リュープリンSR注射用キット11.25mg

に関する資料

本資料に記載された情報に係る権利及び内容の責任は、武田薬品工業株式会社に帰属するものであり、当該情報を適正使用以外の営利目的に利用することはできません。

武田薬品工業株式会社

目次

略号一覧表 2
1.5 起原又は発見の経緯及び開発の経緯 4
1.5.1 起源又は発見の経緯 4
1.5.2 球脊髄性筋萎縮症（SBMA）の病態・疫学 4
1.5.3 球脊髄性筋萎縮症（SBMA）の病因 5
1.5.4 球脊髄性筋萎縮症（SBMA）の治療、問題点 5
1.5.5 開発の経緯 5
1.5.5.1 臨床試験 8
1.5.5.2 予定する効能又は効果、用法及び用量 10
1.5.6 治験相談等の経緯 10
1.5.7 特長及び有用性 11
1.5.8 参考文献 13

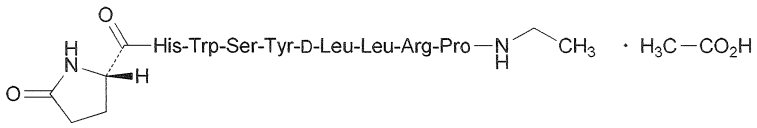
表

表 1.5.1-1　国内における TAP-144-SR の承認状況 4
表 1.5.5-1　開発の経緯 7

図

図 1.5.5-1　臨床開発の概要 6

略号一覧表

略号	一般名 (略称)	化学構造式	由来
TAP-144	リュープロレリン酢酸塩（JAN） leuprorelin (r-INN)		TAP-144

略号一覧表（続き）

略号	略していない表現又は説明
TAP-144-SR(3M)	リュープリン SR 注射用キット 11.25 mg（3 ヵ月製剤） 乳酸重合体（PLA(3M)）を基剤として TAP-144（11.25 mg）をマイクロカプセル化した注射用 12 週間持続型の徐放性製剤（略号の SR は Sustained Release の略）
TAP-144-SR(1M)	リュープリン注射用 3.75 mg 及び同キット 3.75 mg 並びにリュープリン注射用 1.88 mg 及び同キット 1.88 mg（1 ヵ月製剤） 乳酸・グリコール酸共重合体（3:1）（PLGA）を基剤として TAP-144（3.75 mg）をマイクロカプセル化した注射用 4 週間持続型の徐放性製剤
TAP-144-SR(6M)	リュープリン PRO 注射用キット 22.5 mg（6 ヵ月製剤） 乳酸重合体（PLA(6M)）を基剤として TAP-144（22.5 mg）をマイクロカプセル化した注射用 24 週間持続型の徐放性製剤
AR	Androgen receptor［アンドロゲン受容体］
CAG	Cytosine, Adenine, Guanine［シトシン、アデニン、グアニンの 3 塩基配列］
FAS	Full analysis set［最大の解析対象集団］
JASMITT	the Japan SBMA Interventional Trial for TAP-144-SR
LH-RH	Luteining hormone-releasing hormone ［黄体形成ホルモン放出ホルモン］
QOL	Quality of life［生活の質］
SBMA	Spinal and bulbar muscular atrophy［球脊髄性筋萎縮症］

1.5 起原又は発見の経緯及び開発の経緯

1.5.1 起源又は発見の経緯

リュープロレリン酢酸塩（開発コード：TAP-144）は武田薬品工業株式会社で合成された高活性の黄体形成ホルモン放出ホルモン（LH-RH）アゴニストであり、下垂体に作用して性腺刺激ホルモンを分泌させて性腺機能を刺激し、その持続的な刺激によって逆説的抑制効果（paradoxical effect）を惹起させ、下垂体又は性腺における反応性の低下（desensitization）を引き起こす。この作用により性腺機能が抑制され、性ステロイドホルモンの分泌を低下させる。

当社は、TAP-144 の徐放化製剤を開発し、国内において、前立腺癌、閉経前乳癌等の性ホルモン依存性疾患の治療薬として TAP-144-SR(1M)製剤（リュープリン注射用 3.75 mg 及び同キット 3.75 mg 並びにリュープリン注射用 1.88 mg 及び同キット 1.88 mg）、TAP-144-SR(3M)製剤（リュープリン SR 注射用キット 11.25 mg）、TAP-144-SR(6M)製剤（リュープリン PRO 注射用キット 22.5 mg）の製造販売承認を取得し、臨床の場に供している。

本申請は、TAP-144-SR(3M)製剤（リュープリン SR 注射用キット 11.25 mg）（以下、本剤）の球脊髄性筋萎縮症（SBMA）の効能追加に係る一変申請である。

国内における TAP-144-SR の承認状況を表 1.5.1-1 に示した。

表 1.5.1-1　国内における TAP-144-SR の承認状況

製剤		リュープリン PRO 注射用キット 22.5 mg	リュープリン SR 注射用キット 11.25 mg	リュープリン 注射用 3.75 mg、同キット 3.75 mg	リュープリン 注射用 1.88 mg、同キット 1.88 mg
徐放期間		24 週間	12 週間	4 週間	
有効成分（TAP-144）含量		22.5 mg	11.25 mg	3.75 mg	1.88 mg
効能・効果	前立腺癌	○	○	○	－
	閉経前乳癌	○	○	○	－
	子宮内膜症	－	－	○	○
	子宮筋腫	－	－	○	○
	中枢性思春期早発症	－	－	○	○

○：効能・効果取得済み、－：未承認

1.5.2 球脊髄性筋萎縮症（SBMA）の病態・疫学

SBMA は、成人男性のみに発症する下位運動ニューロン疾患であり、四肢近位部の筋力低下・筋萎縮と球麻痺を主症状とする[1][2]。筋力低下の発症は通常 30～60 歳頃であるが、それ以前に手指振戦や筋痛等を自覚している症例が多い。緩徐進行性の経過を辿り、末期には患者は車イス上又は寝たきりの生活を余儀なくされるばかりではなく、誤嚥性肺炎を繰り返しこれが死因となることが多い[3]。神経障害の他、女性化乳房や肝機能障害、耐糖能異常等をしばしば合併する。

欧米では SBMA 患者が地域によっては人口 10 万人あたり 2～7 人の頻度でみられると報告されている[4][5]。国内の SBMA の特定疾患医療受給者証所持者数は平成 26 年度厚生労働省特定疾患調査研究によれば 1223 人となっており、有病率は 10 万人あたり 1～2 人程度と推計される[6]。

1.5.3 球脊髄性筋萎縮症（SBMA）の病因

SBMA の病因は、X 染色体長腕近位部に位置するアンドロゲン受容体（AR）遺伝子第 1 エクソン内のシトシン・アデニン・グアニンの 3 つの塩基の繰返し配列（CAG リピート）の異常延長であり、CAG リピートによる変異 AR が神経細胞の核内に集積して神経細胞の機能を障害し細胞死に至らしめる。この変異 AR は、男性ホルモンと結合することにより、初めて神経細胞の核内に取り込まれるため、男性ホルモンと結合した変異 AR が SBMA の病態の中心的役割を果たしていると考えられている。

1.5.4 球脊髄性筋萎縮症（SBMA）の治療、問題点

SBMA に対してアンドロゲン誘導体等の投与が試みられたこともあるが、その有効性は不明である。現状は症状の進行に応じた運動療法や、誤嚥予防、感染予防等の生活指導を行うとともに、耐糖能異常等の随伴症状への対症療法が実施されている[7]が、国内外において、SBMA に対する有効な治療法は確立しておらず、本効能を有する治療薬はない。

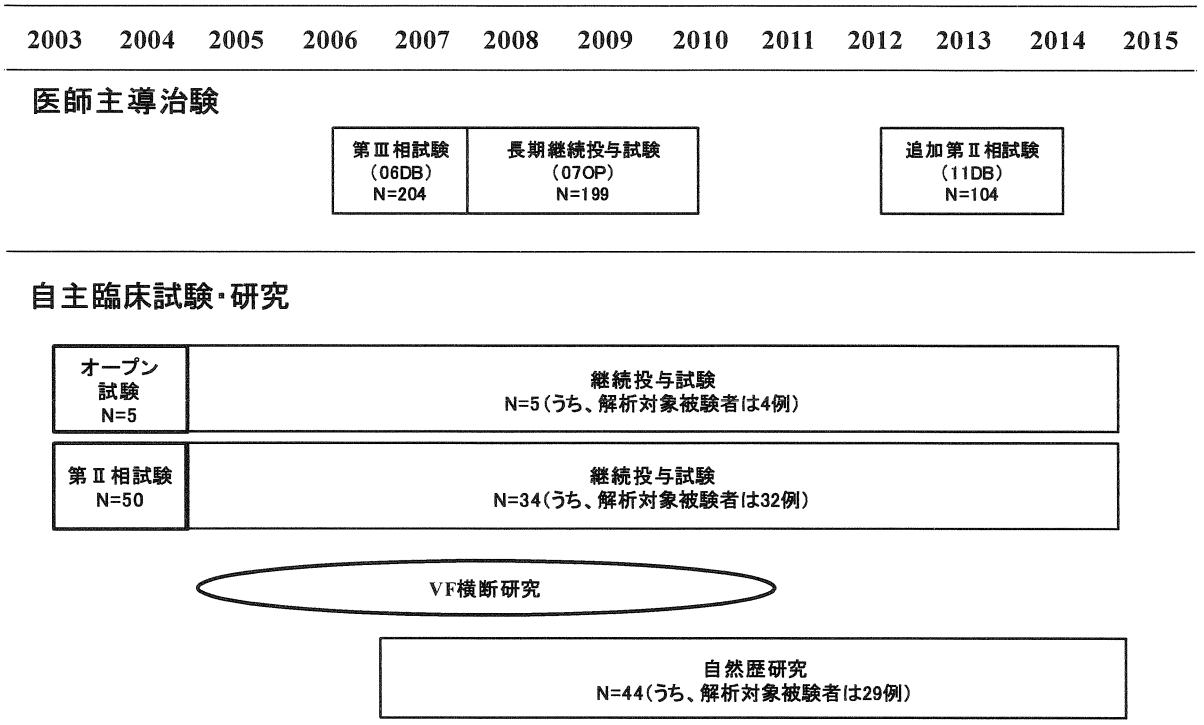
1.5.5 開発の経緯

SBMA 患者を対象とした本剤及び TAP-144-SR(1M)製剤の開発の概要及び経緯について、図 1.5.5-1 及び表 1.5.5-1 に示した。

本申請の適応症である SBMA の発症及び進行の機序に、性ステロイドであるテストステロンが関与していることから、名古屋大学神経内科において、TAP-144-SR に治療効果があるのではないかと考え、病態モデルマウスを用いて薬理作用が検討された。その結果、SBMA モデルマウスで TAP-144-SR(1M)製剤の投与によるテストステロンの分泌低下と運動機能の低下抑制が認められた。

TAP-144-SR(1M)製剤及び本剤の自主臨床第 II 相試験（UMIN000000474 試験：以下、474 試験）は、名古屋大学神経内科において、TAP-144-SR(1M)製剤及び本剤の SBMA に対する治療効果を予備的に検討するための臨床研究として行われた。その結果、TAP-144-SR(1M)製剤及び本剤の投与により、嚥下機能を改善させることが示唆された[8]。

上記第 II 相試験結果に基づき、名古屋大学神経内科において、本剤の SBMA に対する有効性及び安全性の検討と本剤の適応拡大を目的とした多施設共同の医師主導治験として、第 III 相二重盲検比較試験（JASMITT-06DB 試験、以下 06DB 試験）、06DB 試験を終了した被験者を対象とした第 III 相長期継続投与試験（JASMITT-07OP 試験、以下 07OP 試験）を実施した。しかし、06DB 試験の成績では、主要評価項目である咽頭部バリウム残留率を低下させる傾向が本剤投与により示されたものの、その有効性を検証できなかったことから、主要評価項目である咽頭部バリウム残留率の測定方法について検討を行い、新たなバリウム残留率の測定方法を評価する追加第 II 相試験（JASMITT-11DB 試験、以下 11DB 試験）を実施した。なお、2006 年 6 月 9 日に SBMA に対する治療薬として希少疾病用医薬品の指定を受けている。



N：症例数

図 1.5.5-1　臨床開発の概要

表 1.5.5-1　開発の経緯

試験区分 （試験番号）	対象疾患	資料区分	実施時期	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
非臨床試験：薬理試験	SBMA	参考	2002.12～ 2003.4*	★													
自主臨床試験：第 II 相試験 （UMIN000000474 試験）	SBMA	参考	2003.9～ 2007.2	━	━	━	━										
医師主導治験：第 III 相二重盲検比較試験 （JASMITT-06DB）	SBMA	評価	2006.9～ 2008.3				━	━									
医師主導治験：第 III 相長期継続投与試験 （JASMITT-07OP）	SBMA	評価	2007.8～ 2010.2					━	━	━							
医師主導治験：追加第 II 相二重盲検比較試験 （JASMITT-11DB）	SBMA	評価	2012.2～ 2014.2										━	━	━		
[redacted]相談			20[redacted]	[redacted]													
[redacted]相談			20[redacted]														
[redacted]相談			20[redacted]														
[redacted]相談			20[redacted]														

*論文投稿～論文受理時期

1.5.5.1 臨床試験

(1) TAP-144-SR(3M)の SBMA 患者に対する第 III 相二重盲検比較試験（06DB 試験）

：添付資料番号 5.3.5.1-1、5.3.5.1-2（評価）

本治験は、遺伝子検査にて診断が確定した SBMA 患者を対象に本剤投与による有効性及び安全性についてプラセボを対照として評価する、無作為割付二重盲検並行群間比較第 III 相試験であった。

SBMA 患者に対し、本剤 11.25 mg 又はプラセボをそれぞれ 100 例及び 99 例に 12 週ごとに 48 週間投与した。

旧 JASMITT 方式（50%以上除く）（試験計画当初の主要評価項目の評価方法）で測定したデータが得られた被験者 156 例（TAP 群 79 例、プラセボ群 77 例）を対象とした解析では、投与終了時における咽頭部バリウム残留率の投与開始時からの変化量の平均値（90%信頼区間）が TAP 群で-1.01%（-2.69%～0.66%）、プラセボ群で 0.25%（-1.11%～1.61%）であった。群間差（TAP 群－プラセボ群、以下同様）（90%信頼区間）は-1.27%（-3.41%～0.88%）であり、差は認められなかった（p=0.331、2 標本 t 検定）。

新 JASMITT 方式〔試験開始後（開封前）に変更した評価方法〕で測定したデータが得られた被験者 193 例（TAP 群 97 例、プラセボ群 96 例）を対象とした解析では、投与終了時の咽頭部バリウム残留率の投与開始時からの変化量の平均値(90%信頼区間)は TAP 群で-1.55%（-3.73%～0.64%）、プラセボ群で 1.66%（0.08%～3.24%）であった。群間差（90%信頼区間）は-3.21%（-5.89%～-0.52%）であり、TAP 群でプラセボ群と比べ有意な減少がみられたが（p=0.049、2 標本 t 検定）、ベースライン値の群間差について調整した結果、この群間差は有意とならなかった。

また、開封後に追加解析として実施した旧 JASMITT 方式（50%以上含む）の咽頭部バリウム残留率〔194 例（TAP 群 98 例、プラセボ群 96 例）を対象〕は、変化量の平均値（90%信頼区間）は TAP 群で-5.08%（-8.59%～-1.56%）、プラセボ群で 0.18%（-2.90%～3.26%）であり、群間差（TAP 群－プラセボ群）（90%信頼区間）は-5.26%（-9.92%～-0.60%）であった。咽頭部バリウム残留率の投与終了時における投与開始時からの平均変化量はプラセボ群と比べ TAP 群で大きく、群間比較の結果、2 標本 t 検定では p=0.063、Wilcoxon 検定では p=0.118 であった。

副次評価項目のうち、陰嚢皮膚の抗ポリグルタミン抗体陽性細胞数の割合の変化量の平均値（90%信頼区間）は投与終了時に TAP 群で-11.94%（-14.10%～-9.78%）、プラセボ群で 2.74%（0.72%～4.77%）であり、群間差（90%信頼区間）は-14.68%（-17.63%～-11.74%）であった。陰嚢皮膚の抗ポリグルタミン抗体陽性細胞数の割合の平均値は投与開始時からプラセボ群では増加し、TAP 群では減少した（p<0.001、2 標本 t 検定）。

有害事象は TAP 群では 76 例に 380 件発現し、発現頻度（90%信頼区間）は 76.0%（67.9%～82.9%）であった。プラセボ群では 77 例に 273 件発現し、発現頻度（90%信頼区間）は 77.8%（69.8%～84.5%）であった。有害事象の発現頻度に明らかな群間差は認められなかった（p = 0.766、χ^2 検定）。

(2) TAP-144-SR(3M)の SBMA 患者に対する追加第 II 相二重盲検比較試験(11DB 試験)
: 添付資料番号 5.3.5.1-3 (評価)

本治験は、遺伝子検査にて診断が確定した、過去に LH-RH アゴニストが投与されたことのない SBMA 患者（以下、未治療例）を対象に、本剤投与による有効性及び安全性についてプラセボを対照として評価する、無作為割付二重盲検並行群間比較追加第 II 相試験であった。また、本治験の主要評価の対象集団とは別に、過去に LH-RH アゴニストが投与されたことのある患者（以下、既治療例）でも同様の評価を行った。

未治療例に対し、本剤 11.25 mg 又はプラセボを各 42 例に、また既治療例に対してそれぞれ 11 例及び 9 例に 12 週ごとに 48 週間投与した。

主要評価項目の主たる評価指標である初回嚥下後 1 回法で測定した咽頭部バリウム残留率の投与終了時における投与開始時（スクリーニング時）からの変化量は FAS（未治療例）では TAP 群 41 例、プラセボ群 42 例から得られ、主解析である同時調整モデルにより群間比較を行った結果、有意な群間差は認められなかった（$p = 0.697$）。投与終了時における投与開始時からの変化量の調整済み平均値（90%信頼区間）は TAP 群で-2.90%（-7.08%～1.28%）、プラセボ群で-1.82%（-5.77%～2.13%）であり、両群ともに投与開始時からの有意な減少は認められなかった。また、副解析として投与終了時における咽頭部バリウム残留率の投与開始時からの変化量について 2 標本 t 検定で比較した結果も同様であった。

FAS（既治療例）の TAP 群、プラセボ群ともに投与後のいずれの時点でも咽頭部バリウム残留率の平均値は投与開始時と比べて増加する傾向がみられたが、有意な増加ではなかった。いずれの時点でも、咽頭部バリウム残留率の投与開始時からの変化量に有意な群間差はみられなかった。

副次評価項目のうち、陰嚢皮膚の抗ポリグルタミン抗体陽性細胞数の割合について、FAS（未治療例）及び FAS（既治療例）のいずれにおいても有意な改善がみられた。

未治療例では、有害事象は TAP 群では 42 例中 40 例に 168 件発現し、発現頻度（90%信頼区間）は 95.2%（85.8%～99.1%）であった。プラセボ群では 42 例中 36 例に 128 件発現し、発現頻度（90%信頼区間）は 85.7%（73.7%～93.6%）であった。χ^2 検定により群間比較を行ったところ、有害事象の発現頻度に群間差はみられなかった（$p = 0.137$）。

また、既治療例では、有害事象は TAP 群では 11 例中 10 例に 54 件発現し、発現頻度（90%信頼区間）は 90.9%（63.6%～99.5%）であった。プラセボ群では 9 例中 7 例に 19 件発現し、発現頻度（90%信頼区間）は 77.8%（45.0%～95.9%）であった。χ^2 検定により群間比較を行ったところ、有害事象の発現頻度に群間差はみられなかった（$p = 0.413$）。

(3) TAP-144-SR(3M)の SBMA 患者に対する第 III 相長期継続投与試験（07OP 試験）
: 添付資料番号 5.3.5.2-1 (評価)

本治験は、06DB 試験を終了した SBMA 患者を対象として、本剤を 96 週間（06DB 試験の治験薬投与開始日から起算して 144 週間）継続投与した際の有効性及び安全性を非対照試験により評価する、非対照長期継続投与試験であった。

06DB 試験を終了した被験者 199 例〔06DB 試験の TAP 群：100 例、プラセボ群（以下、P 群：99 例〕のうち、再同意を得たうえで長期継続投与試験（07OP 試験）に 196 例〔TAP→TAP 群（06DB 試験で本剤を投与後、07OP 試験で本剤を継続投与）：98 例、P→TAP 群（06DB

試験でプラセボを投与後、07OP 試験で本剤を投与）：98 例〕が登録され、全例が本剤投与を受けた。

旧 JASMITT 方式（50%以上除く）で測定したデータが得られた被験者を対象とした解析では、06DB 試験投与開始 144 週後の咽頭部バリウム残留率の投与開始時からの変化量の平均値（90%信頼区間）は TAP→TAP 群で-1.36%（-3.18%～0.45%）、P→TAP 群で 0.42%（-1.54%～2.37%）であり、両群ともに投与開始時からの有意な変化はみられなかった。平均減少量は P→TAP 群と比べ TAP→TAP 群で大きかったが、群間差（90%信頼区間）は-1.78%（-4.44%～0.88%）であり、有意な群間差はみられなかった。

新 JASMITT 方式で測定したデータが得られた被験者を対象とした場合、投与開始 144 週後の変化量の平均値（90%信頼区間）は TAP→TAP 群で-2.36%（-4.79%～0.06%）、P→TAP 群で 1.29%（-0.96%～3.54%）であり、両群ともに投与開始時からの有意な変化はみられなかった。群間差（90%信頼区間）は-3.65%（-6.94%～-0.37%）であり、平均減少量は P→TAP 群と比べ TAP→TAP 群で有意に大きかったが、投与群との交互作用がみられた。投与開始時の咽頭部バリウム残留率で調整後の従属変数に有意な群間差はみられなかった。

有害事象は TAP→TAP 群では 93 例に 1054 件発現し、発現頻度（90%信頼区間）は 93.0%（87.3%～96.7%）であった。P→TAP 群では 96 例に 940 件発現し、発現頻度（90%信頼区間）は 97.0%（92.4%～99.2%）であった。有害事象の発現頻度に群間差はみられなかった（$p = 0.199$、χ^2 検定）。

1.5.5.2 予定する効能又は効果、用法及び用量

今回の申請は、リュープリン SR 注射用キット 11.25 mg について、以下の効能・効果の追加に係る承認事項一部変更承認申請〔申請区分：（4）新効能医薬品〕を行うものである。

【効能・効果】（下線部：追加効能）
○ 前立腺癌
○ 閉経前乳癌
○ 球脊髄性筋萎縮症の進行抑制

【用法・用量】（変更なし）
通常、成人には 12 週に 1 回リュープロレリン酢酸塩として 11.25 mg を皮下に投与する。投与に際しては、注射針を上にしてプランジャーロッドを押して、懸濁用液全量を粉末部に移動させて、泡立てないように注意しながら、十分に懸濁して用いる。

1.5.6 治験相談等の経緯

本剤の開発に関し、以下の治験相談を行った。

（1）[redacted]相談

[redacted]、20[redacted]年[redacted]月[redacted]日に独立行政法人 医薬品医療機器総合機構（以下、機構）との治験相談[redacted]相談：受付番号[redacted]を行った。その結果、[redacted]を勧められた。

（2）[redacted]相談

[redacted]、治験相談（20[redacted]年[redacted]月[redacted]日 [redacted]相談：受付番号[redacted]）を行った。その結果、[redacted]助言を得た。

（3）[redacted]相談

[redacted]相談（20[redacted]年[redacted]月[redacted]日 [redacted]相談：受付番号[redacted]）した。その結果、[redacted]との助言を得た。

上記を踏まえ、[redacted]との助言が得られた。

（4）[redacted]相談

[redacted]を踏まえ、[redacted]相談（20[redacted]年[redacted]月[redacted]日：受付番号[redacted]）を実施し、[redacted]との助言を得た。

1.5.7 特長及び有用性

SBMA は機能予後の極めて不良な神経変性疾患であるが、国内外において、有効な治療法は確立しておらず、現状は症状の進行に応じた運動療法や、誤嚥予防、感染予防等の生活指導を行うとともに、耐糖能異常等の随伴症状への対症療法が実施されている。また、神経変性という特異で緩徐に進行する病態の分子機構が十分に把握されておらず、さらに対象患者が非常に少ないことから、国内外において治療方法や治療薬の開発が進んでおらず、その治療法の確立が渇望されている。

本剤は、SBMA の病態の中心である変異 AR の核内集積を抑制することで病態の進行を抑制する唯一の SBMA 治療薬である。また、嚥下機能を保持することで SBMA 患者の死因の過半数を占める誤嚥性肺炎を防止するとともに、運動機能を保持することで患者の QOL を維持することが期待できる。SBMA 治療は長期にわたることから、本剤は、12 週ごとの投与により効果を発揮することでも患者の QOL 維持に貢献できる。

また、既承認の前立腺癌患者の安全性プロファイルと比較して大きな違いはみられず、忍容性は良好であると考えられる。

以上のことから、本剤はSBMAの治療薬として有用であると考えた。

1.5.8 参考文献

[1] Kennedy WR, Alter M, Sung JH. Progressive proximal spinal and bulbar muscular atrophy of late onset. A sex-linked recessive trait. Neurology. 1968;18(7):671-80.

[2] Sobue G, Hashizume Y, Mukai E, Hirayama M, Mitsuma T, Takahashi A. X-linked recessive bulbospinal neuronopathy. A clinicopathological study. Brain. 1989;112(Pt1):209-32.

[3] Atsuta N, Watanabe H, Ito M, Banno H, Suzuki K, Katsuno M et al. Natural history of spinal and bulbar muscular atrophy (SBMA): a study of 223 Japanese patients. Brain. 2006;129(Pt 6):1446-55.

[4] Fischbeck KH. Kennedy disease. J Inherit Metab Dis. 1997;20(2):152-58.

[5] Udd B, Juvonen V, Hakamies L, Nieminen A, Wallgren-Pettersson C, Cederquist K et al. High prevalence of Kennedy's disease in Western Finland -- is the syndrome underdiagnosed? Acta Neurol Scand. 1998;98(2):128-33.

[6] 難病情報センター Available from: URL: http://www.nanbyou.or.jp/entry/234.（添付なし）

[7] 勝野雅央, 足立弘明, 坂野晴彦, 祖父江元. 医学と医療の最前線　球脊髄性筋萎縮症の治療法開発. 日本内科学会雑誌. 2004;93(7):1466-72.

[8] Banno H, Katsuno M, Suzuki K, Takeuchi Y, Kawashima M, Suga N et al. Phase 2 trial of leuprorelin in patients with spinal and bulbar muscular atrophy. Ann Neurol. 2009;65(2):140-50.

目次

1.6 外国における使用状況等に関する資料 2

表

表 1.6-1　米国／英国における リュープロレリン酢酸塩の 3 ヵ月製剤（11.25 mg 含有）の許可状況 3

1.6 外国における使用状況等に関する資料

リュープロレリン酢酸塩を含有する製剤として、1985 年に米国で連日注射製剤が販売され、その後、1 ヵ月製剤、3 ヵ月製剤、4 ヵ月製剤、6 ヵ月製剤が開発され販売されている。リュープロレリン酢酸塩の 3 ヵ月製剤は、12 週間持続型の徐放性製剤であり、米国及び欧州を含む世界 70 ヵ国以上（米国、ドイツ、フランス、英国、オーストラリア、カナダ等）で前立腺癌、閉経前乳癌、子宮筋腫、子宮内膜症、中枢性思春期早発症等を適応として販売されている。外国では、いずれの製剤においても球脊髄性筋萎縮症を適応として開発、販売されている国はない（2016 年 10 月現在）。

米国及び英国における 3 ヵ月製剤の許可状況を表 1.6-1 に示す。なお、米国では含有量の異なる複数の製剤が発売されているが、今回申請する製剤と同じ 11.25 mg を含有する製剤について示した。

また、米国及び英国における 3 ヵ月製剤（11.25 mg 含有）の添付文書（和訳及び原文）及び企業中核シートを添付した。

表 1.6-1　米国／英国における
リュープロレリン酢酸塩の 3 ヵ月製剤（11.25 mg 含有）の許可状況

国名	販売名	許可 年月日	剤形	含量	効能・効果 用法・用量
米国	LUPRON DEPOT® -3 Month 11.25 mg	1998 年 7 月 29 日	注射剤	11.25 mg	【効能・効果】 ・子宮内膜症 ・子宮平滑筋腫（類線維腫） 【用法・用量】 子宮内膜症： 3 ヵ月に 1 回筋肉内注射として投与する。推奨治療期間は 6 ヶ月間である。 子宮平滑筋腫（類線維腫）： 3 ヵ月に 1 回単回筋肉内注射として投与する。
英国	PROSTAP® 3 DCS	2011 年 4 月 28 日	注射剤	11.25 mg	【効能・効果】 (i)　転移性前立腺癌 (ii)　局所進行前立腺癌に対する外科的去勢の代替療法 (iii)　ハイリスクの局所前立腺癌患者又は局所進行前立腺癌患者における放射線療法に対するアジュバント療法 (iv)　疾患進行のリスクが高い局所進行前立腺癌患者における根治的前立腺摘除術に対するアジュバント療法 (v)　ハイリスクの局所前立腺癌患者又は局所進行前立腺癌患者における放射線療法前のネオアジュバント療法 (vi)　疼痛緩和及び子宮内膜症病変の軽減を含む子宮内膜症の管理 小児： 中枢性思春期早発症の治療（9 歳未満の女児、10 歳未満の男児） 【用法・用量】 前立腺癌： 通常 3 ヵ月に 1 回､3 ヵ月徐放性注射製剤として 11.25 mg を皮下に投与する。 子宮内膜症： 3 ヵ月に 1 回、11.25 mg を筋肉内に投与する。投与期間は 6 ヵ月間とする。 小児集団： 体重 20 kg 以上の小児 徐放性マイクロカプセル 130.0 mg を溶媒 1 mL に溶かして得た懸濁液 1 mL（リュープロレリン酢酸塩として 11.25 mg）を 3 ヵ月に 1 回、皮下に注射投与する。 体重 20 kg 未満の小児 徐放性マイクロカプセル 130.0 mg を溶媒 1 mL に溶かして得た懸濁液の 0.5 mL（リュープロレリン酢酸塩として 5.625 mg）を 3 ヵ月に 1 回、皮下に注射投与する。

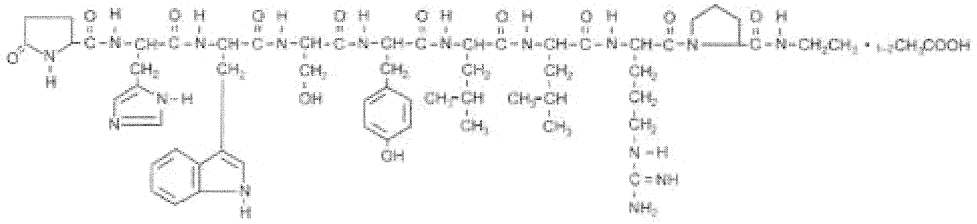
LUPRON DEPOT® -3 Month 11.25 mg

(leuprolide acetate for depot suspension)
3-MONTH FORMULATION

Rx only

DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. 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:



LUPRON DEPOT–3 Month 11.25 mg is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as an intramuscular injection to be given **ONCE EVERY THREE MONTHS.**

The front chamber of LUPRON DEPOT–3 Month 11.25 mg prefilled dual-chamber syringe contains leuprolide acetate (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 (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT–3 Month 11.25 mg, acetic acid is lost, leaving the peptide.

CLINICAL PHARMACOLOGY

Leuprolide acetate is a long-acting GnRH analog. A single injection of LUPRON DEPOT–3 Month 11.25 mg will result in an initial stimulation followed by a prolonged suppression of

pituitary gonadotropins. Repeated dosing at quarterly (LUPRON DEPOT–3 Month 11.25 mg) 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.

Pharmacokinetics

Absorption

Following a single injection of the three month formulation of LUPRON DEPOT–3 Month 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.

Distribution

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%.

Metabolism

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.

In rats and dogs, administration of ^{14}C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

In a pharmacokinetic/pharmacodynamic study of endometriosis patients, intramuscular 11.25 mg LUPRON DEPOT (n=19) every 12 weeks or intramuscular 3.75 mg LUPRON DEPOT (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.

M-I 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.

Excretion

Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Special Populations

The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.

Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

CLINICAL STUDIES

In a pharmacokinetic/pharmacodynamic study of 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.

LUPRON DEPOT–3 Month 11.25 mg induced amenorrhea in 85% (N=17) of subjects during the initial month and 100% during the second month following the injection. All subjects remained amenorrheic through the remainder of the 12-week dosing interval. Episodes of light bleeding and spotting were reported by a majority of subjects during the first month after the

injection and in a few subjects at later time-points. Menses resumed on average 12 weeks (range 2.9 to 20.4 weeks) following the end of the 12-week dosing interval.

LUPRON DEPOT–3 Month 11.25 mg produced similar pharmacodynamic effects in terms of hormonal and menstrual suppression to those achieved with monthly injections of LUPRON DEPOT 3.75 mg during the controlled clinical trials for the management of endometriosis and the anemia caused by uterine fibroids.

Endometriosis

In a Phase IV pharmacokinetic/pharmacodynamic study of patients, LUPRON DEPOT–3 Month 11.25 mg (N=21) was shown to be comparable to monthly LUPRON DEPOT 3.75 mg (N=20) in relieving the clinical signs/symptoms of endometriosis (dysmenorrhea, non-menstrual pelvic pain, pelvic tenderness and pelvic induration). In both treatment groups, suppression of menses was achieved in 100% of the patients who remained in the study for at least 60 days. Suppression is defined as no new menses for at least 60 consecutive days.

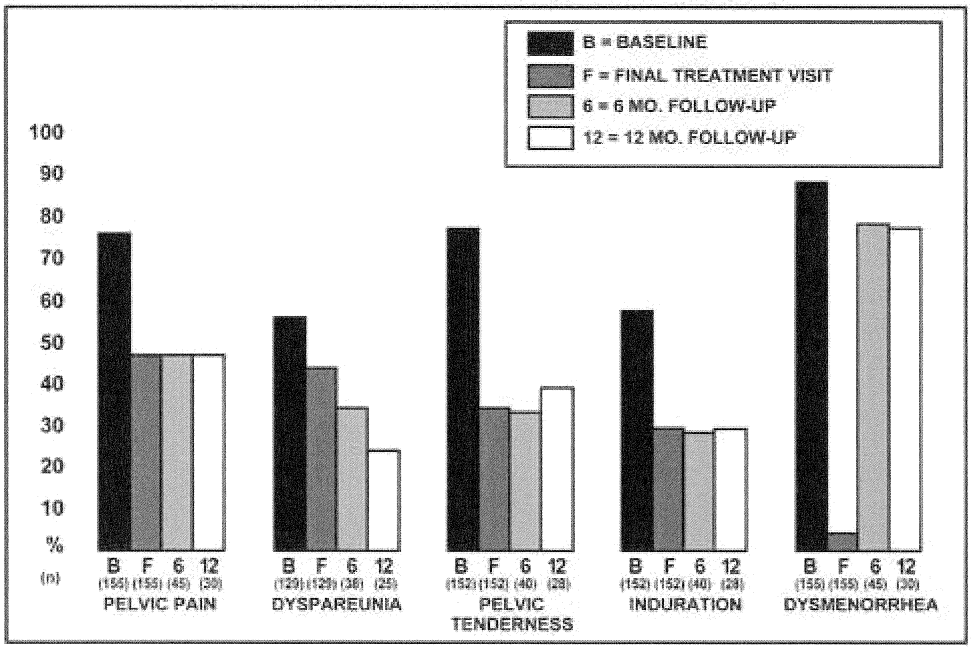
In controlled clinical studies, LUPRON DEPOT 3.75 mg monthly for six months was shown to be comparable to danazol 800 mg/day in relieving the clinical sign/symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and in reducing the size of endometrial implants as evidenced by laparoscopy.

The clinical significance of a decrease in endometriotic lesions is not known at this time, and in addition laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms.

LUPRON DEPOT 3.75 mg monthly induced amenorrhea in 74% and 98% of the patients after the first and second treatment months respectively. Most of the remaining patients reported episodes of only light bleeding or spotting. In the first, second and third post-treatment months, normal menstrual cycles resumed in 7%, 71% and 95% of patients, respectively, excluding those who became pregnant.

Figure 1 illustrates the percent of patients with symptoms at baseline, final treatment visit and sustained relief at 6 and 12 months following discontinuation of treatment for the various symptoms evaluated during the two controlled clinical studies. A total of 166 patients received LUPRON DEPOT 3.75 mg. Seventy-five percent (N=125) of these elected to participate in the follow-up period. Of these patients, 36% and 24% are included in the 6 month and 12 month follow-up analysis, respectively. All the patients who had a pain evaluation at baseline and at a minimum of one treatment visit, are included in the Baseline (B) and final treatment visit (F) analysis.

FIGURE 1 – PERCENT OF PATIENTS WITH SIGN/SYMPTOMS OF ENDOMETRIOSIS AT BASELINE, FINAL TREATMENT VISIT, AND AFTER 6 AND 12 MONTHS OF FOLLOW-UP

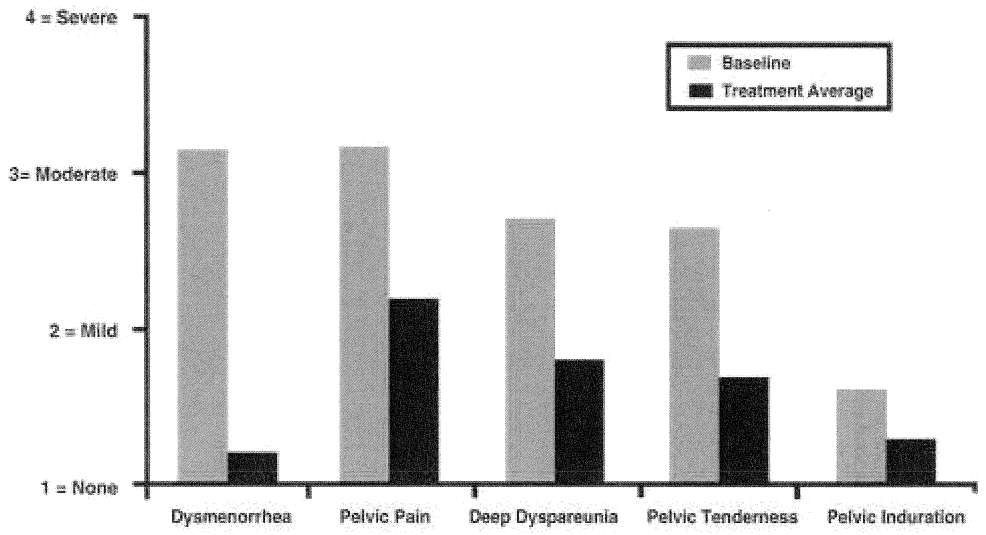


Hormonal add-back therapy

Two clinical studies with a treatment duration of 12 months indicate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) is effective in significantly reducing the loss of bone mineral density associated with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. (All patients in these studies received calcium supplementation with 1000 mg elemental calcium). One controlled, randomized and double-blind study included 51 women treated with LUPRON DEPOT 3.75 mg alone and 55 women treated with LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg (LD/N) daily. The second study was an open label study in which 136 women were treated with monthly LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily. This study confirmed the reduction in loss of bone mineral density that was observed in the controlled study. Suppression of menses was maintained throughout treatment in 84% and 73% of patients receiving LD/N, in the controlled study and open label study, respectively. The median time for menses resumption after treatment with LD/N was 8 weeks.

Figure 2 Illustrates the mean pain scores for the LD/N group from the controlled study.

Figure 2
Treatment Period Mean Pain Scores For LD/N* Patients



* LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily

Uterine Leiomyomata (Fibroids)

LUPRON DEPOT 3.75 mg for a period of three to six months was studied in four controlled clinical trials.

In one of these clinical studies, enrollment was based on hematocrit ≤ 30% and/or hemoglobin ≤ 10.2 g/dL. Administration of LUPRON DEPOT 3.75 mg, concomitantly with iron, produced an increase of ≥ 6% hematocrit and ≥ 2 g/dL hemoglobin in 77% of patients at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of ≥ 36% and hemoglobin of ≥ 12 g/dL, thus allowing for autologous blood donation prior to surgery. At two and three months respectively, 71% and 75% of patients met this criterion (Table 1). These data suggest however, that some patients may benefit from iron alone or 1 to 2 months of LUPRON DEPOT 3.75 mg.

Table 1 PERCENT OF PATIENTS ACHIEVING HEMATOCRIT ≥ 36% AND HEMOGLOBIN ≥ 12 GM/DL

Treatment Group	Week 4	Week 8	Week 12
LUPRON DEPOT 3.75 mg with Iron (N=104)	40*	71†	75*
Iron Alone (N=98)	17	39	49
* P-Value < 0.01			
† P-Value < 0.001			

Excessive vaginal bleeding (menorrhagia or menometrorrhagia) decreased in 80% of patients at three months. Episodes of spotting and menstrual-like bleeding were noted in 16% of patients at final visit.

In this same study, a decrease of ≥25% was seen in uterine and myoma volumes in 60% and 54% of patients respectively. The mean fibroid diameter was 6.3 cm at pretreatment and decreased to 5.6 cm at the end of treatment. LUPRON DEPOT 3.75 mg was found to relieve symptoms of bloating, pelvic pain, and pressure.

In three other controlled clinical trials, enrollment was not based on hematologic status. Mean uterine volume decreased by 41% and myoma volume decreased by 37% at final visit as evidenced by ultrasound or MRI. The mean fibroid diameter was 5.6 cm at pretreatment and decreased to 4.7 cm at the end of treatment. These patients also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Ninety-five percent of these patients became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months respectively.

In addition, posttreatment follow-up was carried out in one clinical trial for a small percentage of LUPRON DEPOT 3.75 mg patients (N=46) among the 77% who demonstrated a ≥ 25% decrease in uterine volume while on therapy. Menses usually returned within two months of cessation of therapy. Mean time to return to pretreatment uterine size was 8.3 months. Regrowth did not appear to be related to pretreatment uterine volume.

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

INDICATIONS AND USAGE

Endometriosis

LUPRON DEPOT–3 Month 11.25 mg is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. LUPRON DEPOT with norethindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms. (Refer also to norethindrone acetate prescribing information for WARNINGS, PRECAUTIONS, CONTRAINDICATIONS and ADVERSE REACTIONS associated with norethindrone acetate). Duration of initial treatment or retreatment should be limited to 6 months.

Uterine Leiomyomata (Fibroids)

LUPRON DEPOT–3 Month 11.25 mg concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. The clinician may wish to consider a one-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. (See **Table 1, CLINICAL STUDIES** section.) LUPRON may be added if the response to iron alone is considered inadequate. Recommended therapy is a single injection of LUPRON DEPOT–3 Month 11.25 mg. This dosage form is indicated only for women for whom three months of hormonal suppression is deemed necessary.

Experience with LUPRON DEPOT–3 Month 11.25 mg in females has been limited to women 18 years of age and older treated for no more than 6 months.

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in LUPRON DEPOT.
2. Undiagnosed abnormal vaginal bleeding.
3. LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. LUPRON DEPOT may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of LUPRON DEPOT throughout gestation. There was increased fetal mortality and decreased fetal weights in rats and rabbits. (See **Pregnancy** section.) The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
4. Use in women who are breast-feeding. (See **Nursing Mothers** section.)
5. Norethindrone acetate is contraindicated in women with the following conditions:
    - Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions
    - Markedly impaired liver function or liver disease
    - Known or suspected carcinoma of the breast

WARNINGS

1. As the effects of LUPRON DEPOT–3 Month 11.25 mg are present throughout the course of therapy, the drug should only be used in patients who require hormonal suppression for at least three months.
2. Experience with LUPRON DEPOT–3 Month 11.25 mg in females has been limited to six months; therefore, exposure should be limited to six months of therapy.
3. Safe use of leuprolide acetate or norethindrone acetate in pregnancy has not been established clinically. Before starting treatment with LUPRON DEPOT pregnancy must be excluded.
4. When used at the recommended dose and dosing interval, LUPRON DEPOT usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking LUPRON DEPOT. Therefore, patients should use non-hormonal methods of contraception. Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the fetus. (See **CONTRAINDICATIONS** section.)
5. During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy.
6. Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported post-marketing.
7. The following applies to co-treatment with LUPRON and norethindrone acetate:

Norethindrone acetate treatment should be discontinued if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking progestogens, the physician should be alert to the earliest manifestations of the disease in women taking norethindrone acetate.

Assessment and management of risk factors for cardiovascular disease is recommended prior to initiation of add-back therapy with norethindrone acetate. Norethindrone acetate should be used with caution in women with risk factors, including lipid abnormalities or cigarette smoking.

PRECAUTIONS

Information for Patients

Patients should be aware of the following information:

1. Since menstruation usually stops with effective doses of LUPRON DEPOT, the patient should notify her physician if regular menstruation persists. Patients missing successive doses of LUPRON DEPOT may experience breakthrough bleeding.
2. Patients should not use LUPRON DEPOT if they are pregnant, breast feeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of the ingredients in LUPRON DEPOT.
3. LUPRON DEPOT is contraindicated for use during pregnancy. Therefore, a non-hormonal method of contraception should be used during treatment. Patients should be advised that if they miss successive doses of LUPRON DEPOT, breakthrough bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.
4. Adverse events occurring in clinical studies with LUPRON DEPOT that are associated with hypoestrogenism include: hot flashes, headaches, emotional lability, decreased libido, acne, myalgia, reduction in breast size, and vaginal dryness. Estrogen levels returned to normal after treatment was discontinued.
5. Patients should be counseled on the possibility of the development or worsening of depression and the occurrence of memory disorders.
6. The induced hypoestrogenic state **also** results in a loss in bone density over the course of treatment, some of which may not be reversible. Clinical studies show that concurrent hormonal therapy with norethindrone acetate 5 mg daily is effective in reducing loss of bone mineral density that occurs with LUPRON. (All patients received calcium supplementation with 1000 mg elemental calcium.) (See ***Changes in Bone Density*** section).
7. If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one six-month course cannot be recommended. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. Retreatment with LUPRON DEPOT alone is not recommended.
8. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, LUPRON DEPOT therapy may

pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with LUPRON DEPOT alone is instituted, and concomitant treatment with norethindrone acetate 5 mg daily should be considered. Retreatment with gonadotropin-releasing hormone analogs, including LUPRON is not advisable in patients with major risk factors for loss of bone mineral content.

9. Because norethindrone acetate may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunctions require careful observation during norethindrone acetate add-back therapy.
10. Patients who have a history of depression should be carefully observed during treatment with norethindrone acetate and norethindrone acetate should be discontinued if severe depression occurs.

Convulsions

There have been postmarketing reports of convulsions in patients on leuprolide acetate therapy. These included patients with and without concurrent medications and comorbid conditions.

Laboratory Tests

See **ADVERSE REACTIONS** section.

Drug Interactions

See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**

Drug/Laboratory Test Interactions

Administration of LUPRON DEPOT in therapeutic doses 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 LUPRON DEPOT may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

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. Although no clinical studies have been completed in children to assess the full reversibility of fertility suppression, animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery.

Pregnancy

Teratogenic Effects

Pregnancy Category X (See **CONTRAINDICATIONS** section). 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, LUPRON DEPOT 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 LUPRON DEPOT in rabbits and with the highest dose (0.024 mg/kg) in rats.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness of LUPRON DEPOT–3 Month 11.25 mg have not been established in pediatric patients. Experience with LUPRON DEPOT for treatment of endometriosis has been limited to women 18 years of age and older. See LUPRON DEPOT-PED® (leuprolide acetate for depot suspension) labeling for the safety and effectiveness in children with central precocious puberty.

Geriatric Use

This product has not been studied in women over 65 years of age and is not indicated in this population.

ADVERSE REACTIONS

Clinical Trials

The **monthly formulation of LUPRON DEPOT 3.75 mg** was utilized in controlled clinical trials that studied the drug in 166 endometriosis and 166 uterine fibroids patients. Adverse events reported in ≥ 5% of patients in either of these populations and thought to be potentially related to drug are noted in the following table.

Table 2 ADVERSE EVENTS REPORTED TO BE CAUSALLY RELATED TO DRUG IN ≥ 5% OF PATIENTS

	Endometriosis (2 Studies)						Uterine Fibroids (4 Studies)			
	LUPRON DEPOT 3.75 mg		Danazol		Placebo		LUPRON DEPOT 3.75 mg		Placebo	
	N=166		N=136		N=31		N=166		N=163	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Body as a Whole										
Asthenia	5	(3)	9	(7)	0	(0)	14	(8.4)	8	(4.9)
General pain	31	(19)	22	(16)	1	(3)	14	(8.4)	10	(6.1)
Headache*	53	(32)	30	(22)	2	(6)	43	(25.9)	29	(17.8)
Cardiovascular System										
Hot flashes/sweats*	139	(84)	77	(57)	9	(29)	121	(72.9)	29	(17.8)
Gastrointestinal System										
Nausea/vomiting	21	(13)	17	(13)	1	(3)	8	(4.8)	6	(3.7)
GI disturbances*	11	(7)	8	(6)	1	(3)	5	(3.0)	2	(1.2)
Metabolic and Nutritional Disorders										
Edema	12	(7)	17	(13)	1	(3)	9	(5.4)	2	(1.2)
Weight gain/loss	22	(13)	36	(26)	0	(0)	5	(3.0)	2	(1.2)
Endocrine System										
Acne	17	(10)	27	(20)	0	(0)	0	(0)	0	(0)
Hirsutism	2	(1)	9	(7)	1	(3)	1	(0.6)	0	(0)
Musculoskeletal System										
Joint disorder*	14	(8)	11	(8)	0	(0)	13	(7.8)	5	(3.1)
Myalgia*	1	(1)	7	(5)	0	(0)	1	(0.6)	0	(0)
Nervous System										
Decreased libido*	19	(11)	6	(4)	0	(0)	3	(1.8)	0	(0)
Depression/emotional lability*	36	(22)	27	(20)	1	(3)	18	(10.8)	7	(4.3)
Dizziness	19	(11)	4	(3)	0	(0)	3	(1.8)	6	(3.7)
Nervousness*	8	(5)	11	(8)	0	(0)	8	(4.8)	1	(0.6)
Neuromuscular disorders*	11	(7)	17	(13)	0	(0)	3	(1.8)	0	(0)

Paresthesias	12	(7)	11	(8)	0	(0)	2	(1.2)	1	(0.6)
Skin and Appendages										
Skin reactions	17	(10)	20	(15)	1	(3)	5	(3.0)	2	(1.2)
Urogenital System										
Breast changes/tenderness/pain*	10	(6)	12	(9)	0	(0)	3	(1.8)	7	(4.3)
Vaginitis*	46	(28)	23	(17)	0	(0)	19	(11.4)	3	(1.8)
In these same studies, symptoms reported in < 5% of patients included: *Body as a Whole* - Body odor, Flu syndrome, Injection site reactions; *Cardiovascular System* - Palpitations, Syncope, Tachycardia; *Digestive System* - Appetite changes, Dry mouth, Thirst; *Endocrine System* - Androgen-like effects; *Hemic and Lymphatic System* - Ecchymosis, Lymphadenopathy; *Nervous System* - Anxiety*, Insomnia/Sleep disorders*, Delusions, Memory disorder, Personality disorder; *Respiratory System* - Rhinitis; *Skin and Appendages* - Alopecia, Hair disorder, Nail disorder; *Special Senses* - Conjunctivitis, Ophthalmologic disorders*, Taste perversion; *Urogenital System* - Dysuria*, Lactation, Menstrual disorders.										
* = Possible effect of decreased estrogen.										

In one controlled clinical trial utilizing the monthly formulation of LUPRON DEPOT, patients diagnosed with uterine fibroids received a higher dose (7.5 mg) of LUPRON DEPOT. Events seen with this dose that were thought to be potentially related to drug and were not seen at the lower dose included glossitis, hypesthesia, lactation, pyelonephritis, and urinary disorders. Generally, a higher incidence of hypoestrogenic effects was observed at the higher dose.

In a pharmacokinetic trial involving 20 healthy female subjects receiving LUPRON DEPOT–3 Month 11.25 mg, a few adverse events were reported with this formulation that were not reported previously. These included face edema, agitation, laryngitis, and ear pain.

In a Phase IV study involving endometriosis patients receiving LUPRON DEPOT 3.75 mg (N=20) or LUPRON DEPOT–3 Month 11.25 mg (N=21), similar adverse events were reported by the two groups of patients. In general the safety profiles of the two formulations were comparable in this study.

Table 3 lists the potentially drug-related adverse events observed in at least 5% of patients in any treatment group, during the first 6 months of treatment in the add-back clinical studies, in which patients were treated with monthly LUPRON DEPOT 3.75 mg with or without norethindrone acetate co-treatment.

Table 3 TREATMENT-RELATED ADVERSE EVENTS OCCURRING IN ≥ 5% OF PATIENTS

	Controlled Study				**Open Label Study**	
	LD - Only* N=51		**LD/N† N=55**		**LD/N† N=136**	
Adverse Events	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Any Adverse Event	50	(98)	53	(96)	126	(93)
Body as a Whole						
Asthenia	9	(18)	10	(18)	15	(11)

Headache/Migraine	33	(65)	28	(51)	63	(46)
Injection Site Reaction	1	(2)	5	(9)	4	(3)
Pain	12	(24)	16	(29)	29	(21)
Cardiovascular System						
Hot flashes/Sweats	50	(98)	48	(87)	78	(57)
Digestive System						
Altered Bowel Function	7	(14)	8	(15)	14	(10)
Changes in Appetite	2	(4)	0	(0)	8	(6)
GI Disturbance	2	(4)	4	(7)	6	(4)
Nausea/Vomiting	13	(25)	16	(29)	17	(13)
Metabolic and Nutritional Disorders						
Edema	0	(0)	5	(9)	9	(7)
Weight Changes	6	(12)	7	(13)	6	(4)
Nervous System						
Anxiety	3	(6)	0	(0)	11	(8)
Depression/Emotional Lability	16	(31)	15	(27)	46	(34)
Dizziness/Vertigo	8	(16)	6	(11)	10	(7)
Insomnia/Sleep Disorder	16	(31)	7	(13)	20	(15)
Libido Changes	5	(10)	2	(4)	10	(7)
Memory Disorder	3	(6)	1	(2)	6	(4)
Nervousness	4	(8)	2	(4)	15	(11)
Neuromuscular Disorder	1	(2)	5	(9)	4	(3)
Skin and Appendages						
Alopecia	0	(0)	5	(9)	4	(3)
Androgen-Like Effects	2	(4)	3	(5)	24	(18)
Skin/Mucous Membrane Reaction	2	(4)	5	(9)	15	(11)
Urogenital System						
Breast Changes/Pain/Tenderness	3	(6)	7	(13)	11	(8)
Menstrual Disorders	1	(2)	0	(0)	7	(5)
Vaginitis	10	(20)	8	(15)	11	(8)
* LD-Only = LUPRON DEPOT 3.75 mg						
† LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg						

In the controlled clinical trial, 50 of 51 (98%) patients in the LD group (LUPRON DEPOT 3.75 mg) and 48 of 55 (87%) patients in the LD/N group (LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily) reported experiencing hot flashes on one or more occasions during treatment. During Month 6 of treatment, 32 of 37 (86%) patients in the LD group and 22 of 38 (58%) patients in the LD/N group reported having experienced hot flashes. The mean number of days on which hot flashes were reported during this month of treatment was 19 and 7 in the LD and LD/N treatment groups, respectively. The mean maximum number of hot flashes in a day during this month of treatment was 5.8 and 1.9 in the LD and LD/N treatment groups, respectively.

Changes in Bone Density

In controlled clinical studies, patients with endometriosis (six months of therapy) or uterine fibroids (three months of therapy) were treated with LUPRON DEPOT 3.75 mg. In endometriosis patients, vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.2% at six months compared with the pretreatment value. Clinical studies demonstrate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) and calcium supplementation is effective in significantly reducing the loss of bone mineral density that occurs with LUPRON treatment, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily was evaluated in two clinical trials. The results from this regimen were similar in both studies. LUPRON DEPOT 3.75 mg was used as a control group in one study. The bone mineral density data of the lumbar spine from these two studies are presented in Table 4.

Table 4 MEAN PERCENT CHANGE FROM BASELINE IN BONE MINERAL DENSITY OF LUMBAR SPINE

	LUPRON DEPOT 3.75 mg		**LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily**			
	Controlled Study		**Controlled Study**		**Open Label Study**	
	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						

In the Phase IV, six-month pharmacokinetic/pharmacodynamic study in endometriosis patients who were treated with LUPRON DEPOT 3.75 mg or LUPRON DEPOT–3 Month 11.25 mg, vertebral bone density measured by DEXA decreased compared with baseline by an average of 3.0% and 2.8% at six months for the two groups, respectively.

When LUPRON DEPOT 3.75 mg was administered for three months in uterine fibroid patients, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2.7% compared with baseline. Six months after discontinuation of therapy, a trend toward recovery was observed. Use of LUPRON DEPOT for longer than three months (uterine fibroids) or six months (endometriosis) or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss **and is not recommended.**

Changes in Laboratory Values During Treatment

Liver Enzymes

Three percent of uterine fibroid patients treated with LUPRON DEPOT 3.75 mg, manifested posttreatment transaminase values that were at least twice the baseline value and above the upper limit of the normal range. None of the laboratory increases were associated with clinical symptoms.

In two other clinical trials, 6 of 191 patients receiving LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily for up to 12 months developed an elevated (at least twice the upper limit of normal) SGPT or GGT. Five of the 6 increases were observed beyond 6 months of treatment. None were associated with an elevated bilirubin concentration.

Lipids

Triglycerides were increased above the upper limit of normal in 12% of the endometriosis patients who received LUPRON DEPOT 3.75 mg and in 32% of the subjects receiving LUPRON DEPOT–3 Month 11.25 mg.

Of those endometriosis and uterine fibroid patients whose pretreatment cholesterol values were in the normal range, mean change following therapy was +16 mg/dL to +17 mg/dL in endometriosis patients and +11 mg/dL to +29 mg/dL in uterine fibroid patients. In the endometriosis treated patients, increases from the pretreatment values were statistically significant ($p<0.03$). There was essentially no increase in the LDL/HDL ratio in patients from either population receiving LUPRON DEPOT 3.75 mg.

In two other clinical trials, LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily were evaluated for 12 months of treatment. LUPRON DEPOT 3.75 mg was used as a control group in one study. Percent changes from baseline for serum lipids and percentages of patients with serum lipid values outside of the normal range in the two studies are summarized in the tables below.

Table 5 SERUM LIPIDS: MEAN PERCENT CHANGES FROM BASELINE VALUES AT TREATMENT WEEK 24

	LUPRON DEPOT 3.75 mg		**LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily**			
	Controlled Study (n=39)		**Controlled Study (n=41)**		**Open Label Study (n=117)**	
	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 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 patients with follow up data returned to pretreatment values.

Table 6 PERCENTAGE OF PATIENTS WITH SERUM LIPID VALUES OUTSIDE OF THE NORMAL RANGE

	LUPRON DEPOT 3.75 mg		**LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily**			
	Controlled Study (n=39)		**Controlled Study (n=41)**		**Open Label Study (n=117)**	
	Wk 0	Wk 24*	Wk 0	Wk 24*	Wk 0	Wk 24*
Total Cholesterol (>240 mg/dL)	15%	23%	15%	20%	6%	7%
HDL Cholesterol (<40 mg/dL)	15%	10%	15%	44%	15%	41%
LDL Cholesterol (>160 mg/dL)	0%	8%	5%	7%	9%	11%
LDL/HDL Ratio (>4.0)	0%	3%	2%	15%	7%	21%
Triglycerides (>200 mg/dL)	13%	13%	12%	10%	5%	9%
* Includes all patients regardless of baseline value.						

Low HDL-cholesterol (<40 mg/dL) and elevated LDL-cholesterol (>160 mg/dL) are recognized risk factors for cardiovascular disease. The long-term significance of the observed treatment-related changes in serum lipids in women with endometriosis is unknown. Therefore assessment of cardiovascular risk factors should be considered prior to initiation of concurrent treatment with LUPRON and norethindrone acetate.

Chemistry

Slight to moderate mean increases were noted for glucose, uric acid, BUN, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, LDH, calcium, and phosphorus. None of these increases were clinically significant. In the hormonal add-back studies LUPRON DEPOT in combination with norethindrone acetate was associated with elevations of GGT and SGPT in 6% to 7% of patients.

Postmarketing

The following adverse reactions have been identified during postapproval use of LUPRON DEPOT. 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 with other dosage forms and in the same and/or different populations, the following adverse events were reported. Like other drugs in this class, mood swings, including depression, have been reported. There have been rare reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of depression or other psychiatric illness. Patients should be counseled on the possibility of development or worsening of depression during treatment with LUPRON.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported. Rash, urticaria, and photosensitivity reactions have also been reported.

Localized reactions including induration and abscess have been reported at the site of injection.

Symptoms consistent with fibromyalgia (eg: joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

Other events reported are:

Hepato-biliary disorder: Rarely reported serious liver injury

Injury, poisoning and procedural complications: Spinal fracture

Investigations: Decreased WBC

Musculoskeletal and Connective tissue disorder: Tenosynovitis-like symptoms

Nervous System Disorder: Convulsion, peripheral neuropathy, paralysis

Vascular Disorder: Hypotension

Cases of serious venous and arterial thromboembolism have been reported, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischemic attack. Although a temporal relationship was reported in some cases, most cases were confounded by risk factors or concomitant medication use. It is unknown if there is a causal association between the use of GnRH analogs and these events.

Pituitary apoplexy

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

See other LUPRON DEPOT and LUPRON Injection package inserts for other events reported in the same and different patient populations.

OVERDOSAGE

In clinical trials using daily subcutaneous leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

LUPRON DEPOT Must Be Administered Under the Supervision of a Physician.

Endometriosis

The recommended duration of treatment with LUPRON DEPOT–3 Month 11.25 mg alone or in combination with norethindrone acetate is six months. The choice of LUPRON DEPOT alone or LUPRON DEPOT plus norethindrone acetate therapy for initial management of the symptoms and signs of endometriosis should be made by the health care professional in consultation with the patient and should take into consideration the risks and benefits of the addition of norethindrone to LUPRON DEPOT alone.

If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT-3 Month 11.25 mg administered every three months and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one six-month course cannot be recommended. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. LUPRON DEPOT alone is not recommended for retreatment. If norethindrone acetate is contraindicated for the individual patient, then retreatment is not recommended.

An assessment of cardiovascular risk and management of risk factors such as cigarette smoking is recommended before beginning treatment with LUPRON DEPOT and norethindrone acetate.

Uterine Leiomyomata (Fibroids)

The recommended dose of LUPRON DEPOT–3 Month 11.25 mg is one injection. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy. If additional treatment with LUPRON DEPOT–3 Month 11.25 mg is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.

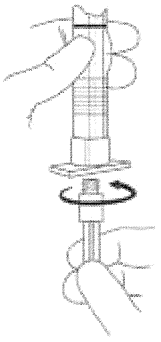
Due to different release characteristics, a fractional dose of the 3-month depot formulation is not equivalent to the same dose of the monthly formulation and should not be given.

For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the following instructions:

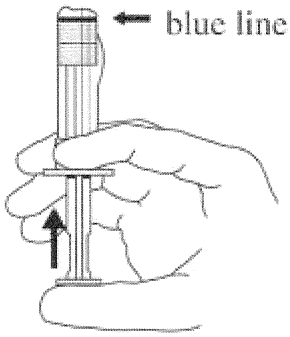
Reconstitution and Administration Instructions

- The lyophilized microspheres are to be reconstituted and administered as a single intramuscular injection.
- Since LUPRON DEPOT does not contain a preservative, the suspension should be injected immediately or discarded if not used within two hours.
- As with other drugs administered by injection, the injection site should be varied periodically.

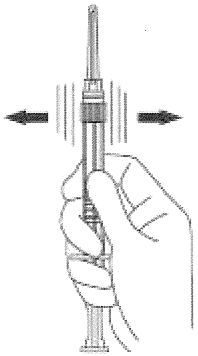
1. The LUPRON DEPOT powder should be visually inspected and the syringe should NOT BE USED if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal prior to mixing with the diluent. The diluent should appear clear.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.



3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is <u>at the blue line</u> in the middle of the barrel.

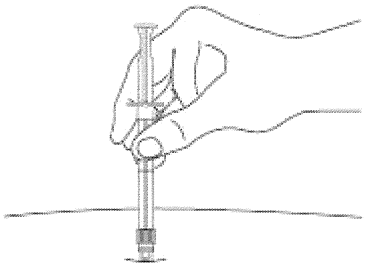


4. Keep the syringe UPRIGHT. Mix the microspheres (powder) thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.

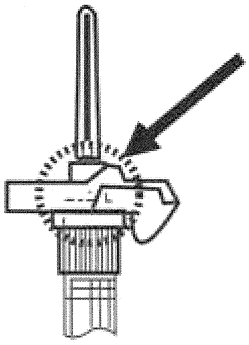


5. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.

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, the intramuscular injection should be performed by inserting the needle at a 90 degree angle into the gluteal area, anterior thigh, or deltoid; injection sites should be alternated.



NOTE: Aspirated blood would be visible just below the luer lock connection if a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent LuproLoc® safety device. If blood is present remove the needle immediately. Do not inject the medication.

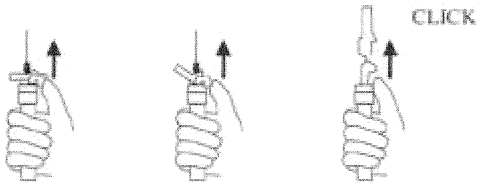


8. Inject the entire contents of the syringe intramuscularly at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT should be mixed and used immediately.

AFTER INJECTION

9. Withdraw the needle. Once the syringe has been withdrawn, activate immediately 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.



ADDITIONAL INFORMATION

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

HOW SUPPLIED

Each LUPRON DEPOT – 3 Month 11.25 mg kit (NDC 0074-3663-03) contains:

- one prefilled dual-chamber syringe
- one plunger
- two alcohol swabs
- a complete prescribing information enclosure

Each syringe contains sterile lyophilized microspheres which are leuprolide acetate incorporated in a biodegradable polymer of polylactic acid. When mixed with 1.5 mL of the diluent, LUPRON DEPOT–3 Month 11.25 mg is administered as a single IM injection **EVERY THREE MONTHS.**

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

REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm*. 2006; 63; 1172-1193.
4. Polovich, M., White, J.M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. Ed.) Pittsburgh, PA: Oncology Nursing Society.

Manufactured for
AbbVie Inc.
North Chicago, IL 60064
by Takeda Pharmaceutical Company Limited
Osaka, Japan 540-8645

03-A892 October, 2013

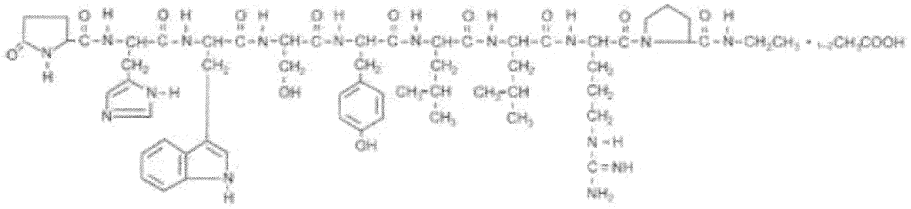
LUPRON DEPOT® -3 Month 11.25 mg

（デポ懸濁液用リュープロレリン酢酸塩）
3ヶ月製剤

処方箋医薬品

組成・性状

リュープロレリン酢酸塩は、天然産生の性腺刺激ホルモン放出ホルモン（GnRH 又は LH-RH）の合成ノナペプチドアナログである。本アナログは天然ホルモンより高い活性をもつ。化学名は 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)であり、化学構造式は以下の通りである。



LUPRON DEPOT -3 Month 11.25 mg は無菌凍結乾燥ミクロスフェアを包含するプレフィルドデュアルチャンバーシリンジで供給され、無菌凍結乾燥ミクロスフェアは希釈液と混合すると筋肉内注射用の懸濁液となる。投与は**3ヶ月に1回**である。

LUPRON DEPOT -3 Month 11.25 mg プレフィルドデュアルチャンバーシリンジの前室にはリュープロレリン酢酸塩（11.25 mg）、乳酸重合体（99.3 mg）、D－マンニトール（19.45 mg）が充填されている。後室の希釈液は、カルメロースナトリウム（7.5 mg）、D－マンニトール（75.0 mg）、ポリソルベート 80（1.5 mg）、注射用水 USP、pH 調整のための氷酢酸 USP を含有する。

LUPRON DEPOT -3 Month 11.25 mg の製造過程で、ペプチドを残して酢酸は失われる。

臨床薬理

リュープロレリン酢酸塩は長時間作用型の GnRH アナログである。LUPRON DEPOT -3 Month 11.25 mg の 1 回注射が初期刺激となり、続いて遷延性の下垂体性腺刺激ホルモン抑制が起こる。3ヶ月に 1 回の間隔で反復投与（LUPRON DEPOT -3 Month 11.25 mg）することで性腺ステロイドの分泌が低下し、その結果、組織及び機能でその維持を性腺ステロイドに依存しているものは不活発になる。この影響は薬剤投与の中止により回復する。

リュープロレリン酢酸塩は経口投与では活性がない。

薬物動態

吸収

女性被験者に対するLUPRON DEPOT -3 Month 11.25 mgの3ヶ月製剤の1回注射後、リュープロレリンの平均血漿中濃度は4時間で36.3 ng/mLであった。リュープロレリンは、投与から3週目に定常状態レベルとなった後、一定の速度で放出され、平均濃度はその後12週目までに検出下限値近くまで徐々に減少すると考えられた。3週目から12週目までの平均（± 標準偏差）リュープロレリン濃度は0.23 ± 0.09 ng/mLであった。しかし、未変化のリュープロレリンと主な不活性代謝物は、この試験で採用された分析法では識別不能であった。定常状態レベルまで急速に減少する前の初期バーストは、1ヶ月製剤で見られた放出パターンと同様であった。

分布

健康な男性ボランティアに対するリュープロレリンの静脈内急速投与後の定常状態時平均分布容積は27 Lであった。ヒト血漿蛋白結合率はin vitroで43%から49%までの幅があった。

代謝

健康な男性ボランティアにおいて、リュープロレリン1 mgを静脈内急速投与した際の平均全身クリアランスは7.6 L/hであり、2－コンパートメントモデルに基づく最終消失半減期は約3時間であった。

ラット及びイヌにおいて^{14}C標識リュープロレリンを投与したところ、より低分子の不活性ペプチドである、ペンタペプチド（代謝物I）、トリペプチド（代謝物II、III）、ジペプチド（代謝物IV）に代謝されることが示された。これらの断片はさらに異化されている可能性がある。

子宮内膜症患者における薬物動態／薬力学試験で、LUPRON DEPOT筋注11.25 mg（n=19）を12週間毎、又はLUPRON DEPOT筋注3.75 mg（n=15）を4週間毎に24週間投与した。エストラジオールの血清中濃度のベースラインからの変化において、二つの治療群間に統計的有意差はなかった。

前立腺癌患者5人で測定した代謝物Iの血漿中濃度は投与後2－6時間で最高濃度に到達し、これは未変化体のピーク濃度の約6%に相当した。投与から1週間後、代謝物Iの平均血漿中濃度はリュープロレリンの平均濃度の約20%であった。

排泄

LUPRON DEPOT 3.75 mgを患者3人に投与した後、用量の5%未満が未変化体及び代謝物Iとして尿中に回収された。

特殊集団

肝臓及び腎臓の機能障害を有する患者における本薬剤の薬物動態は確定されていない。

薬物相互作用

LUPRON DEPOTに関し、薬物動態に基づく薬物－薬物相互作用試験は実施されていない。しかし、リュープロレリン酢酸塩はペプチドであり、いくつかの試験で認められたように、チトクロムP-450酵素ではなく主にペプチダーゼにより分解され、血漿蛋白結合率は約46%にすぎないため、薬物相互作用は発生しないと考えられる。

臨床試験

健康な女性被験者（N=20）における薬物動態／薬力学試験で、個々の被験者について投与後4日目から4週目の間にエストラジオール抑制の発現が認められた。注射後3週目まで、平均エストラジオール濃度（8 pg/mL）は閉経期レベルであった。残りの治療期間を通じ、エストラジオールの平均血清中濃度は閉経期レベルから卵胞期初期レベルまで幅があった。

全被験者において、血清中のエストラジオールは4週目まで20 pg/mL以下に抑制されていた。被験者の80%において、投与間隔である12週目終わりまで抑制（40 pg/mL以下）は継続し、この時点で、このうちの被験者2人の値は40 pg/mLと50 pg/mLの間であった。さらに別の被験者4人では、12週間の投与間隔期間に少なくとも2度続けてエストラジオール値が増加したが（43-240 pg/mLの範囲）、この期間中いずれの被験者においても黄体機能は示唆されなかった。

LUPRON DEPOT -3 Month 11.25 mgは、注射後、1ヶ月目で85%（N=17）、2ヶ月目で100%の被験者において無月経を誘発した。全被験者の無月経は、投与間隔である12週間の残りの期間中継続した。被験者の大多数で注射後1ヶ月目、数人でそれより遅い時点で、軽度の出血、小出血のエピソードが報告された。月経再開は、投与間隔である12週終了後、平均で12週目（幅は2.9週から20.4週）であった。

子宮内膜症の管理及び子宮類線維症を原因とする貧血に関する対照臨床試験において、LUPRON DEPOT 3.75 mgの月1回注射によってホルモン及び月経の抑制が達成された。LUPRON DEPOT -3 Month 11.25 mgはホルモン及び月経の抑制という点で、上記試験で得られたのと同様の薬力学的作用を発揮した。

子宮内膜症

第IV相薬物動態／薬力学試験では、子宮内膜症の臨床徴候／症状（月経困難症、非月経性骨盤痛、骨盤圧痛、骨盤硬化）の緩和において、LUPRON DEPOT -3 Month 11.25 mg（N=21）はLUPRON DEPOT 3.75 mg 1ヶ月製剤（N=20）と同等であることが示された。両治療群において、60日間以上試験に参加した患者の100%で月経抑制が達成された。抑制とは、少なくとも連続60日間、新たな月経がないことと定義されている。

対照臨床試験で、子宮内膜症の臨床徴候／症状（骨盤痛、月経困難症、性交困難、骨盤圧痛、硬化）の緩和、及び腹腔鏡検査で確認された子宮内膜移植サイズの減少において、LUPRON DEPOT 3.75 mg 1ヶ月製剤の6ヶ月間投与はダナゾール800 mg/日と同等であることが示され