SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADENAME OF THE MEDICINAL PRODUCT

DIPHERELINE 0.1 mg, powder and solvent for solution for injection (S.C.).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition of the powder:

Triptorelin ..... 0.0001 g

Mannitol ..... 0.0100 g

For one dose

Composition of the solvent:

Sodium chloride..... 0.009 g

Water for injections q.s. ..... 1 ml

For one ampoule

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection (S.C.)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Female infertility: Management of ovarian stimulation in association with the gonadotrophins (hMG, FSH, hCG) in view of in vitro fertilisation and embrio transfer (I.V.F.E.T.) and other assisted conception techniques.

4.2 Posology and method of administration

Prostate cancer
One daily injection of 0.1 mg triptorelin by subcutaneous route from Day 1 to Day 7, before changing to the prolonged release form.

Female infertility: in combination with gonadotrophins.
One daily subcutaneous injection from Day 2 of the menstrual cycle (at the same time as ovarian stimulation starts) until the day before the day set for induction, i.e. an average period of 10 to 12 days for each attempt.

4.3 Contra-indications

Hypersensitivity to GnRH, its analogues or to one of the constituents.

4.4 Special warnings and special precautions for use

Prostate cancer

Warnings on beginning treatment:
It has been reported that clinical symptoms (particularly bone pain) may worsen on beginning treatment but these cases are isolated and generally transient. These cases justify a careful medical supervision during the first few weeks of treatment, particularly in patients presenting with urinary tract obstruction and in those with vertebral metastases (see Undesirable effects).
For the same reason, particular care should be taken when beginning treatment in patients with premonitory signs of spinal cord compression.
A transitory increase in acid phosphatases may be observed at the beginning of treatment.
Precautions for use:
It may be advantageous to check blood testosterone levels periodically with an accurate method as these should not exceed 1 ng /ml.

Female infertility

Warnings:
Confirm that the patient is not pregnant before prescription of DIPHERELINE 0.1 mg.
The follicular retrieval induced by the injection of triptorelin combined with gonadotrophins may increase markedly in some predisposed patients and particularly in cases of polycystic ovarian disease.
The ovarian response to the triptorelin-gonadotrophin combination may differ with the same doses from one patient to another one, and in certain cases, from one cycle to another in the same patient.

Precautions for use:
The induced ovulation should be monitored under rigorous medical supervision with strict and regular biological and clinical controls: fast plasma oestrogen assay and ultrasonography (see Undesirable effects).
If the ovarian response is excessive, it is recommended to interrupt the stimulation cycle by discontinuing the gonadotrophin injections.

4.5 Interaction with other medicinal products and other forms of interaction

Not applicable.

4.6 Pregnancy and lactation

Pregnancy

At the present time, GnRH analogues are used in combination with gonadotrophins to induce ovulation and therefore encourage pregnancy. Pregnancy is therefore not an indication for these products.
However, experience has shown that after ovulation has been induced in a previous cycle, some women become pregnant without realising it, and undertake a further course to stimulate ovulation.
Data currently available concerning the effects of this type of product during pregnancy are summarised below:

– Animal studies have not shown the product to have any teratogenic effects. No malformations are therefore expected in humans with this product as substances that cause malformations in humans have been found to be teratogenic in well-conducted animals studies in two species so far.

– In clinical studies to date, the use of GnRH analogues in a limited number of pregnant women has not resulted in any malformations or foetotoxicity. Nevertheless, further studies are required to study the consequences of exposure during pregnancy.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

In men

At the beginning of treatment (see Warnings and Precautions for use)
Urinary symptoms, bone pain of metastatic origin and symptoms associated with spinal cord compression from vertebral metastases may be exacerbated when plasma testosterone is initially and transiently increased at the beginning of treatment. These symptoms disappear in one to two weeks.

During the treatment
The most frequently reported undesirable effects (hot flushes, decreased libido, and impotence) are related to the decrease in plasma testosterone levels resulting from the pharmacological effects of the substance, and are similar to those observed with other GnRH analogues. These effects have not been observed during short-term treatment with DIPHERELINE 0.1 mg.

In women
At the beginning of treatment
When used to treat infertility, the combination with gonadotrophins may result in ovarian hyperstimulation. Ovarian hypertrophy, pelvic and/or abdominal pains may be observed (see Warnings and Precautions for use).

During the treatment
The most frequently reported effects, such as hot flushes, vaginal dryness, decreased libido and dyspareunia, are related to pituitary-ovarian blockade.
These effects have not been observed during short-term treatment with DIPHERELINE 0.1 mg.
A few rare cases of headache, arthralgia and myalgia have been reported.

In both men and women
Allergic reactions such as urticaria, rash, pruritus and very occasionally Quincke's oedema have been reported.
A few cases of nausea, vomiting, weight increase, hypertension, mood disorders, visual disturbances, pain at the injection site and fever have been reported.

The prolonged use of GnRH analogues may lead to bone loss, a risk factor for possible osteoporosis. These effects have not been observed during short-term treatment with DIPHERELINE 0.1 mg.

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

GONADOTROPHIN-RELEASING HORMONE ANALOGUE
(L 02 AE04: antineoplastic and immunomodulator).

5.1 Pharmacodynamic properties

Triptorelin is a synthetic decapeptide analogue of natural GnRH (gonadotrophin-releasing hormone).
Studies conducted in humans and in animals have shown that after initial stimulation, the prolonged administration of triptorelin inhibits gonadotrope secretion with consequent suppression of testicular and ovarian function.
Further studies in animals have suggested another mechanism of action: direct effect on the gonads by decreasing the sensitivity of peripheral receptors to GnRH.

Prostate cancer

The administration of a daily dose of triptorelin may initially increase LH and FSH blood levels (flare up) and may consequently increase initial testosterone levels. Continuing the treatment decreases LH and FSH levels to concentrations that result in castration levels of steroids within 2-3 weeks and for as long as the product is administered.

The treatment may improve functional and objective symptoms.

Female infertility

Prolonged treatment with triptorelin inhibits gonadotrope secretion (FSH and LH). The treatment ensures therefore the suppression of the intercurrent endogenous LH peak enabling enhanced quality of folliculogenesis and increased follicular retrieval.

5.2 Pharmacokinetic properties

In healthy adult volunteers

Following subcutaneous injection the resorption of triptorelin (0.1 mg) is quick ($t_{max} = 0.63 \pm 0.26$ hr) with a peak plasma concentration ($C_{max} = 1.85 \pm 0.23$ ng/ml). Elimination is achieved with a biological half-life of 7.6 ± 1.6 hr, after a 3 to 4 hours distribution phase.

Total plasma clearance is: 161 ± 28 ml/min.

Distribution volume is: 1562 ± 158 ml/kg.

In patients with prostate cancer

With subcutaneous administration (0.1 mg), plasma concentrations oscillate between maximum values of 1.28 ± 0.24 ng/ml (Cmax) usually obtained one hour after injection (tmax) and minimum values of 0.28 ± 0.15 ng/ml (Cmin) obtained 24 hours after injection.

Biological half-life is on average 11.7 ± 3.4 hr but varies according to patients, and plasma clearance (118 ± 32 ml/min) reflects slowing of elimination in these patients, whilst distribution volumes are close to those of healthy volunteers (1130 ± 210 ml/kg).

5.3 Preclinical safety data

The molecule did not demonstrate any specific toxicity in animal toxicological studies. The effects observed were related to the pharmacological properties of the substance on the endocrine system.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

Not applicable.

6.2 Shelf-life

2 years

After first opening – use within 24 hours

After reconstitution – use within 24 hours

6.3 Special precautions for storage

Store at 25ºC

6.4 Nature and contents of container

Vial or ampoule (glass) containing the powder and ampoule (glass) containing the solvent.

6.5 Instructions for use/handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

IPSEN PHARMA, FRANCE

65 Quai Georges Gorge

92100 BOULOGNE-BILLACOURT ,France

AUTHORIZATION HOLDER

MEDISON PHARMA Ltd.

P.O.B 7090, PETACH TIKVA

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