1.3.1 Summary of Product Characteristic

1. Name of the medicinal product

Busereline Injection (FLAMEON)

2. Qualitative and quantitative composition

Each ml contains
Buserelin Acetate equivalent to
Buserelin BP 1 mg
Benzyl alcohol BP (As Preservative) 10 mg
Water for Injection USP Q.S.

3. Pharmaceutical form

Solution for Injection.

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of advanced hormone dependent prostatic carcinoma in which suppression of testosterone is indicated. However, not after bilateral orchiectomy (no further reduction of testosterone level by Buserelin to be expected)..

4.2 Posology and method of administration

Initiation of therapy: is most conveniently carried out in hospital; 0.5 ml Buserelin Injection should be injected subcutaneously at 8 hourly intervals for 7 days.

Maintenance therapy: on the 8^{th} day of treatment the patient is changed to intranasal administration of Buserelin Injection.

4.3 Contraindications

Buserelin must not be used if the tumour is found to be insensitive to hormone manipulation or after surgical removal of the testes.

Because of the content of benzyl alcohol, Buserelin Injection must not be given to newborns or premature neonates.

4.4 Special warnings and precautions for use

Buserelin injection is for subcutaneous administration ONLY

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as Buserelin. Patients should be informed accordingly and treated as appropriate if symptoms occur.

In patients with hypertension, blood pressure must be monitored regularly (risk of deterioration of blood pressure levels).

<u>QT Prolongation</u>

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 benefit risk ratio including the potential for Torsade de pointes prior to initiating Suprefact Injection.

The use of LHRH-agonists may be associated with decreased bone density and may lead to osteoporosis and an increased risk of bone fracture (see section 4.8). Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with anticonvulsants or corticosteroids or a family history of osteoporosis). It is recommended to periodically monitor bone mineral density (BMD) and use preventative measures during therapy to prevent osteopenia/osteoporosis.

In some patients treated with GnRH-agonists, change in glucose tolerance is observed (see section 4.8). In diabetic patients blood glucose levels must be checked regularly (risk of deterioration of metabolic control).

The effect can be monitored clinically and by determination of prostate specific antigen (PSA) and testosterone in the serum. Testosterone levels increases in the beginning of the treatment and thereafter decreases during two weeks. After two to four weeks, the testosterone levels have decreased to castration level.

Disease flare (temporary deterioration of the patient's condition) has been reported at the beginning of the treatment. The incidence is variable, but of the order of the 10 %.

Symptoms are usually confined to transient increase in pain, but the exact nature depends on the site of the lesions.

Disease flare is prevented by the prophylactic use of an anti-androgen so it is strongly recommended that administration of an anti-androgen be started as adjunctive therapy (e.g. cyproterone acetate, 300 mg daily) about 5 days before starting treatment. This adjunctive therapy must be continued in parallel with buserelin therapy for 3 to 4 weeks. After this time testosterone levels have usually fallen into the desired range in response to buserelin.

Neurological sequelae have been reported where secondary deposits impinge upon the spinal cord or CNS. In patients with known metastases, e.g. of the spinal column, this adjunctive therapy with an anti-androgen is indispensable to prevent initial complications up to and including, for example, spinal compression and paralysis, arising from a transient activation of the tumour and its metastases (see section 4.8).

Published epidemiological studies suggest a relationship between gonadotrophin releasing hormone (GnRH) agonist treatment and increased risk of cardiovascular disease (such as myocardial infarction, sudden cardiac death, and stroke) and diabetes mellitus.

These risks should be evaluated before initiating and during therapy, and patients should be monitored and treated accordingly.

Due to testosterone suppression, GnRH agonist therapy may increase the risk of anaemia. Patients should be evaluated for this risk and managed accordingly.

Once testosterone levels have started to fall below their baseline concentration clinical improvement should start to become apparent. If testosterone levels do not reach the therapeutic range within 4 weeks (6 weeks at the latest) the dose schedule should be checked to be sure that it is being followed exactly. It is unlikely that a patient who is taking the full dose will not show a suppression of testosterone to the therapeutic range. If this is the case, alternative therapy should be considered.

After the initial determination, testosterone levels should be monitored at 3-monthly intervals. A proportion of patients will have tumours that are not sensitive to hormone manipulation. Absence of clinical improvement in the face of adequate testosterone suppression is diagnostic of this condition, which will not benefit from further therapy with buserelin.

Warnings on excipients

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

This medicine contains 5 mg benzyl alcohol in each dosage unit (0,5 ml) which is equivalent to 10 mg/ml solution.

Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children.

Do not give to your newborn baby (up to 4 weeks old), unless recommended by your doctor.

Do not use for more than a week in young children (less than 3 years old) due to increased risk of accumulation in young children, unless advised by your doctor or pharmacist.

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interaction with other medicinal products and other forms of interaction

During treatment with Buserelin, the effect of antidiabetic agents may be attenuated.

In concomitant treatment with sexual hormones ("add back"), the dosage is to be selected so as to ensure that the overall therapeutic effect is not affected.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Suprefact Injection 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, etc. should be carefully evaluated.

4.6 Fertility, pregnancy and lactation

Suprafact is contraindicated in pregnancy. It is intended for the treatment of advanced prostatic carcinoma, it should not be used in pregnant or lactating women.

Buserelin passed into breast milk in small amounts. Although negative effects on the infant have not been observed, it is recommended that breast-feeding be avoided during treatment with Suprefact in order to prevent the infant from ingesting small quantities of buserelin with breast milk.

4.7 Effects on ability to drive and use machines

Certain adverse effects (e.g. dizziness) may impair the ability to concentrate and react, and therefore constitute a risk in situations where these abilities are of special importance (e.g. operating a vehicle or machinery).

4.8 Undesirable effects

The following CIOMS frequency rating is used: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10 000 to <1/1000); very rare (<1/10 000), not known (cannot be estimated from the available data).

In isolated cases severe hypersensitivity reactions with shock can occur. These may become manifest as reddening of the skin, itching, skin rashes (including urticaria) and allergic asthma with dyspnoea as well as, in isolated cases leading to anaphylactic / anaphylactoid shock.

After administration of the injection, pain or local reaction at the injection site is possible.

At the beginning of treatment, a transient rise in the serum testosterone level usually develops and may lead to temporary activation of the tumour with secondary reactions such as:

- occurrence of exacerbation of bone pain in patients with metastases,

- signs of neurological deficit due to tumour compression with e.g. muscle weakness in the legs,

- impaired micturition, hydronephrosis or lymphostasis,

- thrombosis with pulmonary embolism.

Such reactions can be largely avoided when an anti-androgen is given concomitantly in the initial phase of buserelin treatment (see section 4.4 Precautions and Warnings).

However, even with concomitant anti-androgen therapy, a mild but transient increase in tumour pain as well as a deterioration in general well being may develop in some patients.

<u>Suprefact Injection treatment may also lead to:</u>

Neoplasms benign and malignant – Very rare cases of pituitary adenomas were reported during treatment with LH-RH agonists, including buserelin.

Blood disorders – Very rare cases of thrombocytopenia or leukopenia.

Metabolism and nutrition disorders – Frequent increase or decrease in weight Occasional changes in appetite and increased thirst. Rarely increase or decrease in blood lipid levels. Very rarely, reduction in glucose tolerance which may lead to the worsening of metabolic control in diabetics.

Psychiatric disorders – Frequent nervousness, emotional instability. Occasional anxiety, depression or worsening of existing depression.

Nervous system disorders – Dizziness, headache, sleep disturbances, tiredness, drowsiness. Occasional paraesthesia (especially in the arms or legs), disturbances of memory and concentration.

Eye disorders – Occasional dry eyes (possibly leading to eye irritations in people who wear contact lenses), impaired vision (e.g. blurred vision), feeling of pressure behind the eyes.

Ear and labyrinth disorders – Rare cases of tinnitus, hearing disorders found.

Cardiac disorders – Frequent palpitations.

Frequency unknown: QT prolongation (see sections 4.4 and 4.5)

Vascular disorders – Occasional oedema (of face and extremities) and hot flushes. Very rare cases of a deterioration of blood pressure levels in patients with hypertension.

Gastrointestinal disorders – Frequent lower abdominal pain, stomach ache, nausea, vomiting, diarrhoea, constipation.

Hepato-biliary disorders – Occasional, increase in serum liver enzyme levels (e.g. transaminases), increase in serum bilirubin.

Skin and subcutaneous tissue disorders – Frequent dry skin, acne, increase or decrease in scalp hair (alopecia, hirsutism). Occasional increase or decrease in body hair, splitting nails.

Musculoskeletal and bone disorders – Frequent musculoskeletal discomfort and pain (including shoulder pain/stiffness). The use of LHRH-agonists may be associated with decreased bone density and may lead to osteoporosis and an increased risk of bone fracture. The risk of skeletal fracture increases with the duration of therapy.

Reproductive system and breast disorders – Occasional gynaecomastia (increase in breast size) which is usually painless, atrophy of the testes, decrease in libido and potency (in most patients; result of hormone deprivation).

Most of the effects listed above are directly or indirectly related to the suppression of testosterone by buserelin (symptoms of androgen deficiency).

4.9 Overdose

Overdose may lead to signs and symptoms such as asthenia, headache, nervousness, hot flushes, dizziness, nausea, abdominal pain, oedemas of the lower extremities, and mastodynia as well as to local reactions at the injection site such as pain, haemorrhage and induration. Treatment should be symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents - endocrine therapy - hormones and related agents - gonadotropin releasing hormone analogues - buserelin, ATC code: L02AE01

Buserelin is a synthetic peptide. It is a superactive analogue of natural gonadotrophin releasing hormone (gonadorelin, LHRH or GNRH). After an initial stimulation of gonodotrophin release, it down-regulates the hypothalamic-pituitary-gonadal axis.

5.2 Pharmacokinetic properties

The bioavailability of buserelin after subcutaneous injection is 100%. C_{max} occurs at about 1 Metabolic inactivation by peptidases occurs in the liver and kidney. The drug is also inactivated by pituitary membrane enzymes.

5.3 Preclinical safety data

None Stated

6. Pharmaceutical particulars

6.1 List of excipients
Sodium chloride BP
Sodium dihydrogen phosphate BP.
Sodium hydroxide BP.
Benzyl alcohol BP.
Water for Injections USP.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store Below 30°C. Do not freeze. Protect from light.
Keep out of reach of children.

6.5 Nature and contents of container
10 ml moulded clear glass vials USP type-I plugged with chloro butyl rubber plug and sealed with 20mm flip off aluminium seal.

6.6 Special precautions for disposal and other handling
None

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