Core Safety Profile
Triptorelin 1-month/3-month formulation
ATC-code: L02A E 04
March 2010

4.3 Contraindications

Hypersensitivity to GnRH, its analogues or any other component of the medicinal product (refer to section undesirable effects).

Pregnancy and Lactation period

4.4 Special warnings and precautions for use

The use of GnRH agonists may cause reduction in bone mineral density. In men, preliminary data suggest that the use of a bisphosphonate in combination with an GnRH agonist may reduce bone mineral loss.
Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition).

It should be confirmed that the patient is not pregnant before prescription of triptorelin.

Rarely, treatment with GnRH agonists may reveal the presence of a previously unknown gonadotroph cell pituary adenoma. These patients may present with a pituitary apoplexy characterised by sudden headache, vomiting, visual impairment and ophthalmoplegia.

Mood changes, including depression have been reported. Patients with known depression should be monitored closely during therapy.

Prostate cancer

Initially, triptorelin, like other GnRH agonists, causes a transient increase in serum testosterone levels. As a consequence, isolated cases of transient worsening of signs and symptoms of prostate cancer may occasionally develop during the first weeks of treatment. During the initial phase of treatment, consideration should be given to the additional administration of a suitable anti-androgen to counteract the initial rise in serum testosterone levels and the worsening of clinical symptoms.

A small number of patients may experience a temporary worsening of signs and symptoms of their prostate cancer (tumour flare) and temporary increase in cancer related pain (metastatic pain), which can be managed symptomatically.

As with other GnRH agonists, isolated cases of spinal cord compression or urethral obstruction have been observed. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy (surgical castration) should be considered. Careful monitoring is indicated during the first weeks of treatment, particularly in patients suffering from vertebral metastasis, at the risk of spinal cord compression, and in patients with urinary tract obstruction.

After surgical castration, triptorelin does not induce any further decrease in serum testosterone levels.

Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone loss and may lead to osteoprosis and increased risk of bone fracture.

In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance), or an increased risk of cardiovascular disease during androgen deprivation therapy. However, prospective data did not confirm the link between treatment with GnRH analogues and an increase in cardiovascular mortality. Patients at high risk for metabolic or cardiovascular diseases should be carfully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.

Administration of triptorelin in therapeutic doses result in suppression of the pituitary gonadal system. Normal function is usually restored after treatment is discontinued. Diagnostic tests of pituitary gonadal function conducted during treatment and after discontinuation of therapy with GnRH analogues may therefore be misleading.

Females
Loss of bone mineral density
The use of GnRH agonists is likely to cause reduction in bone mineral density averaging 1% per month during a six month treatment period. Every 10% reduction in bone mineral density is linked with about a two to three times increased fracture risk.
In the majority of women, currently available data suggest that recovery of bone loss occurs after cessation of therapy.
No specific data is available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abusus, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition, e.g. anorexia nervosa). Since reduction in bone mineral density is likely to be more detrimental in these patients, treatment with triptorelin should be considered on an individual basis and only be initiated if the benefits of treatment outweigh the risk following a very careful appraisal. Consideration should be given to additional measures in order to counteract loss of bone mineral density."

Uterine fibromyomas and endometriosis
Used at the recommended dose, triptorelin causes constant hypogonadotrophic amenorrhoea. If genital haemorrhage occurs after the first month, plasma oestradiol levels should be measured and if levels are below 50 pg/ml, possible organic lesions should be investigated.

After withdrawal of treatment, ovarian function resumes and ovulation occurs approximately 2 month after the last injection. A non-hormonal method of contraception should be used throughout treatment including for 1 month after the last injection.

Since menses should stop during triptorelin treatment, the patient should be instructed to notify her physician if regular menstruation persists.

It is recommended that during treatment of uterine fibroids, the size of the fibroid is determined regularly. There have been a few reports of bleeding in patients with submucous fibroids following GnRH analogue therapy. Typically the bleeding has occurred 6 - 10 weeks after the initiation of therapy.

Female infertility
Follicular recruitment, induced by the use of GnRH analogues and gonadotrophins, may be markedly increased in a minority of predisposed patients, particularly in case of Polycystic Ovarian Syndrome.

As with other GnRH analogues there have been reports of ovarian hyperstimulation syndrome (OHSS) associated with the use of triptorelin in combination with gonadotrophins.

In patients with renal or hepatic impairment, triptorelin has a mean terminal half life of 7-8 hours compared to 3-5 hours in healthy subjects. Despite this prolonged exposure, triptorelin is not expected to be present in circulation at the time of embryo transfer.

Precocious puberty
Treatment of children with progressive brain tumours should follow a careful individual appraisal of the risks and benefits.

In girls initial ovarian stimulation at treatment initiation, followed by the treatment-induced oestrogen withdrawal, may lead, in the first month, to vaginal bleeding of mild or moderate intensity.

After discontinuation of treatment the development of puberty characteristics will occur.

Information with regards to future fertility is still limited. In most girls, regular menses will start on average one year after ending the therapy.

Pseudo-precocious puberty (gonadal or adrenal tumour or hyperplasia) and gonadotropin-independent precocious puberty (testicular toxicosis, familial Leydig cell hyperplasia) should be precluded.

Slipped femoral epiphysis can be seen after withdrawal of GnRH treatment. The suggested theory is that the low concentrations of estrogen during treatment with GnRH agonists weakens the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.

4.5 Interaction with other medicinal products and other forms of interaction

When triptorelin is co-administered with drugs affecting pituitary secretion of gonadotrophins caution should be given and it is recommended that the patient's hormonal status should be supervised.

4.6 Pregnancy and lactation

Pregnancy
Triptorelin should not be used during pregnancy since concurrent use of GnRH agonists is associated with a theoretical risk of abortion or foetal abnormality. Prior to treatment, potentially fertile women should be examined carefully to exclude pregnancy. Non-hormonal methods of contraception should be employed during therapy until menses resume.
Pregnancy should be excluded before the triptorelin depot is used for fertilisation treatment. When triptorelin is used in this setting, there is no clinical evidence to suggest a causal connection between triptorelin and any subsequent abnormalities of oocyte development or pregnancy or outcome.

Lactation:
Triptorelin should not be used during breast feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, the ability to drive and use machines may be impaired should the patient experience dizziness, somnolence and visual disturbances being possible undesirable effects of treatment, or resulting from the underlying disease.

4.8 Undesirable effects

Clinical trials experience

General tolerance in men

As seen with other GnRH agonist therapies or after surgical castration, the most commonly observed adverse events related to triptorelin treatment were due to its expected pharmacological effects: Initial increase in testosterone levels, followed by almost complete suppression of testosterone. These effects included hot flushes (50%), erectile dysfunction (4%) and decreased libido (3%).

The following adverse reactions, considered as at least possibly related to triptorelin treatment, were reported. Most of these are known to be related to biochemical or surgical castration.

The frequencies of ADRs in the European SPCs of the several products should be based on the data from clinical studies of the respective MAH (see comment point 18)

System Organ Class	AEs	Additional post-marketing AEs
Blood and lymphatic system disorders	Purpura	
Ear and labyrinth disorders	Tinnitus Vertigo	
Endocrine disorders	Diabetes mellitus	Gynaecomastia
Eye disorders	Abnormal sensation in eye Visual disturbance	Vision blurred
Gastrointestinal disorders	Nausea Abdominal pain Constipation Diarrhoea Vomiting Abdominal distension Dry mouth Dysgeusia Flatulence	
General disorders and administration site conditions	Asthenia Hyperhidrosis Fatigue Injection site erythema Injection site inflammation Injection site pain Injection site reaction Oedema Lethargy Pain Rigors Somnolence Chest pain Dysstasia Influenza like illness Pyrexia	Malaise
Immune system disorders	Anaphylactic reaction Hypersensitivity	Hypersensitivity reaction
Infections and infestations	Nasopharyngitis	
Investigations	Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatinine increased	Blood pressure increased

System Organ Class	AEs	Additional post-marketing AEs
	Blood urea increased Weight increased Blood alkaline phosphatase increased Body temperature increased Weight decreased	
Metabolism and nutrition disorders	Anorexia Gout Increased appetite	
Musculoskeletal and connective tissue disorders	Back pain Musculoskeletal pain Pain in extremity Arthralgia Muscle cramp Muscular weakness Myalgia Joint stiffness Joint swelling Musculoskeletal stiffness Osteoarthritis	Bone pain
Nervous system disorders	Paraesthesia in lower limbs Dizziness Headache Paraesthesia Memory impairment	
Psychiatric disorders	Depression Insomnia Irritability Mood swings Confusional state Decreased activity Euphoric mood	Anxiety and confusional state
Reproductive system and breast disorders	Erectile dysfunction Loss of libido Gynaecomastia Breast pain Testicular atrophy Testicular pain Ejaculation failure	
Respiratory, thoracic and mediastinal disorders	DYSPNOEA ORTHOPNOEA	
Skin and subcutaneous tissue disorders	HYPERHYDROSIS Acne Alopecia Pruritus Rash Blister	Angioneurotic oedema Urticaria
Vascular disorders	Hot flush Hypertension Epistaxis	

System Organ Class	AEs	Additional post-marketing AEs
	Hypotension	

Triptorelin causes a transient increase in circulating testosterone levels within the first week after the initial injection of the sustained release formulation. With this initial increase in circulating testosterone levels, a small percentage of patients (≤ 5%) may experience a temporary worsening of signs and symptoms of their prostate cancer (tumour flare), usually manifested by an increase in urinary symptoms (< 2%) and metastatic pain (5%), which can be managed symptomatically. These symptoms are transient and usually disappear in one to two weeks.

Isolated cases of exacerbation of disease symptoms, either urethral obstruction or spinal cord compression by metastasis have occurred. Therefore, patients with metastatic vertebral lesions and/or with upper or lower urinary tract obstruction should be closely observed during the first few weeks of therapy (see Special warnings and special precautions for use).

The use of GnRH agonists, to treat prostate cancer may be associated with increased bone loss and may lead to osteoporosis and increases the risk of bone fracture.

General tolerance in women (refer to Special Warnings and Precautions for use)

As a consequence of decreased oestrogen levels, the most commonly reported adverse events (expected in 10% of women or more) were headache, libido decreased, sleep disorder, mood altered, dyspareunia, dysmenorrhoea, genital haemorrhage, ovarian hyperstimulation syndrome, ovarian hypertrophy pelvic pain, abdominal pain, vulvovaginal dryness, hyperhidrosis, hot flushes and asthenia.'

The following adverse reactions, considered as at least possibly related to triptorelin treatment, were reported. Most of these are known to be related to biochemical or surgical castration.

The frequencies of ADRs in the European SPCs of the several products should be based on the data from clinical studies of the respective MAH (see comment point 18)

System Organ Class	AEs	Additional post-marketing AEs
Gastrointestinal disorders	Nausea Abdominal pain Abdominal discomfort	Diarrhoea Vomiting
General disorders and administration site conditions	Injection site erythema Injection site inflammation Injection site pain	Pyrexia Malaise
Investigations	Weight increased	Blood pressure increased
Musculoskeletal and connective tissue disorders	Arthralgia Muscle spasms	Myalgia Muscular weakness
Nervous system disorders	Headache Libido decreased	Dizziness
Psychiatric disorders	Sleep disorder Mood altered	Depression Anxiety and confusional state
Reproductive system and breast disorders	Dyspareunia Dysmenorrhoea Genital haemorrhage (including menorrhagia, metrorrhagia) Libido decreased Ovarian hyperstimulation syndrome Ovarian hypertrophy Pelvic pain Vulvovaginal dryness Breast pain	Amenorrhoea
Skin and subcutaneous tissue disorders	Hyperhidrosis	Angioneurotic oedema Pruritus Rash Urticaria
Vascular disorders	Hot flush	
Respiratory, thoracic and mediastinal disorders		Dyspnoea
Eye disorders		Vision blurred Visual disturbance
Ear and labyrinth disorders		Vertigo
Immune system disorders		Hypersensitivity reaction

At the beginning of treatment, the symptoms of endometriosis including pelvic pain, dysmenorrhoea may be exacerbated very commonly (≥ 10%) during the initial transient increase in plasma oestradiol levels. These symptoms are transient and usually disappear in one or two weeks.
Genital haemorrhage including menorrhagia, metrorrhagia may occur in the month following the first injection.
When used to treat infertility, the combination with gonadotrophins may result in ovarian hyperstimulation syndrome. Ovarian hypertrophy, pelvic and/or abdominal pain may be observed.

General tolerance in children (refer to Special Warnings and Precautions for use)

The frequencies of ADRs in the European SPCs of the several products should be based on the data from clinical studies of the respective MAH (see comment point 18)

System Organ Class	AEs	Additional post-marketing AEs
Gastrointestinal disorders		Vomiting Abdominal pain Abdominal discomfort
General disorders and administration site conditions	Pain Erythema Injection site erythema Injection site inflammation Injection site pain	Malaise
Investigations		Blood pressure increased Weight increased
Musculoskeletal and connective tissue disorders		Myalgia
Nervous system disorders	Headache	
Psychiatric disorders		Affect lability Nervousness
Reproductive system and breast disorders	Genital haemorrhage Vaginal bleeding	
Vascular disorders	Hot flush	
Respiratory, thoracic and mediastinal disorders		Epistaxis
Eye disorders		Vision blurred Visual disturbance
Skin and subcutaneous tissue disorders		Angioneurotic oedema Rash Urticaria
Immune system disorders	Hypersensitivity reaction	Hypersensitivity reaction

4.9 Overdose

If overdose occurs, symptomatic management is indicated.

Core Safety Profile
Triptorelin 0.1 mg

4.3 Contraindications

Hypersensitivity to GnRH, its analogues or any other component of the medicinal product (refer to section on undesirable effects).

Pregnancy and Lactation period

4.4 Special warnings and precautions for use

The use of GnRH agonists may cause reduction in bone mineral density. In men, preliminary data suggest that the use of a bisphosphonate in combination with an GnRH agonist may reduce bone mineral loss.
Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition).

It should be confirmed that the patient is not pregnant before prescription of triptorelin.

Rarely, treatment with GnRH agonists may reveal the presence of a previously unknown gonadotroph cell pituary adenoma. These patients may present with a pituitary apoplexy characterised by sudden headache, vomiting, visual impairment and ophthalmoplegia.

Mood changes, including depression have been reported. Patients with known depression should be monitored closely during therapy.

Prostate cancer

Initially, triptorelin, like other GnRH agonists, causes a transient increase in serum testosterone levels. As a consequence, isolated cases of transient worsening of signs and symptoms of prostate cancer may occasionally develop during the first weeks of treatment. During the initial phase of treatment, consideration should be given to the additional administration of a suitable anti-androgen to counteract the initial rise in serum testosterone levels and the worsening of clinical symptoms.

A small number of patients may experience a temporary worsening of signs and symptoms of their prostate cancer (tumour flare) and temporary increase in cancer related pain (metastatic pain), which can be managed symptomatically.

As with other GnRH agonists, isolated cases of spinal cord compression or urethral obstruction have been observed. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy (surgical castration) should be considered. Careful monitoring is indicated during the first weeks of treatment, particularly in patients suffering from vertebral metastasis, at the risk of spinal cord compression, and in patients with urinary tract obstruction.

After surgical castration, triptorelin does not induce any further decrease in serum testosterone levels.

Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone loss and may lead to osteoporosis and increased risk of bone fracture.

In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance), or an increased risk of cardiovascular disease during androgen deprivation therapy. However, prospective data did not confirm the link between treatment with GnRH analogues and an

increase in cardiovascular mortality. Patients at high risk for metabolic or cardiovascular diseases should be carfully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.

Administration of triptorelin in therapeutic doses result in suppression of the pituitary gonadal system. Normal function is usually restored after treatment is discontinued. Diagnostic tests of pituitary gonadal function conducted during treatment and after discontinuation of therapy with GnRH analogues may therefore be misleading.

Females
Loss of bone mineral density
The use of GnRH agonists is likely to cause reduction in bone mineral density averaging 1% per month during a six month treatment period. Every 10% reduction in bone mineral density is linked with about a two to three times increased fracture risk.
In the majority of women, currently available data suggest that recovery of bone loss occurs after cessation of therapy.
No specific data is available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abusus, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition, e.g. anorexia nervosa). Since reduction in bone mineral density is likely to be more detrimental in these patients, treatment with triptorelin should be considered on an individual basis and only be initiated if the benefits of treatment outweigh the risk following a very careful appraisal. Consideration should be given to additional measures in order to counteract loss of bone mineral density."

Female infertility

It should be confirmed that the patient is not pregnant before prescription of triptorelin 0.1 mg.

Follicular recruitment, induced by the use of GnRH analogues and gonadotrophins, may be markedly increased in a minority of predisposed patients, particularly in case of Polycystic Ovarian Syndrome.

As with other GnRH analogues there have been reports of ovarian hyperstimulation syndrome (OHSS) associated with the use of triptorelin in combination with gonadotrophins.

4.5 Interaction with other medicinal products and other forms of interaction

When triptorelin is co-administered with drugs affecting pituitary secretion of gonadotrophins caution should be given and it is recommended that the patient's hormonal status should be supervised.

4.6 Pregnancy and lactation

Pregnancy
Triptorelin should not be used during pregnancy since concurrent use of GnRH agonists is associated with a theoretical risk of abortion or foetal abnormality. Prior to treatment, potentially fertile women should be examined carefully to exclude pregnancy. Non-hormonal methods of contraception should be employed during therapy until menses resume.
Pregnancy should be excluded before the triptorelin depot is used for fertilisation treatment. When triptorelin is used in this setting, there is no clinical evidence to suggest a causal connection between triptorelin and any subsequent abnormalities of oocyte development or pregnancy or outcome.

Lactation:
Triptorelin should not be used during breast feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects of the ability to drive and use machines have been performed. However, due to its pharmacological profile triptorelin is likely to have no or negligible influence on the patient's ability to drive and use machine's

4.8 Undesirable effects

Clinical Trial experience

The adult population enrolled in clinical trials and treated with the triptorelin immediate release formulation included 127 male patients suffering from prostate cancer treated daily for 3 months and about 1000 women who underwent In Vitro Fertilization protocols. The additional detailed safety experience obtained during the clinical studies performed with the 1 Month and 3 Month formulations of triptorelin in men and women has also been included.

The overall analysis of the safety experience reported during the clinical trials included pharmacological class adverse reactions such as a result of hypogonadotrophic hypogonadism or occasionally the initial pituitary–gonadal stimulation.

Adverse Drug Reactions
Frequencies in the European SmPCs should be based on the data from clinical studies of the respective MAH (see comment point 18)

General tolerance in adults

mild to severe hot flushes and hyperhidrosis which do not usually require discontinuation of therapy.

General tolerance in men

At the beginning of treatment (refer to Special Warnings and Precautions for Use): Urinary symptoms, metastatic bone pain and symptoms associated with spinal cord compression from vertebral metastases (back-pain, asthenia, paraesthesia of the lower limbs) may be exacerbated when plasma testosterone is initially and transiently increased at the beginning of treatment. These symptoms are transient and usually disappear in one to two weeks.

During treatment: Libido decreased and erectile dysfunction are related to the decreased plasma testosterone levels resulting from the pharmacological effects of triptorelin.

General tolerance in women

At the beginning of treatment: When used to treat infertility, the combination with gonadotrophins may result in ovarian hyperstimulation syndrome. Ovarian hypertrophy, dyspnoea, pelvic and/or abdominal pain may be observed (refer to Special Warnings and Precautions for Use in paragraph infertility).

At the beginning of treatment with triptorelin 1 Month and 3 Month formulations: Genital haemorrhage including menorrhagia or metrorrhagia may occur in the month following the first injection.

During treatment with triptorelin 1 Month and 3 Month formulations: these adverse reactions showed a general pattern of hypo-oestrogenic events related to pituitary-ovarian blockade such as sleep disorder, headache, mood altered, vulvovaginal dryness and dyspareunia, libido decreased.

During treatment with triptorelin 1 Month formulation: breast pain, muscle spasms, arthralgia, weight increased, nausea, abdominal pain/discomfort, asthenia.

Local tolerance

pain, erythema and inflammation at the injection site.

Post marketing information

During post-marketing surveillance, additional undesirable effects have been reported in women treated for IVF. The undesirable effects are classified by body system organ categories and by decreasing order of frequency of reported effects:

Skin and subcutaneous tissue disorders: hypersensitivity reactions including pruritus, urticaria, rash and angioneurotic oedema (refer to section Contra-Indications).

Nervous system disorders: headache

Eye disorders: episodes of blurred vision or visual disturbance.

4.9 Overdose

No adverse reaction has been reported as a consequence of overdose.