SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lutrate 3 month Depot 22.5 mg powder and solvent for prolonged-release suspension for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 22.5 mg of leuprorelin acetate (equivalent to 21.42 mg leuprorelin free base).

1 mL of reconstituted suspension contains 11.25 mg of leuprorelin acetate.

Excipients with known effect:

Each vial contains from 1.6 to 2.7 mg (<1 mmol) of sodium (as carmellose sodium).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

Powder: white to off-white powder.

Solvent: clear, colorless and particle free solution (pH 5.0 – 7.0).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

(i) Metastatic prostate cancer.

(ii) Locally advanced prostate cancer, as an alternative to surgical castration.

(iii) As an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

(iv) As an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.

(v) As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

4.2 Posology and method of administration

Posology

The usual recommended dose of Lutrate 3 month Depot is 22.5 mg presented as a three months depot injection and administered as a single intramuscular injection every three months.

The dose of Lutrate 3 month Depot allowing the continuous release of leuprorelin acetate over a three month period is incorporated in a depot formulation. The lyophilized powder should be reconstituted and administered as a single intramuscular injection every three months. Intraarterial or intravenous administration must be avoided. The vial of Lutrate 3 month Depot microsphere powder should be reconstituted immediately prior to administration by intramuscular injection. As with other drugs administered regularly by injection, the injection site should be varied periodically.

Lutrate 3 month Depot should not be discontinued when remission or improvement occurs.

Response to Lutrate 3 month Depot therapy should be monitored measuring serum levels of testosterone as well as prostate-specific antigen (PSA) periodically. Clinical studies have shown that testosterone levels increased during the first 4 days of treatment in the majority of non-orchiectomized patients. They then decreased and reached castrate levels by 3-4 weeks. Once attained, castrate levels (defined as concentration of testosterone equal or less than 0.5 ng/mL) were maintained as long as drug therapy continued.

If a patient's response appears to be sub-optimal, then it would be advisable to confirm that serum testosterone levels have reached or are remaining at

castrate levels. Transient increases in acid phosphatase levels sometimes occur early in the treatment period but usually return to normal or near normal values by the 4th week of treatment.

Duration of treatment

Lutrate 3 month Depot should be administered every three months as intramuscular injections.

As a rule, prostate cancer therapy with Lutrate 3 month Depot entails long- term treatment and therapy should not be discontinued when remission or improvement occurs.

Special populations

Paediatric population

The safety and efficacy of Lutrate 3 month Depot in the paediatric patients has not been established. Therefore, Lutrate 3 month Depot is not recommended in children or adolescents until safety and efficacy data become available.

Renal/hepatic impairment

The pharmacokinetics of Lutrate 3 month Depot in hepatically and renally impaired patients has not been determined.

Elderly

In the clinical trial for Lutrate 3 month Depot 22.5 mg, the mean age of the subjects studied was 71.0±9.02 years. Therefore, the labelling reflects the pharmacokinetics, efficacy and safety of Lutrate 3 month Depot in this population.

Method of administration

Lutrate 3 month Depot should be prepared, reconstituted and administered only by healthcare professionals who are familiar with these procedures.

Lutrate 3 month Depot must be administered via the intramuscular route only. Do not administer by any other route. If it is administered subcutaneously by mistake, the patient should be closely monitored since no

data about other administration routes apart from intramuscular is available for Lutrate 3 month Depot. For instructions on reconstitution of the medicinal product before administration, see **section 6.6.**

4.3 Contraindications

Hypersensitivity to the active substance, luteinizing hormone releasing hormone (LHRH) analogues or to any of the excipients listed in section 6.1. Reports of anaphylactic reactions to synthetic LHRH or LHRH agonist analogues have been reported in the medical literature.

Previous orchiectomy.

Lutrate 3 month Depot must not be used as the only treatment in patients with prostate cancer and with evidence of spinal cord compression or spinal metastases.

Lutrate 3 month Depot is not indicated for use in women.

Lutrate 3 month Depot is not indicated for use in paediatric patients.

4.4 Special warnings and precautions for use

Lutrate 1 month Depot injectable suspension must be prepared at the time of use and, after reconstitution, used immediately

Treatment should be discontinued immediately if the patient develops any signs or symptoms suggestive of anaphylaxis/anaphylactic reaction (dyspnoea, asthma, rhinitis, angioneurotic oedema or glottis, hypotension, urticaria, rash, pruritus or interstitial pneumonitis). Patients should be informed before starting treatment, warning them to discontinue it and consult their doctor if any of the above mentioned symptoms occur. Patients who have experienced a hypersensitivity reaction to leuprorelin should be closely monitored and should not be rechallenged with Lutrate 1 month Depot.

Seizures have been reported with the administration of leuprorelin acetate. These cases were observed in patients with a history of seizures, epilepsy, cerebrovascular disorders, anomalies or central nervous system tumours and in patients with concomitant medications that have been associated with seizures for example bupropion and selective inhibitors of serotonin reuptake (SSRIs). Seizures in patients in the absence of the any medical conditions mentioned above have also been reported.

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as leuprorelin acetate. Patients should be informed accordingly and treated as appropriate if symptoms occur.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving leuprorelin. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of leuprorelin should be considered.

Adults

Epidemiological data have shown that during androgen deprivation therapy changes in the metabolic condition (e.g. reduction in glucose tolerance or aggravation of pre-existing diabetes) as well as an increased risk for cardiovascular diseases may occur. However, prospective data did not confirm the link between treatment with GnRH analogues and an increase in cardiovascular mortality. Patients at high risk for metabolic or cardiovascular diseases should be appropriately monitored. Diabetic patients may require more frequent monitoring of blood glucose during treatment with Lutrate 1 month Depot.

Hepatic dysfunction and jaundice with elevated liver enzyme levels have been reported with the use of leuprorelin acetate. Therefore, close observation should be made and appropriate measures taken if necessary.

Fractured spine and paralysis have been reported with leuprorelin treatment

Sportsmen should take precaution as Lutrate 1 month Depot contains an ingredient which may give a positive test result in doping controls.

Men

In the initial stages of Lutrate 1 month Depot treatment, as occurs during treatment with other GnRH agonists, a transient rise in levels of testosterone may occur. In some cases, this may be associated with a "flare" or exacerbation of the tumour growth resulting in temporary worsening of prostate cancer symptoms. These symptoms usually subside on continuation of therapy (see **section 4.8**). "Flare" may manifest itself as systemic or neurological symptoms in some cases (i.e. bone pain). In order to reduce the risk of “flare”, an anti-androgen may be administered beginning 3 days prior to leuprorelin acetate therapy and continuing for the first two to three weeks of treatment. This has been reported to prevent the sequelae of an initial rise in serum testosterone. Also, cases of orchiatrophy and gynecomastia have been described with other GnRH agonists.

In patients treated with leuprorelin acetate, isolated cases of urethral obstruction (with or without haematuria) and spinal cord compression or metastatic vertebral lesions have been observed, which may contribute to paralysis with or without fatal complications. Patients at risk of urethral obstruction, spinal cord compression or metastatic vertebral lesions should be considered carefully and closely supervised in the first few weeks of treatment. These patients should be considered for prophylactic treatment with anti-androgens.

Should urological/neurological complications occur, these should be treated by appropriate specific measures.

Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LHRH agonist. Adding anti-androgenic therapy to the treatment regimen reduces bone loss, but increases the risk of other adverse effects such as clotting problems and oedema. If an anti-androgen is used over a prolonged period, due attention should be paid to the contraindications and precautions associated with its extended use. Patients at risk or with a medical history of osteoporosis should be considered carefully and closely supervised during treatment with leuprorelin acetate (see **section 4.8**).

Response to Lutrate 1 month Depot therapy should be monitored by clinical parameters and by measuring testosterone and PSA serum levels periodically.

Patients may experience metabolic changes (e.g. glucose intolerance or worsening of existing diabetes), hypertension, weight changes and cardiovascular disorders. As would be expected with this class of drug, development or aggravation of diabetes may occur, therefore diabetic patients may require more frequent monitoring of blood glucose during treatment with Lutrate 1 month Depot. Patients at high risk for metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy. Therapy with leuprorelin acetate results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after leuprorelin acetate therapy may be affected.

Increased prothrombin time has been reported in patients under treatment with leuprorelin acetate.

Leuprorelin acetate should be used with precautions in the presence of, cardiovascular disease (including congestive heart failure condition), thromboembolism, oedema, depression and pituitary adenomas.

Leuprorelin acetate should be used with caution in patients with known bleeding disorders, thrombocytopenia or on treatment with anticoagulants.

Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Lutrate 1 month Depot.

Women:

Before starting treatment with leuprorelin acetate, pregnancy must be excluded (see section 4.3).

Since menstruation should stop with effective doses of Lutrate 1 month Depot, the patient should notify her physician if regular menstruation persists.

During treatment with leuprorelin acetate patients should be instructed to prevent conception e.g. with the use of non-hormonal methods until return of menses."

Abnormal bleeding

Prior to administration of Lutrate 1 month Depot, undiagnosed vaginal bleeding must be investigated, diagnosis confirmed and relevant management initiated.

Initial increase in sex steroids
During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiological 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.

Uterine fibroid diagnosis
In the case of uterine fibroids, it is mandatory to confirm the diagnosis of fibroids and exclude an ovarian mass, either visually by laparoscopy or by ultrasonography or other investigative techniques as appropriate, before Lutrate 1 month Depot therapy is instituted.

Uterine fibroids
In women with submucous fibroids there have been reports of severe vaginal bleeding following administration of leuprorelin as a consequence of the acute degeneration of the fibroids. Patients should be warned of the possibility of abnormal bleeding or pain in case earlier surgical intervention is required.

Cervical Resistance
Lutrate 1 month Depot may cause an increase in uterine cervical resistance, which may result in difficulty in dilating the cervix for intrauterine surgical procedures.

Bone density in patients with endometriosis or uterine fibroids
The induced hypo-estrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible. The extent of bone demineralisation due to hypo-estrogenaemia is proportional to time and, consequently, is the event responsible for limiting the duration of therapy to 6 months. The generally accepted level of bone loss with LHRH analogues such as Lutrate 1 month Depot is 5%. In clinical studies the levels varied between 2.3% and 15.7% depending on the method of measurement. During one 6 month treatment period, this bone loss should not be important. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, Lutrate 1 month Depot therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with Lutrate 1 month Depot is instituted.

In women receiving GnRH analogues for the treatment of uterine fibroids, the duration of administration of leuprorelin acetate should be limited to 6 months, as its use is associated with an increased risk of bone mineral loss (see *Bone density*, section 4.4). If it is necessary to resume administration of leuprorelin acetate, changes in bone parameters should be closely followed

Endometriosis
In women receiving GnRH analogues for the treatment of endometriosis, the duration of administration of leuprorelin acetate should be limited to 6 months, as its use is associated with an increased risk of bone mineral loss.

In women receiving GnRH analogues, the addition of HRT (an estrogen and progestogen) has been shown to reduce bone mineral density loss and vasomotor symptoms. Therefore, if appropriate, HRT may be co-administered with leuprorelin acetate, taking into account the risks and benefits of each medicinal product, for up to

12 months if clinically appropriate. If it is necessary to resume administration of leuprorelin acetate, changes in bone parameters should be closely followed.

Advanced and early breast cancer:
In order to ensure adequate ovarian suppression in pre- and perimenopausal women, treatment with leuprorelin should be administered for at least 6-8 weeks prior to commencement of an aromatase inhibitor, and monthly leuprorelin injections should be administered on schedule and without interruption throughout aromatase inhibitor treatment.

Women who are premenopausal at breast cancer diagnosis and who become amenorrhoeic following chemotherapy may or may not have continued estrogen production from the ovaries. Irrespective of menstrual status, premenopausal status should be confirmed following chemotherapy and before commencement of leuprorelin, by blood concentrations of estradiol and FSH within the reference ranges for premenopausal women, in order to avoid unnecessary treatment with leuprorelin in the event of a chemotherapy-induced menopause.

Following commencement of leuprorelin, it is important to confirm adequate ovarian suppression (gonadotrophin analogue induced menopause) by serial assessment of circulating FSH, and estradiol if this subset of women is to be considered for therapy with an aromatase inhibitor, in accordance with current clinical practice recommendations. Accordingly, ovarian suppression should be confirmed by low blood concentrations of FSH and estradiol prior to starting aromatase inhibitor treatment and measurements should be repeated every three months during combination therapy with leuprorelin and an aromatase inhibitor. This is to avoid aromatase inhibitor-induced rebound increase in circulating estrogen, with consequential implications for the breast cancer. Of note, circulating FSH levels are lowered in response to gonadotrophin analogue-induced ovarian suppression (induced menopause), unlike in a natural menopause where FSH levels are elevated.

Patients who have discontinued leuprorelin treatment should also discontinue aromatase inhibitors within 1 month of the last leuprorelin administration.

Particular attention should also be paid to the prescribing information of co-administered medicinal products, such as aromatase inhibitors, tamoxifen, CDK4/6 inhibitors, for relevant safety information when administered in combination with leuprorelin.

Bone mineral density should be assessed before starting treatment with leuprorelin, particularly in women who have additional risk factors for osteoporosis. These patients should be closely monitored and treatment for, or prophylaxis of, osteoporosis should be initiated when appropriate.

The risk of musculoskeletal disorders (including joint or musculoskeletal pain) when a GnRH agonist is used in combination with either an aromatase inhibitor or tamoxifen is approximately 89% with the aromatase inhibitor and approximately 76% with tamoxifen.

Hypertension has been reported as a targeted adverse event at a very common frequency with GnRH agonist in combination with either exemestane or tamoxifen.

Premenopausal women with breast cancer receiving GnRH agonist in combination with either exemestane or tamoxifen should have regular monitoring of cardiovascular risk factors and blood pressure.

Hyperglycaemia and diabetes were reported as targeted adverse events at a common frequency with a GnRH agonist in combination with either exemestane or tamoxifen. Premenopausal women with breast cancer receiving a GnRH agonist in combination with either exemestane or tamoxifen should have regular monitoring of risk factors for diabetes with blood glucose monitoring on a regular basis and appropriate anti-diabetic treatment initiated, if appropriate, according to national guidelines.

Depression has been reported to occur in approximately 50% of patients treated with a GnRH agonist in combination with either tamoxifen or exemestane, but less than 5% of patients had severe depression (grade 3-4). Patients should be informed accordingly and treated as appropriate if symptoms occur. Patients with known depression or depression history should be carefully monitored during therapy.

Treatment of premenopausal women with endocrine responsive early stage breast cancer with leuprorelin in combination with tamoxifen or an aromatase inhibitor should follow a careful individual appraisal of the risks and benefits.

In girls with central precocious puberty:

Before starting the therapy, a precise diagnosis of idiopathic and/or neurogenic central precocious puberty is necessary. In girls, pregnancy must be excluded (see section 4.3).

The therapy is a long-term treatment, adjusted individually. Lutrate 1 month Depot should be administered as precisely as possible in regular monthly periods. An exceptional delay of the injection date for a few days (30 ± 2 days) does not influence the results of the therapy.

In the event of a sterile abscess at the injection site (mostly reported after i.m. injection of higher than the recommended dosage) the absorption of leuprorelin acetate from the depot can be decreased. In this case the hormonal parameters (testosterone, oestradiol) should be monitored at 2-week intervals (see section 4.2).

The treatment of children with progressive brain tumours should follow a careful individual appraisal of the risks and benefits.

The occurrence of vaginal bleeding, spotting and discharge after the first injection may occur as a sign of hormone withdrawal in girls. Vaginal bleeding beyond the first/second month of treatment needs to be investigated.

Bone mineral density (BMD) may decrease during GnRHa therapy for central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.

Slipped femoral epiphysis can be seen after withdrawal of GnRHa treatment. The suggested theory is that the low concentrations of estrogen during treatment with GnRH agonists weakens the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium- free’.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprorelin acetate. However, because leuprorelin 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, pharmacokinetic drug interactions would not be expected to occur.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Lutrate 3 month Depot with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, Pregnancy and lactation

Pregnancy:

Lutrate 3 month Depot is not indicated for use in pregnant women.

Leuprorelin acetate injection may cause foetal harm when administered to a pregnant woman.

Therefore, spontaneous abortion may occur if the drug is administered during pregnancy.

Breast-feeding:

Lutrate 3 month Depot should not be used in women who are breast-feeding.

Fertility:

Studies in animals have shown reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

No specific studies on the effects of Lutrate 3 month Depot on the ability to drive and use machines have been performed. However, the ability to drive and use machines may be impaired due to visual disturbances and dizziness.

4.8 Undesirable effects

Adverse reactions seen with Lutrate 1 month Depot are due mainly to the specific pharmacological action, namely increases and decreases in certain hormone levels.

Men:
Unless otherwise specified, the following safety profile of Lutrate 1 month Depot is based on the results of a phase III clinical trial in which prostate cancer patients were treated with six intramuscular monthly doses of Lutrate 1 month Depot and followed up for total a period of 26 weeks. Most of the treatment-related AEs reported were the usual ones associated with testosterone suppressing therapy.

The most commonly reported adverse reactions with Lutrate 1 month Depot are hot flushes, injection site pain, injection site irritation, night sweats and headache.

The following adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥ 1/1,000 to < 1/100 and not known (cannotbe estimated from the available data)).

Table 1. Number and frequency of ADRs during Lutrate 1 month Depot 3.75 mg therapy.

SOC	Very common	Common	Uncommon	Not known
Metabolism and nutrition disorders		Increased appetite	Anorexia, hypercholesterolemia, hyperlipidemia	
Psychiatric disorders			Sleep disorders, insomnia, libido decreased, mood changes and depression*	
Nervous system disorders		Headache	Somnolence	Idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Hot flush			
Gastrointestinal disorders			Abdominal pain lower, diarrhea, nausea, vomiting	
Hepatobiliary disorders			Hyperbilirubinaemia	
Skin and subcutaneous tissue disorders		Hyperhidrosis, night sweats, cold sweats	Periorbital edema, urticaria, pruritus	
Musculoskeletal, connective tissue and bone disorders		Back pain	Arthralgia, muscle spasms, pain in extremity	

SOC	Very common	Common	Uncommon	Not known
Renal and urinary disorders			Urinary retention, urinary incontinence, pollakiuria	
Respiratory, thoracic and mediastinal disorders				Interstitial lung disease
Reproductive system and breast disorders		Erectile dysfunction	Breast swelling, breast tenderness, ejaculation failure	
Cardiovascular disorders				QT prolongation (see sections 4.4 and 4.5).
General disorders and administration site conditions		Fatigue, asthenia, pyrexia, local adverse reactions (see table 2)	Weakness, feeling hot and cold, feeling jittery	
Investigations			Increased AST, increased ALT, bilirubin increased, gamma-glutamyltransferase increased	

* In a post-marketing study the frequency of mood changes and depression in long term users was common.

In terms of severity, 98% of all treatment-related AEs were mild or moderate. Eighty-nine percentage (89%) of the hot flushes were reported as mild and nine percentage (9%) as moderate. Two cases of hot flushes (0.2%) were reported as severe.

A total of 35 local adverse reactions (LAR) at the injection site were reported by 29 patients (18.1%) during the study.

Local adverse reactions after Lutrate 1 month Depot 3.75mg are those typically reported with other similar products administered via intramuscular injection. Injection site pain, injection site irritation, injection site discomfort, injection site bruising and erythema were the most commonly reported. Uncommonly reported reactions were injection site reaction, swelling, injury and haemorrhage (Table 2)

Table 2. Frequency of patients with local adverse reactions during Lutrate 1 month Depot therapy.

Primary SOC* **PT: General disorders and administration site conditions**	**Patients with related LAR** **%**

Common	
Injection site pain	8.1

Injection site irritation	4.4
Injection site discomfort	1.9
Injection site erythema	1.3
Injection site bruising	1.3
Uncommon	
Injection site reaction	0.6
Injection site swelling	0.6
Injection site injury	0.6
Injection site hemorrhage	0.6

*Subjects may fall into more than one category; LAR: local adverse reaction; SOC: SystemOrgan Class.

In the presence of repeated administrations of Lutrate 1 month Depot, swelling (0.6%), pain (0.6%), bruising (0.6%) and irritation (0.6%) were reported as recurrent local adverse reactions. These events were all reported as not serious and mild. No patient discontinued therapy due to local adverse events.

In a phase I clinical trial (CRO-02-43) carried out in healthy subjects with Leuprolide Depot GP-Pharm 7.5 mg administered at single dose, one case of injection site induration was reported.

Other adverse events which have been reported to occur with leuprorelin acetate treatment include impotence, decrease in libido (both pharmacological consequences of testosterone deprivation), peripheral oedema, pulmonary embolism, palpitations, myalgia, muscle weakness, chills, dyspnoea, peripheral vertigo, rash, amnesia, visual disturbances , skin sensation, anaemia, hypersensitivity reactions (including rash, pruritus, urticaria, wheezing, fever, chills and anaphylactic reactions), weight fluctuation, decreased appetite, dizziness, parasthesiae, paralysis (see Section 4.4), seizure, hypertension, hypotension (see Section 4.4 and 4.5), hepatic function abnormal, hepatic function test abnormal (usually transient), bone pain, weakness of lower extremities, spinal fracture , reduction in bone mineral density, osteoporosis (including spinal fracture, see Section 4.4), urinary tract obstruction, testicular atrophy and gynaecomastia. Pituitary apoplexy has been reported following initial administration in patients with pituitary adenoma Infarction of pre-existing pituitary adenomas has been reported rarely after administration of both short and long acting LHRH agonists. There have been rare reports of thrombocytopenia and leucopoenia. Metabolic syndrome (including hypertension, dyslipidemia, insulin resistance, abnormal glucose tolerance)

Women

Those adverse events occurring most frequently with leuprorelin 1 month Depot are associated with hypo-estrogenism; the most frequently reported are hot flushes, mood swings including depression (occasionally severe), and vaginal dryness.

Estrogen levels return to normal after treatment is discontinued.

The induced hypo-estrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible (see **section 4.4**).

Vaginal haemorrhage may occur during therapy due to acute degeneration of submucous fibroids (see section 4.4).

The following adverse reactions from clinical investigations were listed below by

system organ class and in order of decreasing incidence (very common: ≥1/10;

common: ≥1/100 to <1/10; uncommon: ≥ 1/1,000 to < 1/100, very rare≥ 1/10,000 to <1/1,000 and not known (cannot be estimated from the available data)).

Table 3: Number and frequency of ADRs during leuprorelin 1 month Depot therapy in women.

SOC	Very common	Common	Uncommon	Very rare	Not known
Blood and lymphatic system disorders					anemia (reported in medicinal products of this class), thrombocytopenia, leucopenia
Immune system disorders					hypersensitivity reactions (including rash, pruritus, urticaria and rarely, wheezing and interstitial pneumonitis, anaphylactic reactions)
Metabolism and nutrition disorders		weight fluctuation	decreased appetite, lipids abnormal		Metabolic syndrome (including hypertension, dyslipidemia, insulin resistance, abnormal glucose tolerance)
Psychiatric disorders	insomnia	mood changes (long term use)** depression (see section 4.4)	mood changes (short term use)**		
Nervous system disorders	headache (occasionally severe)	paresthesia, dizziness		pituitary hemorrhage, pituitary apoplexy has been reported following initial administration in patients with pituitary adenoma	paralysis (see section 4.4), seizure Idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)
Eye disorders			visual impairment		
Cardiac disorders			palpitations		
Vascular disorders	hot flush				pulmonary embolism, hypertension, hypotension (see section 4.4)

SOC	Very common	Common	Uncommon	Very rare	Not known
Gastrointestinal disorders		nausea	diarrhea, vomiting		
Hepatobiliary disorders			liver function test abnormal (usually transient)		hepatic function abnormal, jaundice
Skin and subcutaneous tissue disorders		hyperhidrosis	hair loss		
Musculoskeletal, connective tissue and bone disorders	Bone pain	arthralgia, muscle weakness	myalgia		spinal fracture (see section 4.4), reduction in bone mass which may occur with the use of GnRH agonists
Respiratory, thoracic and mediastinal disorders					Interstitial lung disease
Reproductive system and breast disorders		breast tenderness, breast atrophy, vulvovaginal dryness			vaginal haemorrhage, libido decreased
General disorders and administration site conditions		edema peripheral, injection site reaction e.g. injection site induration, erythema, pain abscesses, swelling, nodules, ulcers and necrosis	pyrexia, fatigue		

In women with early breast cancer treated with a GnRH agonist in combination with tamoxifen or an aromatase inhibitor, the following side effects have been seen:

Very common: Nausea, fatigue, musculoskeletal disorders, osteoporosis, hot flushes, hyperhidrosis, insomnia, depression, libido decreased, vulvovaginal dryness, dyspareunia, urinary incontinence, hypertension.

Common: Diabetes mellitus, hyperglycaemia, injection site reaction, hypersensitivity fracture, embolism.

Uncommon: myocardial ischaemia, cerebral ischaemia, central nervous system haemorrhage.

Rare: QT prolongation

Children:
In the initial phase of therapy, a short-term increase as flare-up of the sex hormone level occurs, followed by a decrease to values within the pre-pubertal range. Due to this pharmacological effect, adverse events may occur particularly at the beginning of treatment.

The following adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence (common: ≥1/100 to <1/10; uncommon: ≥ 1/1,000 to < 1/100, very rare: ≥ 1/10,000 to < 1/1,000 and not known (cannot be estimated from the available data)).

Table 4: Number and frequency of ADRs during leuprorelin 1 month Depot therapy in pediatrics.

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Psychiatric disorders		Depression (see section 4.4), emotional lability				
Nervous system disorders		headache			As with other medicinal products of this class, very rare cases of pituitary apoplexy have been reported following initial administration in patients with pituitary adenoma, pituitary haemorrhage.	Seizure Idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)
Gastrointestinal disorders		abdominal pain / abdominal cramps, nausea/vomiting				
Skin and subcutaneous tissue disorders		acne				

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Respiratory, thoracic and mediastinal disorders						interstitial lung disease
Reproductive system and breast disorders		vaginal bleeding, spotting, vaginal discharge**				
General disorders and administration site conditions		injection site reactions (e.g. induration, erythema, pain, abscess, swelling, nodules and necrosis)				
Immune system diseases and symptoms					general allergic reactions (fever, rash, e.g. itching, anaphylactic reactions	

** In general, the occurrence of vaginal spotting with continued treatment (subsequent to possible withdrawal bleeding in the first month of treatment) should be assessed as a sign of potential underdosage. The pituitary suppression should then be determined by an LHRH test

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the MHRA yellow card scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no clinical experience with the effects of an acute overdose of Lutrate 3 month Depot or leuprorelin acetate. In clinical trials using daily subcutaneous leuprorelin acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no AEs differing from those observed with the 1 mg/day dose.

In animal studies, doses of up to 500 times the recommended human dose resulted in dyspnoea, decreased activity and local irritation at the injection site. In cases of overdosage, the patient should be monitored closely and management should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy. Hormones and related agents. Gonadotropin-releasing hormones analogues; ATC code: L02AE02.

Mechanism of action

The chemical name of Leuprorelin acetate is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-L-prolyl-ethylamide.

Leuprorelin acetate is inactive when given orally due to poor membrane permeability and an almost complete inactivation by intestinal proteolytic enzymes.

Leuprorelin acetate has potent LHRH agonist properties when given during short-term and intermittent therapy, however, when administered in a continuous, nonpulsatile manner, LHRH analogs induce inhibition of gonadotropin secretion and suppression of testicular steroidogenesis

Pharmacodynamic effects

Upon binding to pituitary LHRH receptors, leuprorelin acetate produces an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to an acute rise in levels of testosterone and dihydrotestosterone. However, within five to eight days after drug administration, LHRH analogs produce desensitization of the LHRH receptor complex and/or downregulation of the anterior pituitary gland. Due to the fact that there are fewer receptors on the cell surface, cellular stimulation is decreased, and less gonadotropin is synthesized and secreted. Eventually, after several weeks of LHRH agonist therapy, LH and FSH secretion is suppressed. As a result, Leydig cells in the testes cease to produce testosterone, and the serum testosterone concentration declines to a castration level (less than 0.5 ng/mL) in about two to four weeks after initiation of treatment.

Clinical efficacy and safety

In an open-label, multicenter, multiple dose clinical study of Lutrate 3 month Depot 22.5 mg, 163 patients with prostate cancer, were enrolled. The objectives were to determine the efficacy and safety of Lutrate 3 month Depot when given to prostate cancer patients who could benefit from androgen deprivation therapy. Lutrate 3 month Depot was administered intramuscularly in 2 doses with a 3-month interval.

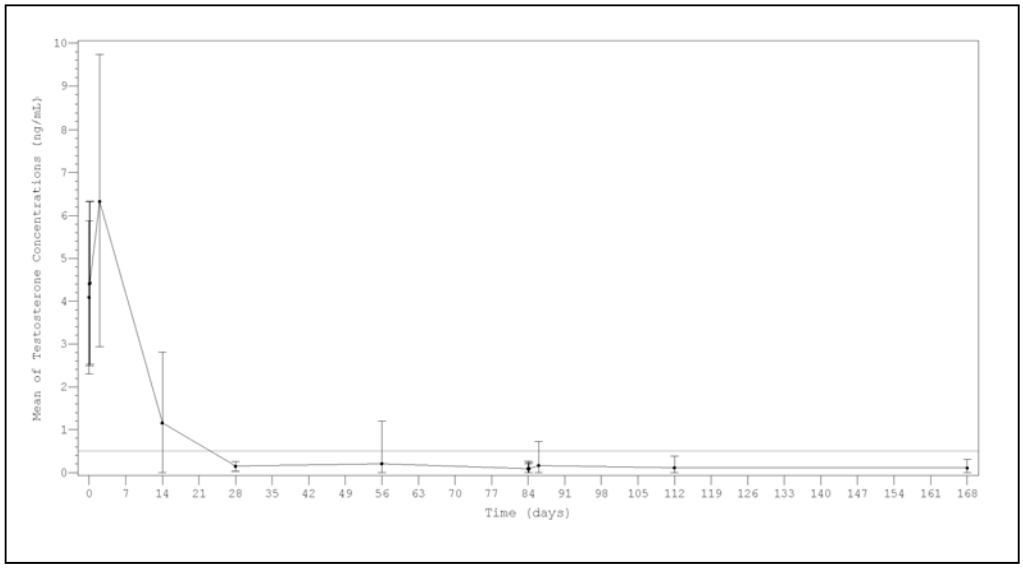
Testosterone levels were monitored at different days during 168 days. Testosterone sampling schedule was at days 0 (1 and 4 hrs), 2, 14, 28, 56, 84 pre-dose, 84 (1h and 4 hrs), 86, 112 and 168. Primary end point was defined as testosterone values $\leq$ 0.5 ng/mL and no missing data assessed at days 28, 84 and 168. For each patient, if testosterone was greater than 0.5 ng/mL or if testosterone data were missing at any of the key time points (ie, Days 28, 84, and 168), the patient was classified as a failure, unless the missing data were due to an event, such as death, unrelated to study drug. Specifically, if at any key time point (Days 28, 84, and 168) missing data were due to an AE related to study drug or treatment, the patient was classified as a failure.

After the first injection the mean testosterone levels rapidly increased from baseline levels (4.09±1.79 ng/mL), reaching peak levels (C_{max}) of 6.33±3.40 ng/mL at the second day. After peaking, testosterone levels fell, and 98.8% (159/161) of the

evaluable patients achieved medical castration at day 28 (defined as testosterone less than 0.5 ng/mL). Additionally, at this time, 77.0% of patients achieved the more stringent criterion of testosterone $\leq$ 0.2 ng/mL. (Figure 1). At day 168, 99.4% of evaluable patients (150/151) presented testosterone level below 0.5 ng/mL and 90.7% were below $\leq$ 0.2 ng/mL.

According to the primary endpoint definition (see definition above) the rate of patients maintaining castration throughout the study was 98.1% (158/161).

Figure 1. Mean (±SD) testosterone plasma levels during two sequential IM doses of Lutrate 3 month Depot 22.5 mg with a 3-month interval



Results from a sensitivity analysis performed considering either single testosterone escapes or missing data as failures, showed castration rates around or above 92% at every time point (Day 28, 97.5% (157/161); Day 56, 93.2% (150/161); Day $84_{predose,}$ 96.9% (156/161); Day $84_{1hour\ post\text{-}dose}$ 91.9% (148/161); Day $84_{4hour\ post\text{-}dose}$ 91.9% (148/161); Day 86 93.8% (151/161); Day 112 92.5% (149/161) and Day 168 93.2% (150/161)).

The frequency of escapes just after the second administration was 6.8% (11/161) and the frequency of testosterone breakthrough response was 6.2% (10/161). None of the transient escapes was associated with LH increase, clinical symptoms or PSA raises.

No drug-related adverse events suggestive of a clinical testosterone flare (urinary retention, spinal cord compression, or exacerbation of bone pain) were reported in any of the patients showing a testosterone breakthrough effect.

Secondary efficacy endpoints included determination of serum LH, FSH and PSA concentrations. By day 14 after the first Lutrate 3 month Depot injection, mean LH and FSH serum levels had decreased below the baseline concentrations. Concentrations remained well below baseline values from day 28 until the end of the study. During the treatment, median PSA serum levels gradually decreased (first month) and then remained constantly below baseline level until the end of the study. However, as expected a wide and expected inter-individual variation in PSA concentrations was observed throughout the study.

5.2 Pharmacokinetic properties

Absorption

Following two sequential injections of Lutrate 3 month Depot administered with a 3-month interval, maximal leuprorelin acetate plasma concentration observed in a sample of prostate cancer patients (N=30) was similar among the two cycles. After first administration (Days 0-84), C_{max} was 46.79±18.008 ng/mL. Mean time to achieve C_{max} (T_{max}) was 0.07 days, corresponding to 1.68 h (range 1.008 – 4.008 h).

Distribution

No drug distribution study was conducted with Lutrate 3 month Depot. However, in healthy male volunteers, the mean steady-state volume of distribution of leuprorelin acetate following bolus intravenous (IV) 1.0 mg dose was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

Elimination

No drug metabolism or excretion studies were conducted with Lutrate 3 month Depot.

Leuprorelin is expected to be metabolised to smaller inactive peptides that may be excreted or further catabolised.

In healthy male volunteers, a 1.0 mg bolus of leuprorelin acetate administered IV 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.

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

Special Populations

Renal/hepatic impairment

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity conducted with leuprorelin acetate.

As expected from its known pharmacological properties, non-clinical studies showed effects on the reproductive systems, which were reversible. In the reproductive toxicity studies, leuprorelin acetate did not show teratogenicity. However, embryotoxicity/lethality was observed in rabbits.

Carcinogenicity studies performed in rats with leuprorelin acetate administered subcutaneously (0.6 to 4 mg/kg/day), showed a dose-related increase in pituitary adenomas. Furthermore a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males was observed, the highest incidence was in the low dose group. Administration of

leuprorelin acetate resulted in inhibition of the growth of certain hormone dependent tumours (prostatic tumours in Noble and Dunning male rats and DMBA-induced mammary tumours in female rats). No such effects were observed in carcinogenicity studies performed in mice. No carcinogenicity studies have been conducted with Lutrate 3 month Depot.

Studies with leuprorelin acetate showed that the product was not mutagenic in a set of in vitro and in vivo assays. No mutagenicity studies have been conducted with Lutrate 3 month Depot.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients of the lyophilizate (vial):

Polysorbate 80

Mannitol (E-421)

Carmellose sodium (E-466)

Triethyl citrate

Poly (lactic acid) (PLA)

Excipients of the solvent (prefilled syringe):

Mannitol (E-421)

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

No other solvent other than the sterile solvent provided for Lutrate 3 month Depot can be used for the reconstitution of Lutrate 3 month Depot powder.

6.3 Shelf life

36 Months unopened.

Once reconstituted with the solvent the suspension obtained should be administered immediately.

6.4 Special precautions for storage

Do not store above 25º C. Do not freeze.

6.5 Nature and contents of container

The commercial kit includes:

1. One (1) type I glass vial containing 22.5 mg of leuprorelin acetate as a freeze-dried powder, sealed with an elastomeric stopper and an aluminium cap with plastic flip-off.
2. One (1) type I glass prefilled syringe containing 2 mL of solvent sealed with an elastomeric cap.
3. One (1) polycarbonate / HDPE adaptor system including one (1) sterile 20 gauge needle.

6.6 Special precautions for disposal

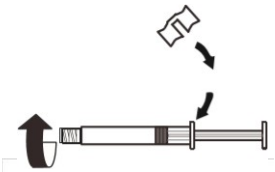
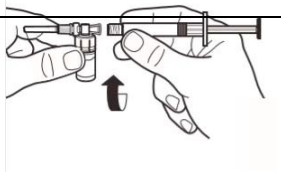
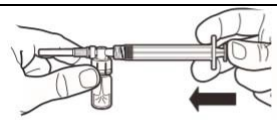
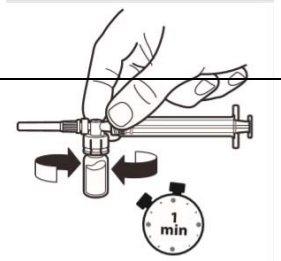
Method of administration

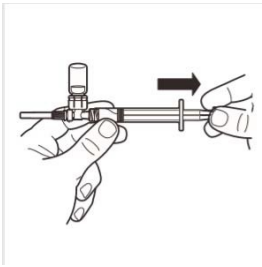
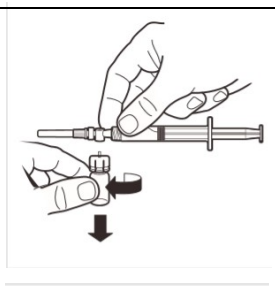
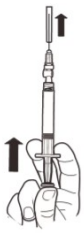
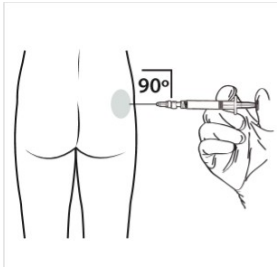
The vial of Lutrate 3 month Depot should be reconstituted immediately prior to administration by single intramuscular injection. Make sure an aseptic technique is followed.

The reconstituted product is a suspension of milky, white colour appearance. **Use the solvent included in the kit. No other solvent can be used for reconstitution of Lutrate 3 month Depot.**

The product is meant for a single injection. Any remaining suspension mustbe discarded.

Reconstitute Lutrate 3 month Depot according to the following instructions. Read carefully before administering the product:

1 	Totally remove the Flip-Off cap from the top of the vial, revealing the rubber stopper. Confirm that no parts of the flip-off cap remain on the vial.
2 	Place the vial in a standing upright position on a table. Peel the cover away from the blister pack containing the vial adapter (MIXJECT). **Do not remove the vial adapter from the blister pack**. Place the blister pack containing the vial adapter firmly on the vial top, **piercing the vial in a totally vertical position. Push down gently until you feel it snap in place**.
3 	Affix the white finger-grip to the syringe **until it snaps. Unscrew** the **rubber cap from the syringe counter-clockwise.** Then, **remove the blister pack from the MIXJECT**
4 	Connect the syringe to the vial adapter by screwing it clockwise into the opening on the side of the vial adapter. **Gently twist the syringe until it stops turning to ensure atight connection.**
5  	While keeping the syringe and vial securely coupled in an upright position, slowly push the plunger to **transfer all thediluent into the vial**.
6	With the syringe still coupled to the vial, **shake the vial gently for approximately one minute until a uniform milky-white suspension is obtained.** To avoid separation of the suspension, **proceed to the next steps without delay.**

7		Invert the MIXJECT system so that the vial is at the top. Grasp the MIXJECT system firmly by the syringe and pull back the plunger rod slowly to draw the reconstituted product into the syringe. Some product may cake or clump at the vial wall. This is considered normal.
8		Disconnect the vial adapter from the MIXJECT-syringe assembly: Grab firmly the syringe and turn the vial (grasping the plastic cap of the adapter) clockwise.
9		Keep the syringe UPRIGHT. With the opposite hand pull the needle cap upward. Advance the plunger to expel the air from the syringe. **The syringe containing** the product is ready for **immediate administration.**
10		Administer the intramuscular injection by inserting theneedle at a 90-degree angle into the gluteal area. **Ensure** that the **full amount of the product is injected**.Injection sites should be alternated.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Merixil Pharma
Office No 28, 2nd Floor, Rose Plaza
I-8 Markaz, Islamabad.

MANUFACTURED BY

GP-PHARM, S.A.
Poligono Industrial Els Vinyets –els Fogars. Sector 2
Carretera comarcal 244, km22

08777 Sant Quintí de Mediona,Barcelona,
Spain.

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OFTHE AUTHORISATION

Date of first Registration / Market Authorization:15th Dec 2017Date of latest renewal: 14th Dec 2027

10 DATE OF REVISION OF THE TEXT