Zoladex LA 10.8mg

4.8 Undesirable effects

The following frequency categories for adverse drug reactions (ADRs) were calculated based on reports from Zoladex clinical trials and post-marketing sources. The most commonly observed adverse reactions include hot flushes, sweating and injection site reactions.
The following convention has been used for classification of frequency: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000) and Not known (cannot be estimated from the available data).
Table: Zoladex LA adverse drug reactions presented by MedDRA System Organ Class

SOC	Frequency	Adverse reaction
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Very rare	Pituitary tumour
Immune system disorders	Uncommon	Drug hypersensitivity
	Rare	Anaphylactic reaction
Endocrine disorders	Very rare	Pituitary haemorrhage
Metabolism and nutrition disorders	Common	Glucose tolerance impaired[a]
Psychiatric disorders	Very common	Libido decreased[b]
	Common	Mood changes, depression
	Very rare	Psychotic disorder
Nervous system disorders	Common	Paraesthesia
		Spinal cord compression
Cardiac disorders	Common	Cardiac failure[f], myocardial infarction[f]
	Not known	QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	Very common	Hot flush[b]
	Common	Blood pressure abnormal[c]
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis[b]
	Common	Rash[d]
	Not known	Alopecia[g]
Musculoskeletal, connective tissue and bone disorders	Common	Bone pain[e]
	Uncommon	Arthralgia
Renal and urinary disorders	Uncommon	Ureteric obstruction
Reproductive system and breast disorders	Very common	Erectile dysfunction
	Common	Gynaecomastia

	Uncommon	Breast tenderness
General disorders and administration site conditions	Common	Injection site reaction
Investigations	Common	Bone density decreased (see section 4.4), weight increased

a A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycaemic control in those with pre-existing diabetes mellitus.
b These are pharmacological effects which seldom require withdrawal of therapy. Hyperhidrosis and hot flushes may continue after stopping Zoladex.
c These may manifest as hypotension or hypertension, have been occasionally observed in patients administered Zoladex. The changes are usually transient, resolving either during continued therapy or after cessation of therapy with Zoladex. Rarely, such changes have been sufficient to require medical intervention, including withdrawal of treatment from Zoladex.
d These are generally mild, often regressing without discontinuation of therapy.
e Initially, prostate cancer patients may experience a temporary increase in bone pain, which can be managed symptomatically.
f Observed in a pharmaco-epidemiology study of LHRH agonists used in the treatment of prostate cancer. The risk appears to be increased when used in combination with anti-androgens.
g Particularly loss of body hair, an expected effect of lowered androgen levels.

Post-marketing experience

A small number of cases of changes in blood count, hepatic dysfunction, pulmonary embolism and interstitial pneumonia have been reported in connection with Zoladex.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard

Zoladex 3.6mg Implant

4.8 Undesirable effects

The following frequency categories for adverse drug reactions (ADRs) were calculated based on reports from Zoladex clinical trials and post-marketing sources. The most commonly observed adverse reactions include hot flushes, sweating and injection site reactions.
The following convention has been used for classification of frequency: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000) and Not known (cannot be estimated from the available data).
Table: Zoladex 3.6 mg adverse drug reactions presented by MedDRA System Organ Class

SOC	Frequency	Males	Females
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Very rare	Pituitary tumour	Pituitary tumour
	Not known	N/A	Degeneration of uterine fibroid
Immune system disorders	Uncommon	Drug hypersensitivity	Drug hypersensitivity
	Rare	Anaphylactic reaction	Anaphylactic reaction
Endocrine disorders	Very rare	Pituitary haemorrhage	Pituitary haemorrhage
Metabolism and nutrition disorders	Common	Glucose tolerance impaired[a]	N/A
	Uncommon	N/A	Hypercalcaemia
Psychiatric disorders	Very common	Libido decreased[b]	Libido decreased[b]
	Common	Mood changes, depression	Mood changes, depression
	Very rare	Psychotic disorder	Psychotic disorder
Nervous system disorders	Common	Paraesthesia	Paraesthesia
		Spinal cord compression	N/A
		N/A	Headache
Cardiac disorders	Common	Cardiac failure[f], myocardial infarction[f]	N/A
	Not known	QT prolongation (see sections 4.4 and 4.5)	QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	Very common	Hot flush[b]	Hot flush[b]
	Common	Blood pressure abnormal[c]	Blood pressure abnormal[c]
Skin and subcutaneous tissue	Very common	Hyperhidrosis[b]	Hyperhidrosis[b], acne[i]
	Common	Rash[d]	Rash[d], alopecia[g]

SOC	Frequency	Males	Females
disorders	Not Known	Alopecia[h]	(see Common)
Musculoskeletal, connective tissue and bone disorders	Common	Bone pain[e]	N/A
		(see Uncommon)	Arthralgia
	Uncommon	Arthralgia	(see Common)
Renal and urinary disorders	Uncommon	Ureteric obstruction	N/A
Reproductive system and breast disorders	Very common	Erectile dysfunction	N/A
		N/A	Vulvovaginal dryness
		N/A	Breast enlargement
	Common	Gynaecomastia	N/A
	Uncommon	Breast tenderness	N/A
	Rare	N/A	Ovarian cyst
		N/A	Ovarian hyperstimulation syndrome (if concomitantly used with gonadotrophins)
	Not known	N/A	Withdrawal bleeding (see section 4.4)
General disorders and administration site conditions	Very common	(see Common)	Injection site reaction
	Common	Injection site reaction	(see Very common)
		N/A	Tumour flare, tumour pain (on initiation of treatment)
Investigations	Common	Bone density decreased (see section 4.4), weight increased	Bone density decreased (see section 4.4), weight increased

a A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycaemic control in those with pre-existing diabetes mellitus.
b These are pharmacological effects which seldom require withdrawal of therapy. Hyperhidrosis and hot flushes may continue after stopping Zoladex.
c These may manifest as hypotension or hypertension, have been occasionally observed in patients administered Zoladex. The changes are usually transient, resolving either during continued therapy or after cessation of therapy with Zoladex. Rarely, such changes have been sufficient to require medical intervention, including withdrawal of treatment from Zoladex.
d These are generally mild, often regressing without discontinuation of therapy.
e Initially, prostate cancer patients may experience a temporary increase in bone pain, which can be managed symptomatically.
f Observed in a pharmaco-epidemiology study of LHRH agonists used in the treatment of prostate cancer. The risk appears to be increased when used in combination with anti-androgens.

g Loss of head hair has been reported in females, including younger patients treated for benign conditions. This is usually mild but occasionally can be severe.
h Particularly loss of body hair, an expected effect of lowered androgen levels.
i In most cases acne was reported within one month after the start of Zoladex.

Post-marketing experience

A small number of cases of changes in blood count, hepatic dysfunction, pulmonary embolism and interstitial pneumonia have been reported in connection with Zoladex.
In addition, the following adverse drug reactions have been reported in women treated for benign gynaecological indications:
Acne, change of body hairs, dry skin, weight gain, increase in serum cholesterol, ovarian hyperstimulation syndrome (if concomitantly used with gonadotropines), vaginitis, vaginal discharge, nervousness, sleep disorder, tiredness, peripheral oedema, myalgias, cramp in the calves, nausea, vomiting, diarrhoea, constipation, abdominal complaints, alterations of voice.
Initially, breast cancer patients may experience a temporary increase in signs and symptoms, which can be managed symptomatically.
Rarely, breast cancer patients with metastases have developed hypercalcaemia on initiation of therapy. In the presence of symptoms indicative of hypercalcaemia (e.g. thirst), hypercalcaemia should be excluded.
Rarely, some women may enter the menopause during treatment with LHRH analogues and not resume menses on cessation of therapy. Whether this is an effect of Zoladex treatment or a reflection of their gynaecological condition is not known.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard

Casodex 150 mg Film-coated Tablets.

4.8 Undesirable effects

In this section, undesirable effects are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to ≤1/100); rare (≥ 1/10,000 to ≤1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data).

Table 1 Frequency of Adverse Reactions

System Organ Class	Frequency	Event
Blood and the lymphatic system disorders	Common	Anaemia
Immune system disorders	Uncommon	Hypersensitivity, angioedema and urticaria
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Common	Decreased libido Depression
Nervous system disorders	Common	Dizziness Somnolence
Cardiac disorders	Not known	QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	Common	Hot flush
Respiratory, thoracic and mediastinal disorders	Uncommon	Interstitial lung disease[e] (fatal outcomes have been reported).
Gastrointestinal disorders	Common	Abdominal pain Constipation Dyspepsia Flatulence Nausea
Hepato-biliary disorders	Common	Hepatotoxicity, jaundice, hypertransaminasaemia[a]
	Rare	Hepatic failure[d] (fatal outcomes have been reported).
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Alopecia Hirsutism/hair re-growth Dry skin[c] Pruritis
	Rare	Photosensitivity reaction
Renal and urinary disorders	Common	Haematuria
Reproductive system and breast disorders	Very common	Gynaecomastia and breast tenderness[b]

	Common	Erectile dysfunction
General disorders and administration site conditions	Very common	Asthenia
	Common	Chest pain Oedema
Investigations	Common	Weight increased

a. Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.
b. The majority of patients receiving Casodex 150 mg as monotherapy experience gynaecomastia and/or breast pain. In studies these symptoms were considered to be severe in up to 5% of the patients. Gynaecomastia may not resolve spontaneously following cessation of therapy, particularly after prolonged treatment.
c. Due to the coding conventions used in the EPC studies, adverse events of 'dry skin' were coded under the COSTART term of 'rash'. No separate frequency descriptor can therefore be determined for the 150 mg Casodex dose however the same frequency as the 50 mg dose is assumed.
d. Listed as an adverse drug reaction following review of post-marketed data. Frequency has been determined from the incidence of reported adverse events of hepatic failure in patients receiving treatment in the open-label Casodex arm of the 150 mg EPC studies.
e. Listed as an adverse drug reaction following review of post-marketed data. Frequency has been determined from the incidence of reported adverse events of interstitial pneumonia in the randomised treatment period of the 150 mg EPC studies.
Increased PT/INR: Accounts of coumarin anticoagulants interacting with Casodex have been reported in postmarketing surveillance (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard.

Prostap 3 DCS

4.8 Undesirable effects

Adverse reactions seen with PROSTAP 3 are due mainly to the specific pharmacological action, namely increases and decreases in certain hormone levels. The following tables list adverse reactions with leuprorelin based on experience from clinical trials as well as from post-marketing experience. Adverse reactions are grouped by MedDRA System Organ Classes and frequency classification. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Men: In cases where a "tumour flare" occurs after PROSTAP 3 therapy, an exacerbation may occur in any symptoms or signs due to disease, for example, bone pain, urinary obstruction, weakness of the lower extremities and paraesthesia. These symptoms subside on continuation of therapy.

Tabulated list of adverse reactions

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders						anaemia (reported in medicinal products of this class), thrombocytopaenia, leucopenia
Immune system disorders						hypersensitivity reactions (including rash, pruritus, urticaria and rarely, wheezing or interstitial pneumonitis, anaphylactic reactions)
Metabolism and nutrition disorders	weight fluctuation	decreased appetite				Lipids abnormal, glucose tolerance abnormal
Psychiatric disorders		insomnia, depression (see Section 4.4), mood changes (long-term use)**	mood changes (short term use)**			

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Nervous system disorders		headache (occasionaly severe)	dizziness, parasthesiae		pituitary apoplexy has been reported following initial administration in patients with pituitary adenoma	paralysis (see Section 4.4), seizure
Eye disorders						visual impairment
Cardiac disorders						palpitations, electrocardiogram QT prolonged (see Sections 4.4 and 4.5)
Vascular disorders	hot flush					pulmonary embolism, hypertension, hypotension (see Section 4.4)
Gastrointestinal disorders		nausea	diarrhoea, vomiting			
Hepatobiliary disorders		hepatic function abnormal, liver function test abnormal (usually transient)				jaundice
Skin and subcutaneous tissue disorders	hyperhydrosis					
Musculoskeletal, connective tissue and bone disorders	muscle weakness, bone pain	arthralgia	myalgia, weakness of lower extremities			spinal fracture (see Section 4.4), reduction in bone mass which may occur with the use of GnRH agonists
Renal and urinary disorders						urinary tract obstruction
Reproductive system and breast disorders	Libido decreased, erectile dysfunction, testicular atrophy	gynaecomastia				

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
General disorders and administration site conditions	Fatigue, injection site reaction, e.g., induration, erythema, pain, abscesses, swelling, nodules, ulcers and necrosis	oedema peripheral				pyrexia

** mood changes (long term use: frequency of 'common' and short term use: frequency of 'uncommon'

Women: Those adverse events occurring most frequently with PROSTAP 3 are associated with hypo-estrogenism; the most frequently reported are hot flushes, mood swings including depression (occasionally severe), and vaginal dryness. Estrogen levels return to normal after treatment is discontinued.

The induced hypo-estrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible (see Section 4.4).

Vaginal haemorrhage may occur during therapy due to acute degeneration of submucous fibroids (see Section 4.4).

Tabulated list of adverse reactions

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders						Anaemia (reported in medicinal products of this class), thrombocytopaenia, leucopenia
Immune system disorders						hypersensitivity reactions (including rash, pruritus, urticaria and rarely, wheezing and interstitial pneumonitis, anaphylactic reactions)
Metabolism and nutrition disorders		weight fluctuation	decreased appetite, lipids abnormal			glucose tolerance abnormal, which may affect diabetic control

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Psychiatric disorders	insomnia	mood altered depression (see Section 4.4)				
Nervous system disorders	headache (occasionally severe)	parasthesiae, dizziness			pituitary haemorrhage has been reported following initial administration in patients with pituitary adenoma	paralysis (see Section 4.4), seizure
Eye disorders			visual impairment			
Cardiac disorders			palpitations			
Vascular disorders	hot flush					pulmonary embolism, hypertension, hypotension (see Section 4.4)
Gastrointestinal disorders		nausea	diarrhoea, vomiting			
Hepatobiliary disorders			liver function test abnormal (usually transient)			hepatic function abnormal, jaundice
Skin and subcutaneous tissue disorders			hair loss			
Musculoskeletal, connective tissue and bone disorders		arthralgia, muscle weakness	myalgia			spinal fracture (see section 4.4), reduction in bone mass which may occur with the use of GnRH agonists
Reproductive system and breast disorders		breast tenderness, breast atrophy, vulvovaginal dryness				vaginal haemorrhage

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
General disorders and administration site conditions		Oedema peripheral, injection site reaction e.g.injection site induration, erythema, pain, abscesses, swelling, nodules, ulcers and necrosis	pyrexia, fatigue			

In Children:

In the initial phase of therapy, a short-term increase as flare-up of the sex hormone level occurs, followed by a decrease to values within the pre-pubertal range. Due to this pharmacological effect, adverse events may occur particularly at the beginning of treatment.

Tabulated list of adverse reactions

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders					Hypersensitivity (fever, rash, e.g. itching, anaphylactic reactions)	
Psychiatric disorders		emotional lability				
Nervous system disorders		headache			pituitary haemorrhage following initial administration in patients with pituitary adenoma	seizure
Gastrointestinal disorders		abdominal pain / abdominal cramps, nausea/vomiting				
Skin and subcutaneous tissue disorders		acne				
Reproductive system and breast disorders		vaginal haemorrhage, spotting**, vaginal discharge				

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
General disorders and administration site conditions		injection site reactions				

** In general, the occurrence of vaginal spotting with continued treatment (subsequent to possible withdrawal bleeding in the first month of treatment) should be assessed as a sign of potential underdosage. The pituitary suppression should then be determined by an LHRH test.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

Prostap SR DCS

4.8 Undesirable effects

Adverse reactions seen with PROSTAP SR are due mainly to the specific pharmacological action, namely increases and decreases in certain hormone levels. The following tables list adverse reactions with leuprorelin based on experience from clinical trials as well as from post-marketing experience. Adverse reactions are grouped by MedDRA System Organ Classes and frequency classification. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Men: In cases where a "tumour flare" occurs after PROSTAP SR therapy, an exacerbation may occur in any symptoms or signs due to disease, for example, bone pain, urinary obstruction, weakness of the lower extremities and paraesthesia. These symptoms subside on continuation of therapy.

Tabulated list of adverse reactions

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders						anaemia (reported in medicinal products of this class), thrombocytopaenia, leucopenia
Immune system disorders						hypersensitivity reactions (including rash, pruritus, urticaria and rarely, wheezing or interstitial pneumonitis, anaphylactic reactions)
Metabolism and nutrition disorders	weight fluctuation	decreased appetite				Lipids abnormal, glucose tolerance abnormal
Psychiatric disorders		insomnia, depression (see Section 4.4), mood changes (long-term use)**	mood changes (short term use)**			
Nervous system disorders		headache (occasionaly severe)	dizziness, parasthesiae		pituitary apoplexy has been reported following initial administration in patients with pituitary adenoma	paralysis (see Section 4.4), seizure

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Eye disorders						visual impairment
Cardiac disorders						palpitations, electrocardiogram QT prolonged (see Sections 4.4 and 4.5)
Vascular disorders	hot flush					pulmonary embolism, hypertension, hypotension (see Section 4.4)
Gastrointestinal disorders		nausea	diarrhoea, vomiting			
Hepatobiliary disorders		hepatic function abnormal, liver function test abnormal (usually transient)				jaundice
Skin and subcutaneous tissue disorders	hyperhydrosis					
Musculoskeletal, connective tissue and bone disorders	muscle weakness, bone pain	arthralgia	myalgia, weakness of lower extremities			spinal fracture (see Section 4.4), reduction in bone mass which may occur with the use of GnRH agonists
Renal and urinary disorders						urinary tract obstruction
Reproductive system and breast disorders	Libido decreased, erectile dysfunction, testicular atrophy	gynaecomastia				
General disorders and administration site conditions	Fatigue, injection site reaction, e.g., induration, erythema, pain, abscesses, swelling, nodules, ulcers and necrosis	oedema peripheral				pyrexia

** mood changes (long term use: frequency of 'common' and short term use: frequency of 'uncommon'

Women: Those adverse events occurring most frequently with PROSTAP SR are associated with hypo-estrogenism; the most frequently reported are hot flushes, mood swings including depression (occasionally severe), and vaginal dryness. Estrogen levels return to normal after treatment is discontinued.

The induced hypo-estrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible (see Section 4.4).

Vaginal haemorrhage may occur during therapy due to acute degeneration of submucous fibroids (see Section 4.4).

Tabulated list of adverse reactions

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders						Anaemia (reported in medicinal products of this class), thrombocytopaenia, leucopenia
Immune system disorders						hypersensitivity reactions (including rash, pruritus, urticaria and rarely, wheezing and interstitial pneumonitis, anaphylactic reactions)
Metabolism and nutrition disorders		weight fluctuation	decreased appetite, lipids abnormal			glucose tolerance abnormal, which may affect diabetic control
Psychiatric disorders	insomnia	mood altered depression (see Section 4.4)				
Nervous system disorders	headache (occasionally severe)	parasthesiae, dizziness			pituitary haemorrhage has been reported following initial administration in patients with pituitary adenoma	paralysis (see Section 4.4), seizure
Eye disorders			visual impairment			
Cardiac disorders			palpitations			

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Vascular disorders	hot flush					pulmonary embolism, hypertension, hypotension (see Section 4.4)
Gastrointestinal disorders		nausea	diarrhoea, vomiting			
Hepatobiliary disorders			liver function test abnormal (usually transient)			hepatic function abnormal, jaundice
Skin and subcutaneous tissue disorders			hair loss			
Musculoskeletal, connective tissue and bone disorders		arthralgia, muscle weakness	myalgia			spinal fracture (see section 4.4), reduction in bone mass which may occur with the use of GnRH agonists
Reproductive system and breast disorders		breast tenderness, breast atrophy, vulvovaginal dryness				vaginal haemorrhage
General disorders and administration site conditions		Oedema peripheral, injection site reaction e.g.injection site induration, erythema, pain, abscesses, swelling, nodules, ulcers and necrosis	pyrexia, fatigue			

In Children: In the initial phase of therapy, a short-term increase as flare-up of the sex hormone level occurs, followed by a decrease to values within the pre-pubertal range. Due to this pharmacological effect, adverse events may occur particularly at the beginning of treatment.

Tabulated list of adverse reactions

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders					Hypersensitivity (fever, rash, e.g. itching, anaphylactic reactions)	
Psychiatric disorders		emotional lability				
Nervous system disorders		headache			pituitary haemorrhage following initial administration in patients with pituitary adenoma	seizure
Gastrointestinal disorders		abdominal pain / abdominal cramps, nausea/vomiting				
Skin and subcutaneous tissue disorders		acne				
Reproductive system and breast disorders		vaginal haemorrhage, spotting**, vaginal discharge				
General disorders and administration site conditions		injection site reactions				

** In general, the occurrence of vaginal spotting with continued treatment (subsequent to possible withdrawal bleeding in the first month of treatment) should be assessed as a sign of potential underdosage. The pituitary suppression should then be determined by an LHRH test

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

Decapeptyl SR 3mg

4.8 Undesirable effects
Clinical trials experience
General tolerance in men
Since patients suffering from locally advanced or metastatic, hormone-dependent prostate cancer are generally old and have other diseases frequently encountered in this aged population, more than 90% of the patients included in clinical trials reported adverse events, and often the causality is difficult to assess. 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. These effects included hot flushes and decreased libido. With the exception of immuno-allergic (rare) and injection site (< 5%) reactions, all adverse events are known to be related to testosterone changes.
The following adverse reactions considered as at least possibly related to triptorelin treatment were reported. Most of these events are known to be related to biochemical or surgical castration.
The frequency of the adverse reactions is classified as follows: very common (**≥**1/10); common (**≥**1/100, < 1/10); uncommon (**≥**1/1000, < 1/100); rare (**≥** 1/10000, < 1/1000).

System Organ Class	**Very Common**	**Common**	**Uncommon**	**Rare**	**Additional post-marketing AEs Frequency not known**
Infections and infestations				Nasopharyngitis	
Blood and lymphatic system disorders			Thrombocytosis		
Immune system disorders		Hypersensitivity		Anaphylactic reaction	Anaphylactic shock
Metabolism and nutrition disorders			Anorexia Diabetes mellitus Gout Hyperlipidaemia Increased appetite		
Psychiatric disorders	Libido decreased	Depression* Loss of libido Mood change*	Insomnia Irritability	Confusional state Decreased activity Euphoric mood	Anxiety
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	

System Organ Class	Very Common	Common	Uncommon	Rare	Additional post-marketing AEs Frequency not known
Eye disorders			Visual impairment	Abnormal sensation in eye Visual disturbance	
Ear and labyrinth disorders			Tinnitus Vertigo		
Cardiac Disorders			Palpitations		QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	Hot flush	Hypertension		Hypotension	
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	Orthopnoea	
Gastrointestinal disorders		Dry mouth Nausea	Abdominal pain Constipation Diarrhoea Vomiting	Abdominal distension Dysgeusia Flatulence	
Skin and subcutaneous tissue disorders	Hyperhidrosis		Acne Alopecia Erythema Pruritus Rash Urticaria	Blister Purpura	Angioneurotic oedema
Musculoskeletal and connective tissue disorders	Back pain	Musculoskeletal pain Pain in extremity	Arthralgia Bone pain Muscle cramp Muscular weakness Myalgia	Joint stiffness Joint swelling Musculoskeletal stiffness Osteoarthritis	
Renal and urinary disorders			Nocturia Urinary retention		Urinary incontinence
Reproductive system and breast disorders	Erectile dysfunction (including ejaculation failure, ejaculation disorder)	Pelvic pain	Breast pain Gynaecomastia Testicular atrophy Testicular pain		

System Organ Class	Very Common	Common	Uncommon	Rare	Additional post-marketing AEs Frequency not known
General disorders and administration site conditions	Asthenia	Injection site reaction (including erythema, inflammation and pain) Oedema	Lethargy Oedema peripheral Pain Rigors Somnolence	Chest pain Dysstasia Influenza like illness Pyrexia	Malaise
Investigations		Weight increased	Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatinine increased Blood pressure increased Blood urea increased Gamma-glutamyl transferase increased Weight decreased	Blood alkaline phosphatase increased	

* This frequency is based on class-effect frequencies common for all GnRH agonists
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 Section 4.4).
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 (see section 4.4)
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 changes, 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 frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1000, < 1/100); rare (≥1/10000, < 1/1000)

System Organ Class	Very Common	Common	Uncommon	Additional post-marketing AEs Frequency not known
Immune system disorders		Hypersensitivity		Anaphylactic shock
Metabolism and nutrition disorders			Decreased appetite Fluid retention	
Psychiatric disorders	Libido decreased Mood disorder Sleep disorder (including insomnia)	Depression* Nervousness	Affect lability Anxiety Depression** Disorientation	Confusional state
Nervous system disorders	Headache	Dizziness	Dysgeusia Hypoasthesia Syncope Memory impairment Disturbance in attention Paraesthesia Tremor	
Eye disorders			Dry eye Visual Impairment	Visual disturbance
Ear and labyrinth disorders			Vertigo	
Cardiac Disorders			Palpitations	
Vascular disorders	Hot flush			Hypertension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	
Gastrointestinal disorders		Abdominal pain Abdominal discomfort Nausea	Abdominal distension Dry mouth Flatulence Mouth ulceration Vomiting	Diarrhoea
Skin and subcutaneous tissue disorders	Acne Hyperhidrosis Seborrhoea		Alopecia Dry skin Hirsutism Onychoclasis Pruritus Rash	Angioneurotic oedema Urticaria

System Organ Class	Very Common	Common	Uncommon	Additional post-marketing AEs Frequency not known
Musculoskeletal and connective tissue disorders		Arthralgia Muscle spasms Pain in extremities	Back pain Myalgia	Muscular weakness
Reproductive system and breast disorders	Breast disorder Dyspareunia Genital bleeding (including vaginal bleeding withdrawal bleed) Ovarian hyperstimulation syndrome Ovarian hypertrophy Pelvic pain Vulvovaginal dryness	Breast pain	Coital bleeding Cystocele Menstrual disorder (including dysmenorrhoea, metrorrhagia and menorrhagia) Ovarian cyst Vaginal discharge	Amenorrhoea
General disorders and administration site conditions	Asthenia	Injection site reaction (including pain, swelling, erythema and inflammation) Oedema peripheral		Malaise Pyrexia
Investigations		Weight increased	Weight decreased	Blood alkaline phosphatase increased Blood pressure increased

*Long term use: This frequency is based on class-effect frequencies common for all GnRH agonists

** Short term use: This frequency is based on class-effect frequencies common for all GnRH agonists

At the beginning of treatment, the symptoms of endometriosis including pelvic pain and dysmenorrhoea may be very commonly exacerbated (≥ 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.

General

Increased lymphocytes count has been reported with patients undergoing GnRH agonist treatment. This secondary lymphocytosis is apparently related to GnRH induced castration and seems to indicate that gonadal hormones are involved in thymic involution.

Breast Cancer

The most commonly observed adverse reactions associated with triptorelin treatment for up to 5 years in combination with either tamoxifen or an aromatase inhibitor in the

TEXT and SOFT studies were hot flush, musculoskeletal disorder, fatigue, insomnia, hyperhidrosis, vulvovaginal dryness and depression.
The frequencies of the adverse reactions reported with triptorelin in combination with tamoxifen (N = 2325) or exemestane (N = 2318) are shown in the following table.
The classifications are as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000).

System Organ Classes	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10,000 to <1/1000**
Cardiac disorders			Myocardial Ischaemia	QT prolongation
Endocrine disorders		Diabetes mellitus (glucose intolerance) Hyperglycaemia		
Gastrointestinal disorders	Nausea			
General disorders and administration site conditions	Fatigue	Injection site reaction		
Immune system disorders		Hypersensitivity		
Musculoskeletal and connective tissue disorders	Musculoskeletal disorder Osteoporosis	Fracture		
Nervous system disorders			Cerebral ischaemia Central nervous system haemorrhage	
Psychiatric disorders	Insomnia Libido decreased Depression			
Renal and urinary disorders	Urinary incontinence			
Reproductive system and breast disorders	Dyspareunia Vulvovaginal dryness			
Skin and subcutaneous tissue disorders	Hyperhidrosis			
Vascular disorders	Hot flushes Hypertension	Embolism		

The ADRs identified above should be used in addition to the triptorelin ADRs identified in men and women in tables above to fully describe the ADR profile for the use of OFS in combination with either exemestane or tamoxifen.
Osteoporosis has been reported with a higher frequency with the use of triptorelin in combination with exemestane than in the combination with tamoxifen (39% versus 25%) (see section 4.4).
Musculoskeletal disorder and fractures were also more commonly reported in the combination with exemestane than in the combination with tamoxifen (89% versus 76% and 6.8% versus 5.2%, respectively)
Hypertension has been reported as a targeted adverse event at a very common frequency with triptorelin in combination with either exemestane or tamoxifen (23% and 22% respectively). Hyperglycaemia and diabetes have been reported as targeted adverse events at a common frequency with triptorelin in combination with either exemestane or tamoxifen (hyperglycaemia: 2.6% and 3.4% respectively; diabetes: 2.3% and 2.3% respectively).
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

Decapeptyl SR 11.25mg

4.8 Undesirable effects
Clinical trials experience
General tolerance in men
Since patients suffering from locally advanced or metastatic, hormone-dependent prostate cancer are generally old and have other diseases frequently encountered in this aged population, more than 90% of the patients included in clinical trials reported adverse events, and often the causality is difficult to assess. 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. These effects included hot flushes and decreased libido. With the exception of immuno-allergic (rare) and injection site (< 5%) reactions, all adverse events are known to be related to testosterone changes.
The following adverse reactions considered as at least possibly related to triptorelin treatment were reported. Most of these events are known to be related to biochemical or surgical castration.
The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1000, < 1/100); rare (≥1/10000, < 1/1000).

System Organ Class	Very Common	Common	Uncommon	Rare	Additional post-marketing AEs Frequency not known
Infections and infestations				Nasopharyngitis	
Blood and lymphatic system disorders			Thrombocytosis		
Immune system disorders		Hypersensitivity		Anaphylactic reaction	Anaphylactic shock
Metabolism and nutrition disorders			Anorexia Diabetes mellitus Gout Hyperlipidaemia Increased appetite		
Psychiatric disorders	Libido decreased	Depression* Loss of libido Mood change*	Insomnia Irritability	Confusional state Decreased activity Euphoric mood	Anxiety
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	

System Organ Class	Very Common	Common	Uncommon	Rare	Additional post-marketing AEs Frequency not known
Eye disorders			Visual impairment	Abnormal sensation in eye Visual disturbance	
Ear and labyrinth disorders			Tinnitus Vertigo		
Cardiac Disorders			Palpitations		QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	Hot flush	Hypertension		Hypotension	
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	Orthopnoea	
Gastrointestinal disorders		Dry mouth Nausea	Abdominal pain Constipation Diarrhoea Vomiting	Abdominal distension Dysgeusia Flatulence	
Skin and subcutaneous tissue disorders	Hyperhidrosis		Acne Alopecia Erythema Pruritus Rash Urticaria	Blister Purpura	Angioneurotic oedema
Musculoskeletal and connective tissue disorders	Back pain	Musculoskeletal pain Pain in extremity	Arthralgia Bone pain Muscle cramp Muscular weakness Myalgia	Joint stiffness Joint swelling Musculoskeletal stiffness Osteoarthritis	
Renal and urinary disorders			Nocturia Urinary retention		Urinary incontinence

System Organ Class	Very Common	Common	Uncommon	Rare	Additional post-marketing AEs Frequency not known
Reproductive system and breast disorders	Erectile dysfunction (including ejaculation failure, ejaculation disorder)	Pelvic pain	Breast pain Gynaecomastia Testicular atrophy Testicular pain		
General disorders and administration site conditions	Asthenia	Injection site reaction (including erythema, inflammation and pain) Oedema	Lethargy Oedema peripheral Pain Rigors Somnolence	Chest pain Dysstasia Influenza like illness Pyrexia	Malaise
Investigations		Weight increased	Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatinine increased Blood pressure increased Blood urea increased Gamma-glutamyl transferase increased Weight decreased	Blood alkaline phosphatase increased	

* This frequency is based on class-effect frequencies common for all GnRH agonists
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 Section 4.4).

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

General tolerance in women (see section 4.4)

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 changes, 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 frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1000, < 1/100); rare (≥1/10000, < 1/1000).

System Organ Class	Very Common	Common	Uncommon	Additional post-marketing AEs Frequency not known
Immune system disorders		Hypersensitivity		Anaphylactic shock
Metabolism and nutrition disorders			Decreased appetite Fluid retention	
Psychiatric disorders	Libido decreased Mood disorder Sleep disorder (including insomnia)	Depression* Nervousness	Affect lability Anxiety Depression** Disorientation	Confusional state
Nervous system disorders	Headache	Dizziness	Dysgeusia Hypoasthesia Syncope Memory impairment Disturbance in attention Paraesthesia Tremor	
Eye disorders			Dry eye Visual Impairment	Visual disturbance
Ear and labyrinth disorders			Vertigo	
Cardiac Disorders			Palpitations	
Vascular disorders	Hot flush			Hypertension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	

System Organ Class	Very Common	Common	Uncommon	Additional post-marketing AEs Frequency not known
Gastrointestinal disorders		Abdominal pain Abdominal discomfort Nausea	Abdominal distension Dry mouth Flatulence Mouth ulceration Vomiting	Diarrhoea
Skin and subcutaneous tissue disorders	Acne Hyperhidrosis Seborrhoea		Alopecia Dry skin Hirsutism Onychoclasis Pruritus Rash	Angioneurotic oedema Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia Muscle spasms Pain in extremities	Back pain Myalgia	Muscular weakness
Reproductive system and breast disorders	Breast disorder Dyspareunia Genital bleeding (including vaginal bleeding withdrawal bleed) Ovarian hyperstimulation syndrome Ovarian hypertrophy Pelvic pain Vulvovaginal dryness	Breast pain	Coital bleeding Cystocele Menstrual disorder (including dysmenorrhoea, metrorrhagia and menorrhagia) Ovarian cyst Vaginal discharge	Amenorrhoea
General disorders and administration site conditions	Asthenia	Injection site reaction (including pain, swelling, erythema and inflammation) Oedema peripheral		Malaise Pyrexia
Investigations		Weight increased	Weight decreased	Blood alkaline phosphatase increased Blood pressure increased

*Long term use: This frequency is based on class-effect frequencies common for all GnRH agonists

** Short term use: This frequency is based on class-effect frequencies common for all GnRH agonists

At the beginning of treatment, the symptoms of endometriosis including pelvic pain and dysmenorrhoea may be very commonly exacerbated (≥ 10%) during the initial

transient increase in plasma oestradiol levels. These symptoms are transient and usually disappear in one to two weeks.
Genital haemorrhage including menorrhagia and metrorrhagia may occur in the month following the first injection.
General tolerance in children (see section 4.4)
The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000, < 1/100).

System Organ Class	Very Common	Common	Uncommon	Additional post-marketing AEs Frequency not known
Immune system disorders		Hypersensitivity		Anaphylactic shock (seen in adult men and women)
Metabolism and Nutrition Disorders			Obesity	
Psychiatric disorders			Mood altered	Affect lability Depression Nervousness
Nervous system disorders		Headache		
Eye disorders			Visual impairment	Visual disturbance
Vascular disorders		Hot flush		Hypertension
Respiratory, thoracic and mediastinal disorders			Epistaxis	
Gastrointestinal disorders		Abdominal pain	Vomiting Constipation Nausea	
Skin and subcutaneous tissue disorders		Acne	Pruritus Rash Urticaria	Angioneurotic oedema
Musculoskeletal and connective tissue disorders			Neck pain	Myalgia
Reproductive system and breast disorders	Vaginal bleeding (including vaginal haemorrhage withdrawal bleed, uterine haemorrhage, vaginal discharge, vaginal bleeding including spotting)		Breast pain	

System Organ Class	Very Common	Common	Uncommon	Additional post-marketing AEs Frequency not known
General disorders and administration site conditions		Injection site reaction (including injection site pain, injection site erythema and injection site inflammation**)**	Malaise	
Investigations		Weight increased		Blood prolactin increased Blood pressure increased

General

Increased lymphocytes count has been reported with patients undergoing GnRH agonist treatment. This secondary lymphocytosis is apparently related to GnRH induced castration and seems to indicate that gonadal hormones are involved in thymic involution.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the
Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

Gonapeptyl Depot 3.75 mg

4.8 Undesirable effects

Adverse experiences reported among patients treated with triptorelin during clinical trials and from post-marketing surveillance are shown below. As a consequence of decreased testosterone or oestrogen levels, most patients are expected to experience adverse reactions, with hot flushes being the most frequently reported (30% in men and 75-100% in women). Additionally, impotence and decreased libido should be expected in 30-40% of male patients, while bleeding/spotting, sweating, vaginal dryness and/or dyspareunia, decrease in libido, headache and mood changes are expected in more than 10% of women.

Due to the fact that the testosterone levels normally increase during the first week of treatment, worsening of symptoms and complaints may occur (e.g. urinary obstruction, skeletal pain due to metastases, compression of the spinal cord, muscular fatigue and lymphatic oedema of the legs). In some cases urinary tract obstruction decreases the kidney function. Neurological compression with asthenia and paraesthesia in the legs has been observed.

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

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 and decreased libido.

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.

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Not known
Men				
Infections and infestations				Nasopharyngitis
Immune system disorders		Hypersensitivity	Anaphylactic reaction	
Metabolism and nutrition disorders			Decreased appetite	Increased appetite, gout, diabetes mellitus
Psychiatric disorders	Libido decreased	Mood changes, depressed mood, depression, sleep disorder		Insomnia, confusional state, decreased activity, euphoric mood, anxiety, loss of libido
Nervous system disorder		Headache		Dizziness, paraesthesia, memory impairment, dysgeusia, somnolence, dysstasia

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Not known
Eye disorders				Abnormal sensation in eye, visual impairment, vision blurred
Ear and labyrinth disorders				Tinnitus, vertigo
Vascular disorders	Hot flushes		Embolism, hypertension	Hypotension
Respiratory, thoracic and mediastinal disorders			Asthma aggravated	Dyspnoea, orthopnoea, epistaxis
Gastrointestinal disorders		Nausea	Abdominal pain upper, dry mouth	Abdominal pain, constipation, diarrhoea, vomiting, abdominal distension, flatulence, gastralgia
Skin and subcutaneous tissue disorders		Hyperhidrosis	Hypotrichosis, alopecia	Acne, pruritus, rash, blister, angioedema, urticaria, purpura
Musculoskeletal and connective tissue disorders	Bone pain	Myalgia, arthralgia		Back pain, musculoskeletal pain, pain in extremity, muscle spasms, muscular weakness, joint stiffness, joint swelling, musculoskeletal stiffness, osteoarthritis
Renal and urinary disorders	Dysuria			
Reproductive system and breast disorders	Erectile dysfunction	Gynaecomastia	Testicular atrophy	Breast pain, testicular pain, ejaculation failure
General disorders and administration site conditions		Fatigue, injection site reaction, injection site pain, irritability		Asthenia, injection site erythema, injection site inflammation, oedema, pain, chills, chest pain, influenza like illness, pyrexia, malaise

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Not known
Investigations			Blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, alanine aminotransferase increased, weight increased, weight decreased	Blood creatinine increased, blood pressure increased, blood urea increased, blood alkaline phosphatase increased, body temperature increased QT prolongation (see section 4.4 and 4.5)

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 changes, 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.

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥ 1/1000 to <1/100)	Not known
Women				
Immune system disorders		Hypersensitivity	Anaphylactic reaction	
Psychiatric disorders	Libido decreased, mood changes, sleep disorder	Depressed mood, depression		Confusional state, anxiety
Nervous system disorder	Headache		Paraesthesia	Dizziness

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥ 1/1000 to <1/100)	Not known
Eye disorders			Visual impairment	Vision blurred
Ear and labyrinth disorders				Vertigo
Vascular disorders	Hot flushes			
Respiratory, thoracic and mediastinal disorders				Dyspnoea
Gastrointestinal disorders	Abdominal pain	Nausea		Abdominal discomfort, diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Hyperhidrosis			Pruritus, rash, angioedema, urticaria
Musculoskeletal and connective tissue disorders	Bone pain	Myalgia, arthralgia	Back pain	Bone disorder(*), muscle spasms, muscular weakness
Reproductive system and breast disorders	Vaginal haemorrhage, vulvovaginal dryness, dyspareunia, dysmenorrhoea, ovarian hyperstimulation syndrome ovarian hypertrophy, pelvic pain			Breast pain, menorrhagia, metrorrhagia, amenorrhoea,
General disorders and administration site conditions	Asthenia	Fatigue, injection site reaction, injection site pain, irritability		Injection site erythema, injection site inflammation, pyrexia, malaise
Investigations			Blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, alanine aminotransferase increased, blood cholesterol increased	Blood pressure increased, weight increased, weight decreased

(*)Slight trabecular bone loss may occur. This is generally reversible within 6-9 months after treatment discontinuation (see section 4.4).

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.
Ovarian hypertrophy, pelvic and/or abdominal pain may be observed.
General tolerance in children (refer to Special Warnings and Precautions for use)

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥ 1/1000 to <1/100)	Not known
Children				
Immune system disorders			Anaphylactic reaction	Hypersensitivity reaction
Psychiatric disorders		Mood changes, depression		Affect lability, nervousness
Nervous system disorder				Headache
Eye disorders				Vision blurred, Visual impairment
Vascular disorders				Hot flushes
Respiratory, thoracic and mediastinal disorders				Epistaxis
Gastrointestinal disorders			Nausea, vomiting	Abdominal discomfort, abdominal pain
Skin and subcutaneous tissue disorders				Rash, angioneurotic edema, urticaria, alopecia, erythema
Musculoskeletal and connective tissue disorders				Epiphysiolysis*, myalgia
Reproductive system and breast disorders			Vaginal haemorrhage, vaginal discharge	Genital haemorrhage
General disorders and administration site conditions				Injection site erythema, injection site inflammation, malaise, pain, injection site pain

Investigations				Blood pressure increased, weight increased

(*)A few cases of slipped capital femoral epiphysis have been reported during use with triptorelin.
Cases of pre-existing pituitary adenomas enlargement were reported during treatment with LH-RH agonists, however it has not yet been observed with triptorelin therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard.

Suprefact Injection

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 eg. 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.

Suprefact treatment may also lead to:

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 leucopenia.

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.

Mood changes, depression. Frequency: Long term use: Common
Short term use: Uncommon

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 (eg 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard