1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Trelstar LA 3,75 mg powder for prolonged-release suspension for injection

Trelstar LA 11,25 mg powder for prolonged-release suspension for injection

Trelstar LA 22,5 mg powder for prolonged-release suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Triptorelin, as triptorelin embonate.

Trelstar LA 3,75 mg: Each vial contains triptorelin embonate equivalent to 3,75 mg triptorelin. After reconstitution in 2 ml of water for injection, 1 ml of reconstituted suspension contains 1,875 mg of triptorelin.

Contains sugar (mannitol). Each dose contains 71 mg mannitol.

Trelstar LA 11,25 mg: Each vial contains triptorelin embonate equivalent to 11,25 mg of triptorelin. After reconstitution in 2 ml water for injection, 1 ml of reconstituted suspension contains 5,625 mg of triptorelin.

Contains sugar (mannitol). Each dose contains 74 mg mannitol.

Trelstar LA 22,5 mg: Each vial contains triptorelin embonate equivalent to 22,5 mg triptorelin. After reconstitution in 2 ml water for injection, 1 ml of reconstituted suspension contains 11,25 mg of triptorelin.

Contains sugar (mannitol). Each dose contains 74 mg mannitol.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for prolonged-release suspension for injection.

White to slightly yellow lyophilised cake.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Trelstar LA is indicated for the treatment of locally advanced or metastatic, hormone-dependent prostate cancer. As an alternative treatment if orchiectomy or the administration of oestrogens are not indicated or are unacceptable to the patient.

4.2 Posology and method of administration

Posology

Trelstar LA must be administered under the supervision of a medical practitioner.

The injection site should be varied periodically.

Since Trelstar LA is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.

The recommended dose of Trelstar LA 3,75 mg is 3,75 mg triptorelin (1 vial) administered once a month (four weeks) as a single subcutaneous or intramuscular injection.

The recommended dose of Trelstar LA 11,25 mg is 11,25 mg of triptorelin (1 vial) administered every three months (twelve weeks) as a single intramuscular injection.

The recommended dose of Trelstar LA 22,5 mg is 22,5 mg triptorelin (1 vial) administered every six months (twenty four weeks) as a single intramuscular injection.

Due to different release characteristics, the dosage strengths are not additive and must be selected based upon the desired dosing schedule.

All three dose regimens provide 3,75 mg triptorelin per month.

Existing evidence does not support superiority of one dose regimen over the others. Therefore, patients' preference for treatment modality and clinical consideration of patients' age and mobility should be considered when determining the treatment of choice in patients with prostate cancer. Sustained-release

formulations have been developed to reduce the number of injections, improve convenience and increase adherence.

Depot formulations may particularly be advantageous for patients preferring improved flexibility with scheduling, less frequent injections, improved comfort, fewer doctor visits, decreased exposure to possible site reactions, decreased cost and fewer missed visits.

Special populations

No dosage adjustment is necessary for patients with renal or hepatic impairment.

Safety and efficacy of Trelstar LA has not been established in neonates, infants, children and adolescents, therefore Trelstar LA is not indicated for the use in these populations.

Method of administration

Refer to section 6.6 for preparation and handling instructions. The prepared injection is a milky, homogeneous suspension without aggregates and the total volume passes through an injection needle.

Following reconstitution, the suspension has to be injected immediately.

4.3 Contraindications

- Hypersensitivity to GnRH (gonadotropin releasing hormone), its analogues or any other component of Trelstar LA (see section 4.8).
- Patients presenting with spinal cord compression. Care should be taken in patients with metastases in the spinal column, in whom compression may occur.
- Patients in whom hormonal therapy has failed.
- Hormone independent prostate carcinoma.
- After orchidectomy (in case of surgical castration triptorelin does not cause further decrease of serum testosterone).
- Trelstar LA is not to be used in women.

4.4 Special warnings and precautions for use

Trelstar, 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 medicines that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition).

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

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with Trelstar LA. Patients should be informed accordingly and treated appropriate if symptoms occur. Patients with known depression should be monitored closely during therapy.

Initially Trelstar LA causes a one to two week increase in serum testosterone levels. As a consequence, cases of short-term worsening of signs and symptoms of prostate cancer may 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. The prostate specific antigen (PSA) and the testosterone plasma levels should be regularly monitored during treatment. Testosterone levels should not exceed 1 ng/ml (1 nmol/l).

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

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 metastases, at the risk of spinal cord compression, and in patients with urinary tract obstruction.

After surgical castration Trelstar LA does not induce any further decrease in serum testosterone levels.

Once the castration levels of testosterone have been achieved by the end of the first month, serum testosterone levels are maintained for as long as the patients receive their:

- monthly injection of Trelstar LA 3,75 (4 weekly) or
- three monthly injection of Trelstar LA 11,25 every 3 months (12 weekly) or
- six monthly injection of Trelstar LA 22,5 every 6 months (24 weekly).

The effectiveness of treatment can be monitored by measuring serum levels of testosterone and PSA.

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.

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 medicines that might prolong the QT interval (see section 4.5) medical practitioners should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Trelstar LA.

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, such as with the Trelstar LA formulations. However, prospective data did not confirm the link between treatment with GnRH analogues (including Trelstar LA) and an increase in cardiovascular mortality. Patients at high risk for metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.

Caution is required with intramuscular injection in patients treated with anticoagulants, due to the potential risk of haematomas at the site of injection.

Administration of Trelstar LA in therapeutic doses results 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.

Porphyria

Trelstar has been reported to be porphyrinogenic.

Excipients

Trelstar LA 3,75 mg, Trelstar LA 11,25 mg and Trelstar LA 22,5 mg contain less than 1 mmol (23 mg) sodium per dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicines and other forms of interaction

When Trelstar LA is co-administered with medicines affecting pituitary secretion of gonadotrophins, caution should be exercised and it is recommended that the patient’s hormonal status should be supervised.

Cytochromes P450 (CYP) are unlikely to be involved in the metabolism or clearance of triptorelin. In addition, *in vitro* data showed that triptorelin was not a significant CYP inhibitor, CYP inducer, P-glycoprotein (P-gP) substrate or inhibitor. Therefore, medicine interactions with Trelstar LA are unlikely.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Trelstar LA with medicines known to prolong the QT interval or medicines able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antidysrhythmic medicines, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

Spironolactone and levodopa can stimulate gonadotrophins (including Trelstar LA) while phenothiazines, dopamine antagonists, digoxin and sex hormones can inhibit gonadotrophin secretion.

4.6 Fertility, pregnancy and lactation

Trelstar LA is not indicated for use in females (see 4.3).

Animal studies have shown effects on reproductive parameters. In chronic toxicity studies at clinically relevant doses, triptorelin induced macro- and microscopic changes in the reproductive organs of male rats, dogs and monkeys. These were considered as a reaction to suppressed gonadal function.

4.7 Effects on ability to drive and use machines

The ability to drive and use machines may be impaired if the patient experiences dizziness, somnolence and visual disturbances. These are possible side effects of treatment (see section 4.8) or may result from the underlying disease.

4.8 Undesirable effects

Since patients suffering from locally advanced or metastatic, hormone-dependent prostate cancer are generally elderly men 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. The most commonly observed adverse events related to Trelstar LA treatment were due to its expected pharmacological effects. These effects included hot flushes, erectile dysfunction and decreased libido.

With the exception of immuno-allergic (rare) and injection site (< 5 %) reactions, all side effects are known to be related to testosterone changes.

The following side effects considered as at least possibly related to Trelstar LA treatment were reported. Most of these events are known to be related to biochemical or surgical castration.

The frequency of the side effects is classified as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10000 to < 1/1 000)

System Organ Class	**Very Common AEs**	**Common AEs**	**Uncommon AEs**	**Rare AEs**	***Additional post-marketing AEs Frequency not known***
Infections and infestations				Nasopharyn-gitis	
Blood and lymphatic system disorders			Thrombo-phlebitis	Purpura	
Immune system disorders				Anaphylactic reaction Hypersensitivity	
Endocrine disorders				Diabetes mellitus	

System Organ Class	Very Common AEs	Common AEs	Uncommon AEs	Rare AEs	*Additional post-marketing AEs Frequency not known*
Metabolism and nutrition disorders			Anorexia, Gout, Increased appetite Elevated enzyme levels (LDH, SGT, AST, ALT)		
Psychiatric disorders		Depression* Mood changes*	Insomnia Irritability	Confusional state Decreased activity Euphoric mood	Anxiety
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	Convulsions
Eye disorders				Abnormal sensation in eye Visual disturbance	Vision blurred
Ear and labyrinth disorders			Tinnitus	Vertigo	
Cardiac disorders					QT prolongation* (see 4.4 and 4.5)
Vascular disorders	Hot flushes	Hypertension		Hypotension	

System Organ Class	Very Common AEs	Common AEs	Uncommon AEs	Rare AEs	*Additional post-marketing AEs Frequency not known*
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Orthopnoea Epistaxis	
Gastro-intestinal disorders		Nausea	Abdominal pain Constipation Diarrhoea Vomiting	Abdominal distension Dry mouth Dysgeusia Flatulence	
Skin and subcutaneous tissue disorders	Hyperhidrosis		Acne Alopecia Pruritus Rash	Blisters	Angioneurotic oedema Urticaria
Musculoske-letal, connective tissue and bone disorders	Back pain	Musculoskele-tal pain Pain in extremity	Arthralgia Muscle cramp Muscular weakness Myalgia	Joint stiffness Joint swelling Musculoskele-tal stiffness Osteoarthritis	Bone pain
Reproductive system and breast disorders		Erectile dysfunction Loss of libido, impotence	Gynaeco-mastia Breast pain Testicular atrophy Testicular pain	Ejaculation failure	

System Organ Class	Very Common AEs	Common AEs	Uncommon AEs	Rare AEs	*Additional post-marketing AEs Frequency not known*
General disorders and administration site conditions	Asthenia	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
Investigations			Increased alanine aminotrans-ferase Increased aspartate aminotrans-ferase, Increased blood creatinine, Increased blood urea, Increased weight	Increased blood alkaline phosphatase Increased body temperature Decreased weight	

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

Trelstar LA causes an 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 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 Trelstar LA to treat prostate cancer may be associated with increased bone loss and may lead to osteoporosis and increases the risk of bone fracture. This may also lead to an incorrect diagnosis of bone metastases.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the SAHPRA website.

4.9 Overdose

The pharmaceutical properties of Trelstar LA and its mode of administration make accidental or intentional overdosage unlikely. There is no human experience of overdosage.

Animal tests suggest that the intended therapeutic effects on sex hormone concentration and on the reproductive tract will be evident with higher doses of Trelstar LA.

If overdose occurs, symptomatic management is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

21.12 Hormone inhibitors

Triptorelin, a gonadotropin releasing hormone **(**GnRH) agonist, acts as a potent inhibitor of gonadotrophin secretion when given continuously and in therapeutic doses. In males, animal and human studies show that after administration of triptorelin there is an initial increase in circulating levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone for 2 to 4 weeks.

However, chronic and continuous administration of triptorelin results in decreased LH and FSH secretion and suppression of testicular and ovarian steroidogenesis. A reduction of serum testosterone levels into the range normally seen in surgically castrated men occurs approximately 2 to 4 weeks after initiation of therapy.

This results in accessory sexual organ atrophy. These effects are generally reversible upon discontinuation of triptorelin.

5.2 Pharmacokinetic properties

Absorption

Following a single intramuscular injection of Trelstar LA 3,75 mg in healthy male volunteers, mean peak triptorelin serum concentration was 28,4 ng/ml at 1 to 3 hours and 0,084 ng/ml at 4 weeks. Absolute bioavailability of intramuscular triptorelin relative to intravenous triptorelin was approximately 83 %. After repeated monthly intramuscular administration of Trelstar LA 3,75 mg, no significant accumulation has been observed.

Following a single intramuscular injection of Trelstar LA 11,25 mg in patients with prostate cancer, t_{max} was 2 (2 to 6) hours and C_{max} (0 to 85 days) was 37,1 (22,4 to 57,4) ng/ml. Triptorelin did not accumulate over 9 months of treatment.

Following a single intramuscular injection of Trelstar LA 22,5 mg in patients with prostate cancer, t_{max} was 3 (2 to 12) hours and C_{max} (0 to 169 days) was 40,0 (22,2 to 76,8) ng/ml. Triptorelin did not accumulate over 12 months of treatment.

Distribution

Results of pharmacokinetic investigations conducted in healthy men indicate that after intravenous bolus administration, triptorelin is distributed and eliminated according to a 3-compartment model and corresponding half-lives are approximately 6 minutes, 45 minutes, and 3 hours.

The volume of distribution at steady state of triptorelin following intravenous administration of 0,5 mg triptorelin acetate is approximately 30 ℓ in healthy male volunteers. Since there is no evidence that triptorelin at clinically relevant concentrations binds to plasma proteins, medicinal product interactions involving binding-site displacement are unlikely.

Biotransformation

Metabolites of triptorelin have not been determined in humans. However, human pharmacokinetic data suggest that C-terminal fragments produced by tissue degradation are either completely degraded within tissues or are rapidly further degraded in plasma or cleared by the kidneys.

Elimination

Triptorelin is eliminated by both the liver and the kidneys. Following intravenous administration of 0,5 mg triptorelin to healthy male volunteers, 42 % of the dose was excreted in urine as intact triptorelin, which increased to 62 % in patients with hepatic impairment. Since creatinine clearance (CLcr) in healthy volunteers was 150 mℓ/min and only 90 mℓ/min in patients with hepatic impairment, this indicates that the liver is a major site of triptorelin elimination. In these healthy volunteers, the true terminal half-life of triptorelin was 2,8 hours and total clearance of triptorelin 212 mℓ/min, the latter being dependent on a combination of hepatic and renal elimination.

Special populations

Following intravenous administration of 0,5 mg triptorelin to patients with moderate renal insufficiency (CLcr 40 mℓ/min), triptorelin had an elimination half-life of 6,7 hours, 7,81 hours in patients with severe renal insufficiency (CLcr 8,9 mℓ/min) and 7,65 hours in patients with impaired hepatic function (CLcr 89,9 mℓ/min).

The effects of age and race on triptorelin pharmacokinetics have not been systematically studied. However, pharmacokinetic data obtained in young healthy male volunteers aged 20 to 22 years with an elevated creatinine clearance (approximately 150 mℓ/min) indicated that triptorelin was eliminated twice as fast in the young population. This is related to the fact that triptorelin clearance is correlated to total creatinine clearance, which is well known to decrease with age.

No dose adjustment is recommended in patients with renal or hepatic impairment.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic relationship of triptorelin is not straightforward to assess, since it is non-linear and time-dependent. Thus, after acute administration in naïve patients, triptorelin induces a dose-dependent increase of LH and FSH responses.

When administered as a sustained release formulation, triptorelin stimulates LH and FSH secretion during the first days post dosing and, in consequence, testosterone secretion. As shown by the results of the different bioequivalence studies, the maximal increase in testosterone is reached after around 4 days with an equivalent C_{max} which is independent from the release rate of triptorelin. This initial response is not maintained despite continuous exposure to triptorelin and is followed by a progressive and equivalent decrease of testosterone levels. In this case too, the extent of triptorelin exposure can vary markedly without affecting the overall effect on testosterone serum levels.

Summary of clinical studies

Trelstar LA 3,75 mg:

Following a single intramuscular injection of Trelstar LA 3,75 mg to healthy male volunteers, serum testosterone levels first increased by peaking on Day 4 and thereafter declined to low levels by 4 weeks. By week 8, following this single injection, low levels of testosterone were no longer maintained. A similar serum testosterone profile was observed in patients with advanced prostate cancer when injected intramuscularly with triptorelin embonate and following the second injection testosterone levels were maintained within the castrate range.

Trelstar LA 11,25 mg:

Administration of Trelstar LA 11,25 mg to patients with advanced prostate cancer as an intramuscular injection for a total of 3 doses (9 months) resulted in both achievement of castration levels of testosterone in 97,6 % and 92,5 % of patients receiving 3-month and 1-month formulations respectively, after four weeks and maintenance of castration levels of testosterone from month 2 through month 9 of treatment.

Trelstar LA 22,5 mg:

Administration of Trelstar LA 22,5 mg to patients with advanced prostate cancer as an intramuscular injection for a total of 2 doses (12 months) resulted in both achievement of castration levels of testosterone in 97,5 % of patients after four weeks and maintenance of castration levels of testosterone in 93,0 % of the patients from month 2 through month 12 of treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Poly(d,l-lactide-co-glycolide)

Carmellose sodium

Mannitol

Polysorbate 80

6.2 Incompatibilities

Trelstar LA must not be mixed with other medicines except the one mentioned in 6.6.

6.3 Shelf-life

Trelstar LA 3,75 mg: 36 months.

Trelstar LA 11,25 mg: Powder: 36 months.

Trelstar LA 22,5 mg: Powder: 36 months.

After reconstitution the suspension should be used immediately.

From a microbial point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8 °C.

6.4 Special precautions for storage

Store at or below 25 ˚C. Keep container in outer carton.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of the container

Trelstar 3,75 mg: 6 ml tinted (after gamma irradiation) Type I glass vial closed with a 20 mm grey bromobutyl rubber Type I stopper with an aluminium seal and purple flip-off plastic cap.

Trelstar LA 11,25 mg: 6 ml tinted (after gamma irradiation) Type I glass vial closed with a 20 mm grey bromobutyl rubber Type I stopper with an aluminium seal and yellow green plastic flip-off plastic cap.

Trelstar LA 22,5 mg: 6 ml tinted (after gamma irradiation) Type I glass vial closed with a 20 mm grey bromobutyl rubber Type I stopper with an aluminium seal and dark green flip-off plastic cap.

Each box contains 1 or 3 vials.

Not all pack sizes may necessarily be marketed.

6.6 Special precautions for disposal and other handling

Handling and disposal

The suspension for injection must be reconstituted using an aseptic technique.

The powder should be suspended immediately before use.

For single use only. Any unused suspension should be discarded.

Used injection needles should be disposed in a designated sharp container.

The powder is to be suspended in 2 ml water for injection. Using an injection needle, the solvent is drawn up into an injection syringe and transferred to the vial containing the powder. The vial should be gently swinged to completely disperse the powder to obtain a homogenous milky suspension. Do not invert the vial. The suspension obtained is drawn back into the injection syringe. The injection needle should be changed and the suspension should be injected immediately.

The suspension should be injected relatively rapidly and in a steady and uninterrupted manner in order to avoid potential blockage of the needle. The suspension should be discarded if it is not administered immediately after reconstitution. See section 6.3.

7 HOLDER OF THE CERTIFICATE OF REGISTATION

Pharmacare Limited

Building 12, Healthcare Park

Woodlands drive

Woodmead, 2191

8 REGISTRATION NUMBERS

Trelstar LA 3,75 mg: 52/21.12/0034

Trelstar LA 11,25 mg: 52/21.12/0035

Trelstar LA 22,5 mg: 52/21.12/0036

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 July 2021

10 DATE OF REVISION OF THE TEXT

13 July 2021

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