TAPROS® DEPOT 1.88 mg
LEUPRORELIN ACETATE

1 NAME OF THE MEDICINAL PRODUCT

TAPROS®

2 COMPOSITION

Each vial contains 1.88 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

1. 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.
2. Treatment of central precocious puberty.

4.2 Posology and Method of Administration

1. 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.

2. 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

All patient populations
- Hypersensitivity to leuprorelin, Gn-RH derivatives, 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

PRECAUTION

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 to loss of suppression of 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 females (adult and pubescent pediatric females)

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

Adult females (Endometriosis)

Metabolic changes and cardiovascular risk

Inhibition of endogenous sex hormone production, such as during 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.

Other precautions

- 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.
- Prior to administration of TAPROS, undiagnosed abnormal vaginal bleeding must be investigated, diagnosis confirmed and relevant management initiated (see Contraindications, 4.3).
- 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 discontinue.
- 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.
- During the period of the treatment, the patient should be instructed to prevent conception with the use of non-hormonal methods.

Bone mineral loss

Long-term estrogen deprivation by bilateral oophorectomy, ovarian ablation 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). A decrease in bone mass may occur owing to estrogen reducing effect of TAPROS.

Therefore, as a rule, this drug should not be administered to patients with endometriosis for more than 6 months. (The safety of administration for more than 6 months has not been established). When it is inevitable to administer this drug for a long period or to resume its administration, the drug should be carefully administered after the bone mass is examined as far as possible.

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.

Careful administration :

Endometriosis

TAPROS should be administered with care in the patients with submucous myoma, bleeding symptom may be aggravated.

Other precautions :

It has been reported that the benign pituitary adenoma was observed in rats in a study in which this drug was administered subcutaneously in dose 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.

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

Precautions 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

4.5 Interaction with other medicaments and other forms of interaction

Endometriosis

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

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

Other adverse reactions

Endometriosis and central precocious puberty

- Since a depressed state may occur (<0.1%-<5%), the patient's condition should be closely observed.

	≧ 5%	0.1% - < 5%	< 0.1%	Frequency unknown

		≥ 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 spasm, decreased bone mass, increased serum phosphorus or hypercalcemia		Osteoporosis (including vertebral body fractures)
4)	Dermatologic		Acne, dry skin, alopecia, hypertrichosis or nail abnormality		
5)	Psycho-neurologic		Sleepiness, irritated feeling, hypomnesia, decreased attentiveness or paresthesia		Pseudotumor cerebri / idiopathic intracranial hypertension
6)	Hypersensitivity		Rash or pruritus		
7)	Hepatic (close observation should be made)		Increased AST(GOT), ALT(GPT), ALP, LDH, γGTP or bilirubin	Jaundice	
8)	Gastrointestinal		Nausea, vomiting, anorexia, abdominal pain, feeling of enlarged abdomen, diarrhea, constipation, stomatitis or thirst		
9)	Cardiovascular		Palpitation or increased blood pressure		

	≥ 5%	0.1% - < 5%	< 0.1%	Frequency unknown
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 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 abnor-mality 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

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 excipients

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°C, avoiding heat.

No refrigeration necessary.

6.4 Package

Box, 1 vial and 1 ampoule (diluent)

Reg. No. DKI0870700244C1

DOCTOR'S PRESCRIPTION IS REQUIRED FOR THE USE OF THIS PREPARATION
HARUS DENGAN RESEP DOKTER

Based on CCDS ver.19.0

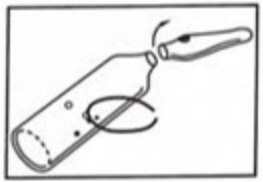
Takeda

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

Cara Melarutkan dan Penyuntikan

1. Sama seperti sediaan injeksi lain, seluruh pekerjaan melarutkan dan penyuntikan dilakukan secara aseptis. Usahakan seluruh cairan pelarut di dalam ampul berada di bagian bawah dengan cara mengetuk perlahan-lahan bagian atas ampul dengan jari.

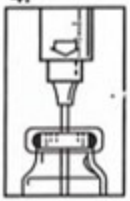
2. **Penting : Ampul ini telah dirancang sehingga akan pecah pada satu arah saja.**



Untuk membuka ampul, patahkan ujung ampul pada arah yang menjauhi bintik biru hanya dengan sedikit tekanan. Bila ujung ampul tidak dapat dipatahkan dengan mudah jangan dipaksa dengan menggunakan tekanan lebih besar. Ubah posisi ampul dan patahkan pada arah yang tepat menjauhi bintik biru.

3.

4.



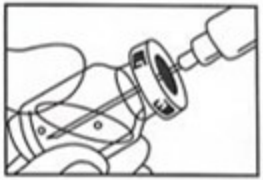
Dengan menggunakan spuit dan jarum no.23 ambil 2 ml cairan pelarut.

Bukalah tutup plastik vial kemudian suntikkan pelarut ke dalam vial.

5.

Kocok vial untuk melarutkan partikel-partikel sehingga membentuk suspensi. Cairan seperti susu.

6.



Ambil seluruh cairan dalam vial ke dalam spuit seperti no.3

7. Suntikkan segera secara subkutan atau intramuscular.

8. Buang sisa pelarut, ampul dan vial. Seluruh komponen tidak berbahaya. Tidak diperlukan cara khusus untuk pembuangannya.

Takeda

DISETUJUI OLEH BPOM : 23/08/2023

PT. Takeda Indonesia, Bekasi, Indonesia

ID REG : EREG10023512300038; EREG10023512300039; EREG10023512300040.

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