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**DIPHERELINE S.R. 11.25 mg,
powder and solvent for suspension for injection (I.M.),
3-month sustained release form**

SUMMARY OF PRODUCT CHARACTERISTICS

APPENDIX I

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1. NAME OF THE MEDICINAL PRODUCT

DIPHERELINE S.R. 11.25 mg, powder and solvent for suspension for injection (I.M.), 3-month sustained release form

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Triptorelin 11.25 mg*
(as triptorelin pamoate)

for one unit dose.

* Taking into consideration the characteristics of the pharmaceutical form, each vial contains a triptorelin pamoate content corresponding to 15 mg of triptorelin.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection (I.M.), sustained release form.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Prostate cancer

Treatment of prostate cancer with metastases.

A favourable effect of the treatment is all the more pronounced and more frequent if the patient has not previously received another hormone treatment.

Genital and extragenital endometriosis (stage I to IV)

Treatment should not be administered for more than 6 months (see Undesirable effects). It is not recommended to undertake a second course of treatment by triptorelin or by another GnRH analogue.

4.2. Posology and method of administration

Prostate cancer

One intramuscular injection of DIPHERELINE S.R. 11.25 mg which is repeated every 3 months.

Endometriosis

One intramuscular injection of DIPHERELINE S.R. 11.25 mg repeated every 3 months.

The treatment must be initiated in the first five days of the menstrual cycle.

Treatment duration: this depends on the initial severity of the endometriosis and the changes observed in the clinical features (functional and anatomical) during treatment. In principle, endometriosis should be treated for at least 3 months and for at most 6 months. It is not recommended to start a second treatment course with triptorelin or another GnRH analogue.

NB: The sustained released form must be injected in strict compliance with the instructions given in the package leaflet. Any incomplete injections resulting in the loss of suspension volumes greater than the volume generally remaining in the injection syringe must be reported.

4.3. Contraindications

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

4.4. Special warnings and special precautions for use

Special warnings

Prostate cancer

Warning at beginning of treatment:

It has been reported that clinical symptoms (particularly bone pain) may worsen on starting the treatment but these cases are isolated and generally transient. These cases merit particularly attentive medical supervision over the first few weeks of treatment, notably 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 starting treatment in patients with premonitory signs of medullar compression.

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

Endometriosis

Confirm that patient is not pregnant before beginning the treatment.

Precautions for use:

Prostate cancer

It may be advantageous to check blood testosterone levels periodically as these should not exceed 1 ng /ml.

Endometriosis

The administration of DIPHERELINE S.R. 11.25 mg results in constant hypogonadotropic amenorrhoea. The onset of metrorrhagia in the course of treatment, apart from the first month, is abnormal and plasma oestradiol levels should therefore be verified. Should this level be less than 50 pg/ml, possible associated organic lesions should be sought.

Ovarian function resumes after the treatment is withdrawn and the first menses occur on average 134 days after the last injection. Contraception should therefore be envisaged in the 15 days following treatment withdrawal, i.e. three and a half months after the injection.

4.5. Interaction with other medicinal products and other forms of interaction

Not applicable.

4.6. Pregnancy and lactation

Pregnancy

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 to date.
- in clinical studies conducted to date, the inadvertent 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.

Breast-feeding

As no information concerning the transfer of this medicinal product into mother's milk or its possible effects in the breast-fed infant is available this medicinal product should not be used during breast-feeding.

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 medullary compression from spinal 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.

In women

At beginning of the treatment

Endometriosis-related symptoms (pelvic pain, dysmenorrhoea) may be exacerbated during the initial and transient increase in plasma oestradiol levels and should disappear in one or two weeks.

Metrorrhagia may occur in the month following the first injection.

During the treatment

The most frequently reported effects such as hot flushes, vaginal dryness, decreased libido and dyspareunia are related to pituitary-ovarian blockade.

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 gain, hypertension, mood disorders, visual disturbances, pain at the injection site and fever have been reported.

Prolonged use of GnRH analogues may lead to bone loss, a risk factor for possible osteoporosis.

4.9. Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

GONADOTROPHIN-RELEASING HORMONE ANALOGUE

ATC code: L02AE04 (antineoplastic and immunomodulator)

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, continued administration of triptorelin inhibits gonadotrophin secretion with consequent suppression of testicular and ovarian function.

The administration of DIPHERELINE S.R. 11.25 mg may initially increase blood LH and FSH levels and consequently increase testosterone levels (flare-up) in men and oestradiol levels in women. Prolonged treatment decreases LH and FSH levels to concentrations that result in castration levels of testosterone and oestradiol within about 20 days after injection and for as long as the product is released.

The prolonged treatment with triptorelin suppresses oestradiol secretion in women and thus enables resting of ectopic endometrial tissue.

5.2. Pharmacokinetic properties

Following intramuscular injection of DIPHERELINE S.R. 11.25 mg in patients (men and women), a peak plasma concentration of triptorelin is observed about 3 hours after injection. After a declining concentration phase, which continues during the first month, circulating triptorelin levels remain constant until the end of the third month following the injection.

5.3. Preclinical safety data

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

The resorption of the product is complete in 120 days.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Composition of the powder:

D, L lactide coglycolide polymers; mannitol; carmellose sodium; polysorbate 80.

Composition of the solvent:

Mannitol; water for injections.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Do not store above 25°C.

Inject immediately after reconstitution of the suspension.

6.5. Nature and contents of container

Powder in a 4 ml vial (glass) with a stopper (elastomer) and cap (aluminium) and an ampoule (glass) containing 2 ml of solvent; box containing 1 vial and 1 ampoule with 1 syringe and 2 needles.

6.6. Instructions for use/handling

The powder should be suspended in the specific solvent immediately before injection by shaking the vial gently until a milky liquid is obtained.

7. MARKETING AUTHORISATION HOLDER

BEAUFOUR IPSEN PHARMA
24 rue Erlanger
75781 PARIS CEDEX 16

8. MARKETING AUTHORISATION NUMBER

341 256.5: Powder in a 4-ml vial (glass) with a stopper (elastomer) and cap (aluminium) and an ampoule (glass) containing 2 ml of solvent; box containing 1 vial and 1 ampoule with 1 syringe and 2 needles.

9. DATE OF FIRST AUTHORISATION

June 1996.

10. DATE OF REVISION OF THE TEXT

11. IMPORTER

MEDISON PHARMA
10 Hashiloach St. POB 7090
PETACH TIKVA 49170

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