TAPROS ® DEPOT 3.75 mg
LEUPRORELIN ACETATE

1 NAME OF THE MEDICINAL PRODUCT

TAPROS ® DEPOT 3.75 mg

2 COMPOSITION

Each vial contains 3.75 mg Leuprorelin Acetate
For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White powder and clear, colorless solvent for suspension for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of prostatic cancer with metastase.
- Treatment of endometriosis at genital and extragenital localization (from stage I to stage IV).
  The clinical knowledge concerning the endometriosis treatment is limited to women over 18 years old.
  The treatment duration is limited to 6 months.
- Pre-operative management of uterine myoma (fibroid) to reduce their size and associated bleeding.
- Treatment of central precocious puberty.
- Breast cancer in pre-menopausal and peri-menopausal women, provided endocrine treatment is indicated.

It is not recommended to start a second treatment period with Tapros or with another Gn-RH analogue.

4.2 Posology and method of administration

- Prostatic cancer and breast cancer
  One subcutaneous injection which will be renewed every four weeks.
- Endometriosis
  Usually, for adults, 3.75 mg of leuprorelin acetate is administered subcutaneously or intramuscularly once every 4 weeks for a period of 6 months only.
  However, when the patient's weight is less than 50 kg, 1.88 preparation may be used.
  The treatment should start during the five first days of the menstrual cycle.

- Uterine myoma (fibroid)
  One subcutaneous or intramuscular injection will be renewed every 4 weeks.
  The treatment should start during the five first days of the menstrual cycle.

- Central precocious puberty
  Usually, a dose of 30 µg/kg administer subcutaneously once every 4 weeks. Depending upon the patient's condition, the dosage may be increased up to 90 µg/kg.
  The safety of Tapros in prematures, newborns, and nursing infants has not been established.

4.3 Contraindications

<u>All patient populations</u>

- Hypersensitivity to Gn-RH, to Gn-RH analogues or to one of the components.

All females (adult and pubescent pediatric females)

- Vaginal bleedings of non determined origin.
- Pregnancy. Do not use when pregnancy. The non pregnancy must be confirmed before treatment.
- Nursing. Because of the lack of data regarding TAPROS excretion in milk and its potential effects on nursing mothers, TAPROS will not have to be used in this case.

4.4 Special Warnings and Precautions for use

All patient populations

Since Tapros is a sustained release preparation with its action lasting 4 weeks, administration at an interval exceeding 4 weeks may lead to the recurrence of an increase in the serum level of gonadotropic hormone due loss of suppression of to the pituitary-gonad system , resulting in a transient aggravation of the clinical condition. Therefore, the method of administering once every 4 weeks should be observed.

Seizures:

Postmarketing reports of seizures have been observed in patients treated with leuprorelin acetate and these events have been reported in both children and adults, and in those with or without a history of epilepsy, seizure disorders or risk factors for seizures.

Depression

There is an increased risk of depression in patients undergoing treatment with leuprorelin acetate and patients should be monitored as appropriate.

All adult populations

Bone mineral loss

Long-term estrogen deprivation by bilateral oophorectomy, ovarian ablation or administration of GnRH analogues or long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone mineral loss which, in patients with additional risk factors, may lead to osteoporosis and increased risk of bone fracture (see Undesirable Effects, 4.8).

Metabolic changes and cardiovascular risk

Inhibition of endogenous sex hormone production, such as during androgen deprivation therapy (as identified from epidemiological data) or estrogen deprivation (e.g. in menopausal females), is associated with metabolic changes (e.g. reduction in glucose tolerance or aggravation of pre-existing diabetes) as well as an increased risk for cardiovascular disease (see Undesirable Effects, 4.8). However, prospective data did not confirm a 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.

All females (adult and pubescent pediatric females)

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

Adult females

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

Endometriosis, Uterine myoma (fibroid), Breast cancer indications

In the early period after first administration of this medicinal product, transient aggravation of the clinical condition may occur. However, this may disappear in the course of continued administration.

Prior to administration of leuprorelin acetate, undiagnosed abnormal vaginal bleeding must be investigated, diagnosis confirmed and relevant management initiated.

Endometriosis, Uterine myoma (fibroid) indication

- The incidence of adverse reactions generally tends to increase with an increase in dose. Thus, in setting the dose, careful attention should be paid to the body weight.
- In administration of TAPROS, care should be taken to differentiate a similar disease (malignant tumor, etc) from endometriosis, uterine myoma. If during administration of TAPROS, any growing phyma is found or no improvement is seen in the clinical symptom, the administration should be discontinued.

Endometriosis indication

- 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 Mineral loss, 4.4). If it is necessary to resume administration of leuprorelin acetate, changes in bone parameters should be closely followed.

Uterine myoma (fibroids) indication

- 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 mineral loss, 4.4). If it is necessary to resume administration of leuprorelin acetate, changes in bone parameters should be closely followed.
- Severe vaginal bleeding may be observed during treatment with this medicinal product. Therefore, close observation should be made, and if any abnormality is observed, appropriate measures should be taken.

Breast cancer indication

- When starting treatment with TAPROS, absence /presence of hormone receptor expression should be confirmed as a rule. When hormone receptor expression is confirmed to be negative, TAPROS should not be used.
- Since TAPROS is an agent for endocrine therapy, use of this drug for premenopausal breast cancer should be limited to patients for whom treatment with TAPROS is considered appropriate under the supervision of a physician who has adequate knowledge and experience in medication for cancer.
- In antitumor effect is not obtained with TAPROS and any progression of the tumor is observed, the administration should be discontinued.

<u>Adult males (Prostate cancer)</u>

- Since Tapros is an agent for endocrine therapy, use of this drug for prostate cancer should be limited to patients for whom treatment with TAPROS is considered appropriate under the supervision of a physician who has adequate knowledge and experience in medication for cancer.
- ***Flare phenomenon***

  Aggravation of the signs and symptoms of prostate cancer may occur following a transient increase in serum testosterone level in the early period after initiation of treatment, for example urinary tract obstruction and hematuria (as urinary symptoms). In patients with spinal cord compression due to metastasis to the spine, bone pain, weakness of lower extremities and paresthesia (as neurologic symptoms) may also occur (*see Undesirable Effects, 4.8*).

Therefore, particular care should be taken in patients with metastasis to the spine and those with urinary tract obstruction. Careful observation should be made during the first several weeks after initiation of the treatment.

- ***QT prolongation:***

  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 risks and benefits including the potential for Torsade de pointes prior to initiating leuprorelin acetate.

Pediatric patients (Central precocious puberty)

- LH-RH test should be performed at regular intervals. When suppression of the action of LH and FSH in blood is not achieved, the administration of this drug should be discontinued.
- The treatment of children with progressive brain tumours should follow a careful individual appraisal of the risks and benefits.
- Bone mineral density (BMD) may decrease during GnRH analogue therapy in children with 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.

Pseudotumor cerebri / idiopathic intracranial hypertension

Pseudotumor cerebri (PTC)/idiopathic intracranial hypertension has been reported in pediatric patients receiving leuprorelin acetate. Patients should be monitored for signs and symptoms of PTC, including papilledema, headache, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea. If PTC is confirmed permanently discontinue use of leuprorelin acetate and treat the patient in accordance with the established treatment guidelines.

PRECAUTION FOR INDICATION

Uterine myoma (fibroid) indication

It should be noted that the treatment of uterine myoma with TAPROS is not a radical treatment. Therefore, this drug should be used as a means of providing conservative treatment until operation on patients requiring operation or providing premenopausal conservative treatment. For hypogastralgia and low back pain, the effect of this drug is not observed at the early period after administration. During such a period, therefore, appropriate symptomatic treatment should be given.

CAREFUL ADMINISTRATION :

TAPROS should be administered with care in the following patients :

Endometriosis, uterine myoma (fibroid), breast cancer

Patients with submucous myoma, bleeding symptom may be aggravated. Therefore, close observations should be made. The patient should be instructed to contact the attending physician in case of any aggravation of the bleeding symptom

Central precocious puberty

In the early period after the first administration of TAPROS, a transient elevation of the serum level of estrogen may occur owing to the stimulating effect of TAPROS, as a highly active LH-RH derivative, on the pituitary-gonad system, resulting in a transient aggravation of clinical condition. However, such an aggravation usually disappears in the course of continued administration.

Breast cancer

In the early period after the first administration of TAPROS, a transient elevation of the serum level of estrogen may occur owing to the stimulating effect of TAPROS, as a highly active LH-RH derivative, on the pituitary-gonad system, resulting in a transient aggravation of bone pain, etc. In such a case, symptomatic treatment should be given.

PRECAUTION CONCERNING USE

- Route of administration
  Tapros should be used only by the subcutaneous or intramuscular route. [Intravenous injection of Tapros may induce thrombosis].
- Method of administration
  For subcutaneous injection, the following cautions should be exercised.
  - The site for subcutaneous injection should be the brachial, abdominal or gluteal region.
  - The injection site should be changed each time. The repeated injection should not be given at the same site.
  - The check should be made to see that the needle is not piercing a blood vessel.
  - The patients should be instructed not to massage the injection site.
- Preparation :
  - The injectable solution should be prepared at the time of use and be used immediately after reconstituting.
  - If any sedimentation is noticed in the suspension of vial product, such suspension should be used after swirling gently, avoiding formation of bubbles, to resuspend the particles uniformly.
- Use immediately after reconstitution

Other Precautions

For all indications

It has been reported that the benign pituitary adenoma was observed in rats in a study in which this drug was administered subcutaneously in doses of 0.8, 3.6 and 16 mg (as leuprorelin acetate)/kg at 4-week intervals for 1 year and another study in which an aqueous injectable solution of Leuprorelin Acetate was similarly administered in doses of 0.6,1.5 and 4 mg/kg/day for 2 years.

Endometriosis, uterine myoma (fibroid), central precocious puberty, breast cancer

It has been reported that the administration of TAPROS brought about venous thrombosis or pulmonary embolism.

Prostate cancer

It has been reported that the administration of TAPROS brought about cerebral infarction, venous thrombosis or pulmonary embolism.

4.5 Interaction with other medicaments and other forms of interaction

TAPROS should be administered with care when coadministered with sex hormone preparations.
There is no specific data to described in each data sheet.

Prostate cancer Indication

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of leuprorelin acetate 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, should be carefully evaluated (see Section 4.4).

4.6 Pregnancy and lactation

This drug should not be administered to pregnant females or nursing mothers.

4.7 Effects on ability to drive and use machines

TAPROS can influence the ability to drive and use machines due to visual disturbances and dizziness.

4.8 Undesirable effects

Adverse reactions

Clinically significant adverse reaction :

- Since **interstitial lung disease**, accompanied by fever, coughing, dyspnea, abnormal chest X-ray, etc. may occur (<0.1%), the patient's condition should be closely observed. If any abnormality is observed, appropriate measures, such as treatment with adrenal cortical hormones, should be taken.
- Since anaphylactoid symptoms may occur (<0.1%), careful inquiry should be made, and close observation should be made after the administration of Tapros. If any abnormality is observed, appropriate measures should be taken.
- **Hepatic dysfunction or jaundice**, with increased AST(GOT), ALT(GPT) etc., may occur (frequency unknown). Therefore, close observation should be made, and if any abnormality is observed, appropriate measures should be taken.
- **Metabolic syndrome (including hypertension, dyslipidemia, Development or aggravation of diabetes** may occur (frequency unknown). If any abnormality is observed, appropriate measures should be taken.
- **Pituitary apoplexy** has been reported in patients with pituitary adenoma (frequency unknown). Therefore, if headache, vision impairment, visual field disorder, etc. are observed immediately after the first dose of Tapros, appropriate measures, such as surgical treatment, should be taken after conducting examination.
- **Thromboembolic event, such as myocardial infarction, cerebral infarction, venous thrombosis, pulmonary embolism**, may occur (frequency unknown). Therefore, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of administration, should be taken

Prostatic cancer

- Since a depressed state may occur (<0.1%)/ mood changes , the patient's condition should be closed observed.
- Elevation of serum testosterone level due to the stimulation effect of Tapros on the pituitary-gonad system may bring about a transient aggravation of bone pain, ureteral obstruction or spinal cord compression (≥ 5%). If any of such symptoms occurs, appropriate measures, such, as pertinent symptomatic treatment, should be taken.
- Since cardiac failure may occur (0.1 - <5%), close observation should be made. If any abnormality is observed, appropriate measures, such as discontinuation of administration, should be taken.

	≥5%	0.1% - < 5%	< 0.1%	Frequency unknown
1) Hepatic Close observation should be made	Increased LDH	Jaundice, or increased AST(GOT), ALT(GPT), γ-GTP or ALP		

	≥5%	0.1% - < 5%	< 0.1%	Frequency unknown
2) Endocrine	Hot flushes, feeling of warmth	Headache, insomnia, facial hot flushes, dizziness, diaphoresis, decreased libido, erectile dysfunction, gynecomastia, testicular atrophy or discomfort in the perineal region		
3) Musculoskeletal		Arthralgia, bone pain, pain in the shoulder, low back or limbs, or difficulty in walking, stiffness of fingers or other joints	Muscle ache or decreased bone mass	Osteoporosis (including vertebral body fractures)
4) Dermatologic		Dermatitis, or hair growth on the head		
5) Urinary		Pollakiuria, hematuria or increased BUN		
6) Cardiovascular		ECG abnormalities or increased cardiothoracic ratio		
7) Hematologic		Anemia or platelet count decreased		White blood cell decreased
8) Gastrointestinal		Nausea, vomiting, anorexia or constipation	Diarrhea	
9) Hypersensitivity		Rash or pruritus		
10) Administration site		Pain, induration and redness		Reactions at the injection site such as abscess, swelling, ulcer, pruritus, granuloma, mass,

	≥5%	0.1% - < 5%	< 0.1%	Frequency unknown
				warmth, and necrosis
15) Others	Fatigue	Edema, pressure sensation of chest, rigor, malaise, numbness of lips or limbs, weight increase, paresthesia, deafness, tinnitus, fever, increased total cholesterol, triglyceride or uric acid, hyperkalemia, or increased blood sugar level.	Weakness	Seizures, visual impairment

Endometriosis, Uterine myoma (fibroid) , Breast cancer and Central precocious puberty

- Since a depressed state like climacteric disturbance e.g resulting from estrogen reducing effect may occur (0.1% -<5%)), the patient's condition should be closely observed.

		≥ 5%	0.1% - < 5%	< 0.1%	Frequency unknown
1)	Symptoms resulting from decreased estrogen	Hot flushes, feeling of warmth, feeling of hot flushes, shoulder stiffness, headache , insomnia, dizziness or diaphoresis	Decreased libido, coldness, visual disturbance or emotional liability		
2)	Female reproductive		Metrorrhagia, Vaginal dryness, coital pain, Vulvovaginitis, increased fluor, ovarian hyperstimulation syndrome, or pain, swelling or atrophy of the breast		
3)	Musculo-skeletal	Pains, such as arthralgia and bone pain	Stiffness of fingers or other joints, lumbar pain, muscle ache, muscular		Osteoporosis (including vertebral body

		≧ 5%	0.1% - < 5%	< 0.1%	Frequency unknown
			spasm, decreased bone mass, increased serum phosphorus or hypercalcemia		fractures)
4)	Dermatologic		Acne, dry skin, alopecia, hypertrichosis or nail abnormality		
5)	Psycho-neurologic		Sleepiness, irritated feeling, hypomnesia, decreased attentiveness or paresthesia		Pseudotum or cerebri / idiopathic intracranial hypertensi on
6)	Hypersensitivi ty		Rash or pruritus		
7)	Hepatic close observation should be made		Increased AST(GOT), ALT(GPT), ALP, LDH, γGTP or bilirubin	Jaundice	
8)	Gastrointestin al		Nausea, vomiting, anorexia, abdominal pain, feeling of enlarged abdomen, diarrhea, constipation, stomatitis or thirst		
9)	Cardiovascular		Palpitation or increased blood pressure		
10)	Hematologic		Red blood cell count increased, anemia, white blood cell decreased, platelet count decreased or prolonged partial thromboplastin time		
11)	Urinary		Pollakiuria, dysuria or		

		≧ 5%	0.1% - < 5%	< 0.1%	Frequency unknown
			increased BUN		
12)	Administration site		Pain, induration and redness		Reactions at the injection site, such as abscess, swelling, ulcer, pruritus, granuloma, mass, warmth and necrosis
13)	Others		Fatigue, malaise, weakness, numbness of lips or limbs, carpal tunnel syndrome, tinnitus, deafness, chest discomfort, edema, weight increase, pain of lower extremities, respiratory distress, fever, increased total cholesterol, LDL cholesterol or triglyceride, or hyperkalemia	Weight decrease, taste abnormality or abnormal thyroid function	Seizures

4.9 Overdose

In case of overdose, the patients should be monitored closely and management should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacological properties

Leuprorelin is a synthetic nonapeptide analogue of natural Gn-RH. The studies performed in human as well as in animals have demonstrated that, after an initial stimulation, the prolonged administration of leuprorelin induces a decrease of gonadotropin secretion, consequently suppressing the testicular function in men, and inducing an atrophy of the uterine and ectopic endometrial tissue in women. This effect is reversible upon discontinuation of drug therapy.
Through some studies in animals, another mechanism of action has been evoked : a direct effect by the decrease of sensitivity of the gonadotropin receptors.

In human, after administration of the first dose, an increase in circulating levels of LH and FSH is induced, leading to an initial increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in men and estradiol in women). The pursuit of the treatment leads to a decreased in LH and FSH levels, inducing within 3 to 4 weeks, to androgen or estrogen levels equivalent to those obtained after castration or menopause, as long as drug administration continues.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipient

CoPolymer (DL-Lactic acid / Glycolic acid) (3:1), Mannitol.

Solutions
CMC, Mannitol, Polysorbate 80, water for injection

6.2 Incompatibilities

This drug must be injected alone.

6.3 Special precaution for Storage

Store below 30^{o}C, avoiding heat.
No refrigeration necessary.

6.4 Package

Box, 1 vial and 1 ampoule (diluent)

Reg. No. DKI9270700244A1

Based on CCDS ver 19.0

DOCTOR'S PRESCRIPTION IS REQUIRED FOR THE USE OF THIS PREPARATION

HARUS DENGAN RESEP DOKTER

Takeda

Manufactured by Takeda Pharmaceutical Company Limited, Osaka, Japan
Imported & packed by PT. Takeda Indonesia, Bekasi, Indonesia