approved indications. Pharmacists will verify the indication before dispensing Lupron.

Findings:

- Leuprolide is synthetic peptic of the naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH), acts as an inhibitor of gonadotropin secretion when given continuously. It is 80-100 times more active than the naturally occurring hormone. Injection of Depot Lupron initially stimulates pituitary gonadotropins followed by prolonged suppression. Repeated dosing at monthly intervals results in decreased secretion of gonadal steroids; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.
- Continuous therapy results in decreased levels of LH and FSH in all patients:
 - In children with central precocious puberty, stimulated and basal gonadotropins (testosterone, estradiol) are reduced to prepubertal levels.
 - Testosterone is reduced to castrate levels.
 - Pre-menopausal females, estrogens are reduced to post-menopausal levels.
 - The decrease occurs within two to four weeks after initiation of treatment.
- Time to onset of clinical effect
 - Endometriosis 3.75 mg q month
 - Amenorrhea induced in 74% and 98% of patients after the first and second treatment months respectively.
 - Normal menstrual cycles resume in 7%, 71%, and 95% in the first, second and third post-treatment months.
 - Prostatic Cancer
 - 7.5 mg q month
 - Serum testosterone suppressed to the castrate range within 30 days of the initial depot injection in 94% (51/54), tumor response: no progression 77% by week 12, in an open-label, non-comparative, multicenter clinical study.
 - Leiomyomata (fibroids)
 - 3.75 mg q month
 - Amenorrhea induced in 4%, 25%, and 61% during the first, second, and third treatment months respectively.
 - Menses usually returned within two months of cessation of therapy.
 - Increase of $\geq 6\%$ hematocrit and ≥ 2 g/dl hemoglobin in 77% of patients at 3 months when given in combination with iron.

Hemoglobin ≥ 12 gm/dl			
	Week 4	Week 8	Week 12
Lupron Depot 3.75 mg with Iron	41%	71%	79%
Iron Alone	17%	40%	56%

- 11.25 mg
 - *The 3 month 11.25 mg Depot Lupron produced similar pharmacokinetic/pharmacodynamic effects in terms of hormonal and menstrual suppression to those achieved with monthly injections of 3.75 mg during controlled clinical trials for the management of endometrioses and anemia caused by uterine fibroids. There was no statistically significant difference in changes of serum estradiol concentrations form baseline between the 2 treatment groups.*
- Leuprolide's plasma half-life 3 hours, metabolism and excretion have not ben determined.
- Serum levels with depot formulations plateau within two days after dosing and remain relatively stable for 4-5 weeks.
- The depot formulations are identical in composition in the 3.75 and 7.5 mg monthly dosage forms (dl-lactic and glycolic acids copolymer). The depot dosage form given less frequently than every month contain polylactic acid instead of D lactic and glycolic acids copolymer to delay drug release.
- 86% of orders in Bon Secours Richmond are for the 7.5 mg Depot size.

FDA Approved Indications					
Dosage Form	Indications	Dosage	Frequency	Serum Levels	Cost
Lupron	Children with Central Precocious puberty,	50 mcg/kg	Every day	No data	\$359.92
	Advanced prostatic cancer	1 mg	Every day		
Lupron Depot 3.75 mg	Endometriosis, Anemia due to Leiomyomata (fibroids) with iron	3.75 mg	Once a month for maximum of 6 months; For up to 3 months	Peak(4 hours post dose) 4.6-10.2 ng/ml Steady State is obtained 2 days after dose and maintained for 4-5 weeks with a level of 0.3 ng/ml	\$435.99 Reimbursement \$191.87
Lupron Depot 7.5 mg	Palliative treatment of advance prostatic cancer	7.5 mg	Once a Month	Peak (4 hours post dose) 20 ng/ml, 0.36 ng/ml at 4 weeks	\$504.70 Reimbursement \$331.86
Lupron Depot 11.25 mg	Endometriosis, Anemia Leiomyomata (fibroids),	11.25 mg	Once every 3 months Once	Peak (4 hours post dose) 36.3 ng/ml Mean steady state levels from week 3-12: 0.23 ng/ml	\$952.22
Lupron Depot 22.5 mg	Palliative treatment of advance prostatic cancer	22.5 mg	Once every 3 months	Peak 49 ng/ml at 4 hours, 0.67 ng/ml at 12 weeks	\$1514.10
Lupron Depot 30 mg	Palliative treatment of advance prostatic cancer	30 mg	Once every 4 months	Peak 59 ng/ml at 4 hours, Mean 0.44 ng/ml from week 3.5 to week 16 , 0.3 ng/ml at 16 weeks	\$2018.80

Lupron Depot Formulations					
	D lactic and glycolic acids copolymer or polylactic acid*	D mannitol	Carboxymethyl-cellulose	Polysorbate 80	Purified Gelatin
Lupron Depot 3.75	33.1	56.6	5 mg	1 mg	0.65 mg
Lupron Depot 7.5 mg	66.2	63.2	5 mg	1 mg	1.3 mg
Lupron Depot 11.25 mg	99.3*	94.45	7.5	1.5	

Literature

Acta Obstet Gynecol Scand 2001 Oct;80(10):956-8 Related

Randomized double-blind study evaluating the efficacy on uterine fibroids shrinkage and on intra-operative blood loss of different length of leuprolide acetate depot treatment before myomectomy. Jasonni VM, D'Anna R, Mancuso A, Caruso C, Corrado F, Leonardi I. Departments of Obstetrics and Gynaecology, University of Modena and Reggio Emilia, Modena, Italy.

OBJECT: To determine whether length of pre-operative treatment with gonadotrophin-releasing hormone agonists (GnRHa) may have different effects on uterine shrinkage and intra-operative blood loss, 36 patients with symptomatic uterine fibroids awaiting myomectomy were randomly divided into two groups. METHOD: Twenty patients received long-term GnRHa administration, six monthly depot injections of leuprolide acetate (LA), while 16 patients were treated with two monthly LA injections before surgery. The hemoglobin concentration and estradiol, follicle-stimulating hormone and luteinizing hormone concentrations were measured before and after treatment in both groups. RESULTS: Uterine volume decreased in the long-term treated group from 680+/-276 cm³ to 486+/-195 cm³ (36%) after two and to 388+/-172 cm³ (51%) after six LA injections. In the short-term treated group the basal uterine volume decreased from 745+/-320 cm³ to 456+/-177 cm³ (39%) after two LA injections. The uterine volume decrease was statistically significant (p<0.05) after two LA injections in both groups while the decrease observed between two and six LA injections was not significant (p>0.05). The intra-operative blood-loss was not significantly different between the two groups studied, 315+/-93 cm³ and 336+/-88 cm³. CONCLUSION: Two pre-operative GnRHa depot injections offer similar results, in terms of uterine shrinkage and intra-operative blood loss, and a longer treatment seems to be justified in cases of anemia.

BJOG 2000 Mar;107(3):323-8 Comment in: BJOG. 2000 Oct;107(10):1323-4.

A double-blind randomised trial of leuprorelin acetate prior to hysterectomy for dysfunctional uterine bleeding. Weeks AD, Duffy SR, Walker JJ. Department of Obstetrics and Gynaecology, St James's Hospital, Leeds, UK.

OBJECTIVE: To evaluate the use of pre-operative leuprorelin acetate for reducing the morbidity from hysterectomy for nonfibroid menorrhagia. DESIGN: A double-blind, randomised, placebo-controlled trial. SETTING: Gynaecology department in a large university teaching hospital. SAMPLE: Fifty-one women without uterine fibroids awaiting abdominal or vaginal hysterectomy for dysfunctional uterine bleeding. METHODS: Participants received leuprorelin acetate or placebo for eight weeks prior to hysterectomy. MAIN OUTCOME MEASURES: Operative blood loss, operative difficulty, first day morphine use, speed of return to 'normal health'. RESULTS: The study and control groups were similar as regards prognostic factors. Two women in the study group withdrew because of side-effects. Although a 34% reduction in uterine volume was seen in those treated with leuprorelin, there were no significant differences in operative blood loss (183 mL in the study group vs 285 mL in controls, P = 0.27), operation time (39 vs

49 min, $P = 0.64$) or operative difficulty (visual analogue scale 3.0 vs 4.0, $P = 0.09$). Furthermore, there was no difference between the groups in post-operative morbidity or rate of recovery. **CONCLUSIONS:** *Treating women with leuprorelin acetate for 8 weeks prior to surgery for nonfibroid menorrhagia has no significant operative or post-operative benefits.*

Am J Obstet Gynecol 1998 Jan;178(1 Pt 1):108-12 Related Articles, Links

A prospective randomized study to evaluate leuprolide acetate treatment before laparoscopic myomectomy: efficacy and ultrasonographic predictors. Zullo F, Pellicano M, De Stefano R, Zupi E, Mastrantonio P. Department of Gynecologic and Pediatric Sciences, Reggio Calabria University, Catanzaro, Italy.

OBJECTIVE: Aims of our study were as follows: (1) to evaluate the therapeutic efficacy of the preoperative administration of a gonadotropin-releasing hormone analog before laparoscopic myomectomy and (2) to assess whether any ultrasonographic parameter of the fibroids (number, size, Doppler velocimetry, or echogenicity) was of prognostic value. **STUDY DESIGN:** A prospective randomized study was performed on 67 patients with symptomatic uterine fibroids that were mainly intramural; these patients were undergoing laparoscopic myomectomy. Patients were randomized either to preoperative administration of two injections of a depot formulation of leuprolide acetate 28 days apart (group A, $n = 35$) or to direct surgery (group B, $n = 32$). In each group we studied the number, volume, and echogenicity of the larger fibroids; the resistance index of uterine arteries and of fibroid vessels; hematologic parameters; operative time; and blood loss. **RESULTS:** The two groups did not differ significantly in basal ultrasonographic parameters and hematologic data. Postoperatively, the red blood cell count and the serum hemoglobin and iron levels were significantly ($p < 0.05$) lower in group B. Both blood loss ($p < 0.01$) and operative time ($p < 0.05$) were significantly lower in group A. However, the operative time was significantly longer when the main fibroid was markedly hypoechoic, probably because the increased softness of the tumor after leuprolide acetate pretreatment makes its enucleation much more cumbersome. **CONCLUSION:** Our data confirm the therapeutic efficacy of preoperative administration of a gonadotropin-releasing hormone analog before laparoscopic myomectomy in reducing the blood loss and in decreasing the operative time. This preoperative course of leuprolide acetate in hypoechoic fibroids, because of the further reduction of the density of the myomas, causes a significant ($p < 0.05$) increase in operative time.

Am J Obstet Gynecol 1994 Jun;170(6):1744-8; discussion 1748-51 Related Articles, Links Comment in: Am J Obstet Gynecol. 1995 May;172(5):1650-1. Gonadotropin-releasing hormone agonist use before hysterectomy. Stovall TG, Summit RL Jr, Washburn SA, Ling FW. Department of Obstetrics and Gynecology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC 27157-1066.

OBJECTIVE: Our purpose was to compare the effects of leuprolide acetate in patients with symptomatic uterine leiomyoma before hysterectomy. **STUDY DESIGN:** Group I ($n = 90$) included patients with a pretreatment uterine size of 14 to 18 gestational weeks and group II ($n = 60$) included patients with uteri > 18 weeks' gestational size. Patients in both groups were randomized to either immediate hysterectomy or 2 months of preoperative gonadotropin-releasing hormone agonist. **RESULTS:** All patients in the two groups with a pretreatment hemoglobin < 11.0 gm/dl randomized to agonist had a significant ($p < 0.05$) increase ($> \text{or} = 1.5$ gm/dl) in hemoglobin level. Patients in group I who received preoperative agonist were more likely to undergo vaginal hysterectomy (80% vs 13%, $p < 0.05$) than were patients who did not receive preoperative agonist. Patients undergoing vaginal hysterectomy had a shorter hospital stay, decreased operative blood loss, and a shorter convalescence period than did those undergoing abdominal hysterectomy. In group II, in spite of a mean uterine volume reduction of 51.3%, intraoperative morbidity, operative blood loss, hospital stay, and postoperative convalescence period did not differ between treatment arms. **CONCLUSION:** *The preoperative administration of gonadotropin-releasing hormone agonist in patients with a uterus of 14 to 18 weeks' size increases the use of vaginal hysterectomy, decreases intraoperative blood loss, and shortens hospital stay and convalescence. Preoperative gonadotropin-releasing hormone agonist for patients with a preoperative hemoglobin < 11.0 gm/dl reduces the risk of preoperative transfusion. Preoperative gonadotropin-releasing hormone use in the nonanemic patient with a uterine size $> \text{or} = 18$ weeks' gestational size does not appear to lower operative morbidity.*

Urol Int 1998;60 Suppl 1:9-16; discussion 16-7 Related Articles, Comparison of LH-RH analogue 1-month depot and 3-month depot by their hormone levels and pharmacokinetic profile in patients with advanced prostate cancer. Tunn UW, Bargelloni U, Cosciani S, Fiaccavento G, Guazzieri S, Pagano F. Urology Department, Academic Hospital, Offenbach, Germany.

In an open, randomized phase II pharmacokinetic study conducted in Germany and Italy, a total of 42 patients with advanced or metastatic prostate cancer (PCa) were treated for 9 months with the luteinizing hormone-releasing hormone analogue (LH-RH-a) leuprorelin acetate depot in two different formulations. Fifteen patients received the 1-month depot and 27 patients received the newly developed 3-month depot, containing 3.75 mg and 11.25 mg, respectively. In both groups, subcutaneous injections of leuprorelin acetate injected monthly or at 3-month intervals produced a complete down-regulation of the pituitary and led to persistent suppression of testosterone and dihydrotestosterone to the castrate range ($< \text{or} = 50$ ng/dl for testosterone) within the first month of treatment, which thereafter could be maintained over the entire observation period of 9 months. In 10 patients, pretreatment with an antiandrogen for the prevention of clinical flare-up resulted in a slightly more profound and earlier drop in serum testosterone. The 3-month depot showed a higher median peak serum concentration (C_{max}) of leuprorelin at 20.8 ng/ml than the 1-month depot at 10.7 ng/ml but, conversely, this did not influence the rise in serum testosterone levels. C_{max} occurred at 3 h for the 3-month and at 1 h for the 1-month depot formulation. During the steady state, constant release could be detected, starting on day 3 and day 7 for the 1-month and 3-month depot, respectively. A marked decrease in median prostate-specific antigen levels of 97.8% (1-month depot) and 96.6% (3-month depot) compared with baseline was observed, indicating an objective clinical response for more than 80% of all patients in both arms. Based on European Organization for Research and Treatment of Cancer criteria, the best response in terms of

complete/partial remissions and stabilization was comparable in the two arms at 86.7% (1-month depot) and 85.2% (3-month depot). 6.7% in the 1-month group and 3% in the 3-month depot group showed progression of the disease. The most common side effects in both treatment groups were related to hormone deprivation. Both formulations of the potent LH-RH-a leuprolide acetate were highly effective in the treatment of advanced PCa and led to comparable endocrine and clinical effects.

Dig Dis Sci 1998 Jun;43(6):1347-55 Related Articles, Links

Effect of leuprolide acetate in treatment of abdominal pain and nausea in premenopausal women with functional bowel disease: a double-blind, placebo-controlled, randomized study. Mathias JR, Clench MH, Abell TL, Koch KL, Lehman G, Robinson M, Rothstein R, Snape WJ. University of Texas Medical Branch, Galveston, USA.

We have previously reported impressive results in using a gonadotropin-releasing hormone analog, leuprolide acetate (Lupron), in the treatment of moderate to severe symptoms (especially abdominal pain and nausea) in patients with functional bowel disease (FBD). Pain is the hallmark of patients with FBD, and there is no consistent therapy for the treatment of these patients. The purpose of the present study was to expand the investigation to study similar patients (menstruating females) in a multicenter, double-blind, placebo-controlled, randomized study using Lupron Depot (which delivers a continuous dose of drug for one month), 3.75 mg (N = 32) or 7.5 mg (N = 33), or placebo (N = 35) given intramuscularly every four weeks for 16 weeks. Symptoms were assessed using daily diary cards to record abdominal pain, nausea, vomiting, early satiety, anorexia, bloating, and altered bowel habits. Additional assessment tools were quality of life questionnaires, psychological profile, oral-to-cecal transit using the hydrogen breath test, antroduodenal manometry, reproductive hormone levels, and global evaluations by both patient and investigator. Patients in both Lupron Depot-treated groups showed consistent improvement in symptoms; however, *only the Lupron Depot 7.5 mg group showed a significant improvement for abdominal pain and nausea compared to placebo (P < 0.001)*. Patient quality of life assessments and global evaluations completed by both patient and investigators were highly significant compared to placebo (P < 0.001). All reproductive hormone levels significantly decreased for both Lupron Depot-treated groups by week 4 and were significantly different compared to placebo at week 16 (P < 0.001). This study shows that leuprolide acetate is effective in controlling the debilitating symptoms of abdominal pain and nausea in patients with FBD.

Dig Dis Sci 1994 Jun;39(6):1163-70 Related Articles, Links Comment in: Dig Dis Sci. 1995 Jun;40(6):1405-7.

Effect of leuprolide acetate in patients with functional bowel disease. Long-term follow-up after double-blind, placebo-controlled study. Mathias JR, Clench MH, Roberts PH, Reeves-Darby VG. Department of Internal Medicine, University of Texas Medical Branch, Galveston 77555-0764.

We initially investigated the effects of a gonadotropin-releasing hormone analog, leuprolide acetate, in 28 patients with moderate to severe functional bowel disease in a phase-II, randomized, double-blind, and placebo-controlled study using Lupron Depot 3.75 mg (which delivers a continuous low dose of drug for one month) or placebo given intramuscularly. After completing that 12-week study period during which their symptoms had improved significantly (P < 0.01-0.5), the 28 patients were allowed to continue receiving leuprolide acetate; they were monitored for an additional 40 weeks. Of those 28, 25 (89%) finished the 52-week treatment. Drug administration was changed from the monthly low-dose form of leuprolide acetate to a daily subcutaneous dose that was gradually increased from 0.5 mg daily to an effective therapeutic dose (1.0-1.5 mg). All subjects received estrogen replacement during this period. Continued use of leuprolide acetate at maximum therapeutic dosage and over longer periods of time produced even more striking and significant changes in the disabling and debilitating symptoms of functional bowel disease. Nausea, abdominal pain, early satiety, anorexia, and abdominal distension decreased markedly (P < 0.0001) and vomiting was also reduced (P < 0.01) more than in the short-term, low-dosage, double-blind study. Combined total symptom scores and overall assessment also changed significantly in the long-term phase (both P < 0.0001).

Dig Dis Sci 1994 Jun;39(6):1155-62 Related Articles, Links Comment in: Dig Dis Sci. 1995 Jun;40(6):1405-7.

Effect of leuprolide acetate in patients with moderate to severe functional bowel disease. Double-blind, placebo-controlled study. Mathias JR, Clench MH, Reeves-Darby VG, Fox LM, Hsu PH, Roberts PH, Smith LL, Stiglich NJ. Department of Internal Medicine, University of Texas Medical Branch, Galveston 77555-0764.

Moderate to severe functional bowel disease results in debilitating abdominal pain, nausea, intermittent vomiting, early satiety, bloating, abdominal distension, and/or altered bowel habits. Because it occurs approximately 20-30 times more frequently in women than in men and its symptoms often coincide with the menstrual cycle, we hypothesized that reproductive steroids may antagonize diseased nerves of the gastrointestinal tract, enhancing the expression of symptoms. No effective or consistent therapy has existed for these patients. We prospectively investigated the effect of a gonadotropin-releasing hormone analog, leuprolide acetate, in 30 women with symptoms of moderate to severe functional bowel disease. The study was phase II, randomized, double blind, and placebo controlled. Lupron Depot 3.75 mg (which delivers a continuous low dose of drug for one month) or placebo were given intramuscularly monthly for three months. Symptom scores were assessed at each four-week visit. Follicle-stimulating hormone, luteinizing hormone, estradiol, and progesterone levels were assessed before and after therapy. Patients treated with low-dose leuprolide improved progressively and significantly in scores for nausea, vomiting, bloating, abdominal pain, and early satiety, and for overall symptoms (P < 0.01-0.05). All hormone levels decreased significantly (P < 0.05) except luteinizing hormone (P = 0.054).