SCHEDULING STATUS:

S4 **GONAPEPTYL**® Depot Powder for injection

S1 **GONAPEPTYL®** Depot Injection vehicle

PROPRIETARY NAME AND DOSAGE FORM:

GONAPEPTYL® Depot Powder for injection

GONAPEPTYL® Depot Injection vehicle

COMPOSITION:

GONAPEPTYL® Depot Powder for injection: Each glass syringe contains Triptorelin 3,75 mg

GONAPEPTYL® Depot Injection vehicle: Each 1 ml contains dextran 104,0 mg and water for injection to 1 ml.

PHARMACOLOGICAL CLASSIFICATION:

A. 21.10 Tropic hormones (**GONAPEPTYL®** Depot Powder for injection)

A.34 Other (**GONAPEPTYL®** Depot Injection vehicle)

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

Triptorelin is a synthetic decapeptide (DTrp6-LHRH) analogue of LHRH. Triptorelin initially stimulates the pituitary to release LH and FSH resulting in an increase of serum testosterone concentrations in men and serum oestrogen concentrations in women. However, prolonged exposure will result in desensitisation of the pituitary, causing a decrease of FSH and LH levels and, in consequence, a decrease in testicular and ovarian function.

Other studies in animals indicate a further mechanism of action: direct gonadal action by decreasing the sensitivity of the peripheral receptors to LHRH.

A transient increase in acid phosphatase may be observed at the beginning of the treatment.

Pharmacokinetic properties:

After intramuscular or subcutaneous application of triptorelin depot formulation, a rapid increase in concentration of triptorelin in plasma is seen, with a maximum in the first hours. Thereafter the triptorelin concentration declines notably within 24 hours. On day 4, the values reach a second maximum, falling below the detection limit in the biexponential curve after 44 days. After subcutaneous injection, the triptorelin increase is more gradual and in a lower concentration than after intramuscular injection. The decline in triptorelin concentration after subcutaneous injection takes longer, with values falling below the detection limit after 65 days.

The systemic bioavailability of the active component from the intramuscular depot is 38,3 % and 25,5 % in the first 13 days in men and women respectively. Further release is linear at 0,92 % of the dose per day on average in men and 0,73 % in women. Bioavailability of the subcutaneous application is 69 % of intramuscular availability in men.

Triptorelin is inactivated in the liver and kidneys.

INDICATIONS:

- Treatment of advanced prostate carcinoma for which hormonal therapy is considered.
- Symptomatic uterine myomas, when suppression of the ovarian hormonogenesis is indicated as a preoperative measure to reduce the size of individual myomas prior to scheduled myomen nucleation or hysterectomy.
- Symptomatic endometriosis confirmed by laparoscopy, when suppression of the ovarian hormonogenesis is indicated to the extent that surgical therapy is not primarily indicated.
- Treatment of central precocious puberty (CPP) in previously untreated girls.

CONTRAINDICATIONS:

- Hypersensitivity to any of the ingredients.
- Patients presenting with spinal cord compression. Care should be taken in patients with metastases in the spinal column, in whom compression may occur.
- Patients in whom hormonal therapy has failed.

In men:

- Hormone independent prostate carcinoma.
- After orchiectomy (in case of surgical castration triptorelin does not cause further decrease of serum testosterone).

In women:

- Pregnancy and lactation
- Clinically manifest osteoporosis

In children:

- Progressive brain tumours.

WARNINGS:

Men:

The initial transient increase of serum testosterone has been associated with a temporary aggravation of symptoms of the disease (see “Side Effects and Special Precautions”). The prostate-specific antigen (PSA) and the testosterone plasma levels should be regularly monitored during treatment. Testosterone levels should not exceed 1 ng/ml (1 nmol/l).

Women:

GONAPEPTYL® should be prescribed only after careful diagnosis (e.g. laparoscopy).

A supervening metrorrhagia in the course of the treatment is abnormal (except in the first month) and should lead to verification of plasma oestrogen level. Should this level be less than 50 pg/ml, possible associated organic lesions should be sought.

Non-hormonal methods of contraception should be employed during therapy and must be continued until menses are resumed.

Oestrogen-containing products may not be used during treatment with **GONAPEPTYL®.**

During treatment of uterine myomas, the size of the uterus and myoma should be determined regularly, e.g. by means of ultrasonography (see “Side Effects and Special Precautions”).

Treatment should not exceed a duration of 6 months due to a decrease in bone density. After withdrawal of treatment, the bone loss is generally reversible within 6 – 9 months.

Children:

The chronological age at the beginning of therapy should be under 8 years in girls.

Pseudo-precocious puberty (gonadal or adrenal tumour or hyperplasia) should be precluded.

INTERACTIONS:

Oestrogen-containing medicinal products should not be used during treatment with **GONAPEPTYL®.**

PREGNANCY AND LACTATION:

GONAPEPTYL® should not be used during pregnancy and lactation (See “Contraindications”).

DOSAGE AND DIRECTIONS FOR USE:

Note: It is important that the directions for administering the injection be followed rigorously as per separate instruction card. Any incomplete injection kit must be reported.
After reconstitution of the suspension, the injection should be administered **immediately**.
Any unused portion must be discarded.

One syringe to be injected once every 28 days either subcutaneously (e.g. into the skin of the abdomen, the buttock or thigh) or deep intramuscularly. The injection site should be changed each time.

Prostate carcinoma:

One injection, equivalent to 3,75 mg triptorelin, every four weeks (28 days).

Uterine myomas and endometriosis:

One injection, equivalent to 3,75 mg triptorelin, every four weeks (28 days). The treatment should be initiated in the first 5 days of the cycle.

The duration of the treatment depends on the initial degree of severity of endometriosis, on the evolution of its clinical manifestations and on the evolution of the volume of the uterine myomas, determined by ultrasonography during the course of treatment.

Normally, the maximum attainable result is achieved after 3 – 4 injections. In view of the possible effect on bone density, therapy should not exceed a duration of 6 months. Menstruation will resume 7-12 weeks after the final injection, but may vary in individual cases.

Central Precocious Puberty:

Initially: One injection on days 0, 14 and 28.

Maintenance dose: One injection every 4 weeks (28 days). Should the effect be insufficient, the injections may be given every three weeks.
Dosage should be based on body weight. Children weighing less than 20 kg to be injected with 1,875 mg (half dose), children between 20 and 30 kg to receive 2,5 mg (2/3 dose) and children with more than 30 kg body weight to be injected with 3,75 mg triptorelin (full dose).

Treatment should be stopped if a bone maturation of older than 12 years in girls has been achieved.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side Effects

***Prostatic carcinoma*:**

Initiation of the treatment is followed by a transient accentuation of clinical signs and symptoms (in particular bone pains). This requires careful medical supervision during the first week of treatment especially in patients presenting with urinary tract obstruction due to metastases and/or spinal metastases.

These effects are usually transient, disappearing in one to two weeks with continued treatment. However, the possibility of a temporary exacerbation of the symptoms during the first weeks of treatment must be borne in mind with patients presenting a risk of neurological disorder or urinary obstruction. Administration of an anti-androgen one week before and up to four weeks after **GONAPEPTYL®** Depot Powder for injection treatment may help to prevent side effects.

Men and women:

Immune system disorders

Less frequent: Hypersensitivity reaction, e.g. itching, skin rash, fever and anaphylaxis may occur. These reactions may include both local injection site reactions and systemic symptoms.

General disorders and administration site conditions

Frequent: Temporary pain at the injection site may occur.

Less frequent: After subcutaneous injection, some patients may notice foreign body reactions at the injection site.

Metabolism disorders

Less frequent: Elevated enzyme levels (LDH, γGT, AST, ALT).

Nervous system disorders

Frequent: Depressive mood and irritation; fatigue; sleep disturbances; hot flushes.

Gastrointestinal disorders

Frequent: Nausea.

Musculoskeletal disorders

Frequent: Myalgia and arthralgia.

Men:

Blood disorders

Less frequent: Trombophlebitis.

Reproductive system and breast disorders

Frequent: Gynecomastia; loss of libido and impotence.

Less frequent: Testicular atrophy.

Nervous system disorders

Frequent: Perspiration; paraesthesia; asthenia; compression of the spinal cord.

Vascular disorders

Less frequent: Hypertension; lymphatic oedema of the legs.

Metabolism disorders

Less frequent: Loss of appetite and weight changes.

Skin disorders

Less frequent: Reduced growth of beard and hair loss on chest, arms and legs.

Renal and urinary disorders

Less frequent: Urinary obstruction with decreased kidney function.

Musculoskeletal disorders

Less frequent: Skeletal pain and muscular fatigue.

Due to increased testosterone levels in men during the first week of treatment, worsening of symptoms and complaints may occur.

Women:

Blood disorders

Less frequent: Decrease in plasma oestrogen levels; slightly elevated serum cholesterol.

Reproductive system disorders

Less frequent: Vaginal dryness and/or dyspareunia; withdrawal bleeding, spotting, loss of libido.

Nervous system disorders

Less frequent: Nervousness and mood swings; paraesthesia.

Musculoskeletal and bone disorders

Less frequent: Backache; trabecular bone loss may occur which is usually reversible within 6 – 9 months after withdrawal of therapy.

Eye disorders

Less frequent: Visual disturbance.

Children:

Reproductive system disorders

Less frequent: Vaginal bleeding and discharge may occur.

Gastrointestinal disorders

Less frequent: Vomiting and nausea.

Nervous system disorders

Less frequent: Headache.

Special Precautions

During treatment of uterine myomas the size of the uterus and myoma should be determined regularly, e.g. by means of ultrasonography. Disproportional fast reduction of uterus size in comparison with the reduction of myoma tissue has in isolated cases led to bleeding and sepsis.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See “Side effects and Special precautions”.

Treatment is symptomatic and supportive.

IDENTIFICATION:

GONAPEPTYL® Depot Powder for injection: White or faintly yellow microcapsules in 2,25 ml pre-filled glass syringes.

GONAPEPTYL® Depot Injection vehicle: Clear, colourless to slightly yellow, aqueous liquid in 2,25 ml pre-filled glass syringes.

After reconstitution: Homogenous, milky white to faintly yellow suspension.

PRESENTATION:

GONAPEPTYL® Depot Powder for injection is filled into 2,25 ml glass syringes

GONAPEPTYL® Depot Injection vehicle is filled into 2,25 ml glass syringes.

STORAGE INSTRUCTIONS:

Store at 2 – 8 °C, protected from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

GONAPEPTYL® Depot Powder for injection: 37/21.10/0408

GONAPEPTYL® Depot Injection vehicle: 37/34/0409

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF

REGISTRATION:

FERRING (PTY) LTD

Route 21 Corporate park

6 Regency Drive

Irene X 30

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

24 June 2005

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