Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Salvacyl, 11.25 mg powder and solvent for prolonged-release suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 11.25 mg of triptorelin, as triptorelin embonate.

After reconstitution in the 2 ml solvent, the reconstituted solution contains 11.25 mg of triptorelin, as triptorelin embonate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection
- Powder: White to slightly yellow powder
- Solvent: Clear solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Salvacyl is indicatedfor the reversible reduction of testosterone to castrate levels in order to decrease sexual drive in adult men with severe sexual deviations.
The treatment with Salvacyl is to be initiated and controlled by a psychiatrist. The treatment should be given in combination with psychotherapy, in order to decrease deviating sexual behaviour.

4.2 Posology and method of administration

Posology
The recommended dose of Salvacyl is 11.25 mg triptorelin (1 vial) administered every twelve weeks as a single intramuscular injection.

Paediatric population
The safety and efficacy of Salvacyl in children have not been established. Salvacyl is not indicated for use in neonates, infants, children and adolescents.

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

Method of administration
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Precautions to be taken before handling or administrating the medicinal product.
Since Salvacyl is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.
Salvacyl must be administered under the supervision of a medically qualified person (nurse or physician).
The therapeutic benefit should be monitored regularly, for example prior to any new injection.
The injection site should be varied periodically.

4.3 Contraindications

- Patients with serious osteoporosis.
- Hypersensitivity to gonadotropin releasing hormone (GnRH), its analogues or to any other component of the medicinal product (see section 4.8) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Treatment with Salvacyl should be considered on an individual basis and only be initiated if the benefits of treatment outweigh the risk following a very careful appraisal.

Initially triptorelin causes a transient increase in serum testosterone levels. During the initial phase of treatment, the patient should be closely monitored by the treating psychiatrist and consideration should be given to the additional administration of a suitable anti-androgen to counteract the initial rise in serum testosterone levels in order to control possible increase in sexual drive if considered appropriate.

Following treatment interruption, there is a risk of an increased sensitivity to the restored testosterone, which can lead to a highly increased sexual drive. For this reason, the addition of an adequate anti-androgen before stopping Salvacyl treatment should be considered.

Once the castration levels of testosterone have been achieved by the end of the first month, they are maintained for as long as the patient receives their injection every twelve weeks.

The evaluation of the treatment effect is essentially clinical. A clinical assessment of the treatment effect should be done regularly, e.g. before each 3-month injection of triptorelin. Serum testosterone levels may be measured in case there is a doubt of treatment effect, which could be related to compliance to triptorelin treatment or to a technical problem with the injection.

Caution is required in patients treated with anti-coagulants, due to the potential risk of haematomas at the site of injection.

Administration of triptorelin 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 a GnRH agonist may therefore be misleading.

Long term androgen deprivation either by bilateral orchidectomy or administration of GnRH analogues is associated with increased risk of bone loss and may lead to osteoporosis and increased risk of bone fracture. Preliminary data suggest that the use of a bisphosphonate in combination with a 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).

Bone mineral density may be assessed before the start of treatment and may be followed regularly during the treatment.

In order to prevent the treatment-related bone loss, lifestyle modification including smoking cessation, moderation of alcohol consumption and regular weight bearing exercise are recommended. Adequate dietary calcium and vitamin D intake should also be maintained.

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

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

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

Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Salvacyl.

In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance, fatty liver), and 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 carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.

Due to androgen deprivation, treatment with analogues of the GnRH can increase the risk of anaemia. This risk should be assessed in treated patients and monitored appropriately.

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. essentially 'sodium-free'.

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 exercised and it is recommended that the patient's hormonal status should be supervised.
Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Salvacyl with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, pregnancy and lactation

Salvacyl is not indicated for use in females.
Animal studies have shown effects on reproductive parameters (see section 5.3).

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.

4.8 Undesirable effects

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 include hot flushes, erectile dysfunction (observed in more than 10% of the patients). With the exception of hypersensitivity reactions (rare) and injection site pain (<5%), all adverse events are known to be related to testosterone changes. The long-term use of synthetic GnRH analogues may be associated with increased bone loss and may lead to osteoporosis and increases the risk of bone fracture.

The following adverse reactions considered as at least possibly related to triptorelin treatment were reported in clinical studies performed in men suffering from advanced prostate cancer and in healthy male volunteers. 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 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); not known (cannot be estimated from the available data).

System Organ Class	***Very Common AEs***	***Common AEs***	***Uncommon AEs***	***Rare AEs***	***Additional post-marketing AEs Frequency not known***
Blood and lymphatic system disorders			Thrombocytosis		Anaemia
Cardiac disorders			Palpitations		QT prolongation* (see sections 4.4 and 4.5)
Ear and labyrinth			Tinnitus Vertigo		

disorders					
Endocrine disorders					Pituitary apoplexy**
Eye disorders			Visual impairment	Abnormal sensation in eye Visual disturbance	
Gastrointestinal disorders		Dry mouth Nausea	Abdominal pain Constipation Diarrhoea Vomiting	Abdominal distension Dysgeusia Flatulence	
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
Immune system disorders		Hypersensitivity		Anaphylactic reaction	Anaphylactic shock
Infections and infestations				Nasopharyngitis	
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	
Metabolism and nutrition disorders			Anorexia Diabetes mellitus Gout Hyperlipidaemia Increased appetite		
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	
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	
Psychiatric disorders	Libido decreased	Loss of libido Depression* Mood changes*	Insomnia Irritability	Confusional state Decreased activity Euphoric mood	Anxiety
Renal and urinary			Nocturia Urinary retention		Urinary incontinence

disorders					
Reproductive system and breast disorders	Erectile dysfunction (including ejaculation failure, ejaculation disorder)	Pelvic pain	Gynaecomastia Breast pain Testicular atrophy Testicular pain		
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	Orthopnoea	
Skin and subcutaneous tissue disorders	Hyperhidrosis		Acne Alopecia Erythema Pruritus Rash Urticaria	Blister Purpura	Angioneurotic oedema
Vascular disorders	Hot flush	Hypertension		Hypotension	

*This frequency is based on class-effect frequencies common for all GnRH agonists.
**Reported following initial administration in patients with pituitary adenoma

Reporting of suspected adverse reactions
Reporting of 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 HPRA Pharmacovigilance: Website: www.hpra.ie.

4.9 Overdose

The pharmaceutical form of Salvacyl and its route of administration make accidental or intentional overdose unlikely. Animal tests suggest that no effect other than the intended therapeutic effects on sex hormone concentration and on the reproductive tract will be evident with higher doses of Salvacyl. If overdose occurs, symptomatic management is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophin releasing hormone analogues.
ATC code: L02A E04
Mechanism of action and pharmacodynamic effects
Triptorelin, a GnRH agonist, acts as a potent inhibitor of gonadotrophin secretion when given continuously and in therapeutic doses. Studies in men show that after the administration of triptorelin there is an initial and transient increase in circulating levels of luteinising hormone (LH), follicle stimulating hormone (FSH), and testosterone.

However, chronic and continuous administration of triptorelin to men results in decreased LH and FSH secretion and suppression of testicular steroidogenesis. A reduction of serum testosterone levels into the range normally seen after surgical castration 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 the medicinal product.
Testosterone plays a major role in the regulation of sexuality, aggression, cognition, emotion, and personality. In particular, it is a major determinant of sexual desire, fantasies and behaviour, and basically controls the frequency, duration and magnitude of spontaneous erections. The effects of testosterone (and of its reduced metabolite 5α-dihydrotestosterone [DHT]) are mediated through their actions on the intracellular androgen receptor.

Clinical efficacy and safety
Administration of Salvacyl as an intramuscular injection for a total of 3 doses (9 months) resulted in achievement of castration levels of testosterone in 97.6% of patients with advanced prostate cancer after four weeks of treatment, which was maintained from month 2 through month 9 of treatment in 94.1% of the patients.

5.2 Pharmacokinetic properties

Absorption:
Following a single intramuscular injection of Salvacyl, t_{max} was 2 (2-6) hours and C_{max} (0-85 days) was 37.1 (22.4-57.4) ng/ml. Triptorelin did not accumulate over 9 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 is approximately 30 l in healthy men.
Biotransformation:
Metabolism of triptorelin has not been determined in humans.
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. In these healthy volunteers, the true terminal half-life of triptorelin was 2.8 hours and total clearance of triptorelin 212 ml/min.
Special populations:
Triptorelin clearance decreases with impaired renal or liver function. Following intravenous administration of 0.5 mg triptorelin to subjects with moderate renal insufficiency (Cl_{creat} 40 ml/min), triptorelin had a clearance of 120 ml/min; 88.6 ml/min in subjects with severe renal insufficiency (Cl_{creat} 8.9 ml/min) and 57.8 ml/min in patients with mild to moderate impaired hepatic function (Cl_{creat} 89.9 ml/min).
Because of the large safety margin of Salvacyl, no dose adjustment is recommended in patients with renal or hepatic impairment.
The effects of age and race on triptorelin pharmacokinetics have not been systematically studied.

Pharmacokinetic/pharmacodynamics relationship
The pharmacokinetics/pharmacodynamics relationship of triptorelin is not straightforward to assess, since it is non-linear and time-dependent. Thus, after acute administration in naive subjects, 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.

5.3 Preclinical safety data

The toxicity of triptorelin towards extragenital organs is low.
The observed effects were mainly related to the excessive pharmacological effects of triptorelin.
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 to reflect the suppressed gonadal function caused by the pharmacological activity of the compound. The changes were partly reversed during recovery. After subcutaneous administration of 10 micrograms/kg to rats on days 6 to 15 of gestation, triptorelin did not elicit any embryotoxicity, teratogenicity, or any effects on the development of the offspring (F1 generation) or their reproductive performance. At 100 micrograms/kg, a reduction in maternal weight gain and an increased number of resorptions were observed.

Triptorelin is not mutagenic *in vitro* or *in vivo*. In mice, no carcinogenic effect has been shown with triptorelin at doses up to 6000 micrograms/kg after 18 months of treatment. A 23-month carcinogenicity study in rats has shown an almost 100% incidence of benign pituitary tumours at each dose level, leading to premature death. The increased incidence in pituitary tumours in rats is a common effect associated with GnRH agonist treatment. The clinical relevance of this is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Poly (D, L-lactide-co-glycolide)

mannitol
carmellose sodium
polysorbate 80.

Solvent:
Water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.
After reconstitution, chemical and physical in use stability has been demonstrated for 24 hours at 25°C. From a microbiological 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 to 8°C.

6.4 Special precautions for storage

Do not store above 25°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder vial: 6 ml septum transparent light brown vial (type I glass) with bromobutyl stopper and aluminium cap with yellow-green flip-off cover.
Solvent ampoule: transparent, colourless ampoule (type I glass) containing 2 ml of sterile solvent for suspension.

Box of:
1 vial, 1 ampoule and 1 blister containing a kit of 1 empty injection syringe of polypropylene and 2 injection needles (one with safety device for injection and one without safety device for reconstitution).

6.6 Special precautions for disposal and other handling

The suspension for injection must be reconstituted using an aseptic technique and only using the ampoule of solvent for injection.

The instructions for reconstitution hereafter and in the leaflet must be strictly followed.

The solvent should be drawn into the syringe provided using the reconstitution needle (20 G, without safety system) and transferred to the vial containing the powder. The suspension should be reconstituted by swirling the vial gently from side to side for long enough until a homogeneous, milky suspension is formed. Do not invert the vial.

It is important to check there is no unsuspended powder in the vial. The suspension obtained should then be drawn back into the syringe, without inverting the vial. The reconstitution needle should then be changed and the injection needle (20 G, with safety device) used to administer the product.

As the product is a suspension, the injection should be administered immediately after reconstitution to prevent precipitation.

For single use only. After use, the safety system should be activated using a one-handed technique. Either by pushing the tab forward with the finger, or by pushing the sheath to a flat surface. In both cases press down with a firm quick motion until a distinct audible click is heard. It should be visually confirmed that the needle is fully engaged under the lock. Used needles, any unused suspension or other waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ipsen Pharmaceuticals Limited
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8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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