Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Viridal Duo 20 microgram /ml, Powder and Solvent for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alprostadil 20 micrograms (used as a 1:1 clathrate complex with alfadex).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Double chamber glass cartridge containing lyophilised powder and solvent for reconstitution (isotonic sodium chloride solution).

The powder is white and the isotonic sodium chloride solution is clear, colourless liquid without a special odour. The powder is freely soluble within 60 seconds when dissolved in isotonic sodium chloride solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Viridal Duo is indicated in adult males:

- as an adjunct to the diagnostic evaluation of erectile dysfunction.
- for treatment of erectile dysfunction.

4.2 Posology and method of administration

Posology

Adults:

Treatment initiation and dose titration
Injections for treatment initiation, diagnostic evaluation and dose titration must be performed by the treating physician. He will determine an individual dose suitable to produce an erectile response for diagnostic purposes. For erectile dysfunction of neurological origin, the starting dose is 1.25mcg. For all other patients, the recommended starting dose is 2.5 mcg. Dose adjustments may be performed in increments of about 2.5 mcg to 5 mcg Viridal Duo. Most of the patients require between 10 and 20 mcg per injection. Some patients may need to be titrated to higher doses. Doses exceeding 20 mcg should be prescribed with particular care in-patients with cardiovascular risk factors. The dose per injection should never exceed 40 mcg.

Dosage for self-injection therapy at home
Before starting treatment at home, each patient or the patient’s partner has to be taught by a physician how to prepare the drug and perform the injection. In no cases should the injection therapy be started without precise instructions by the physician. The patient should only use his optimum individual dosage, which has been pre-determined by his physician using the above-mentioned procedure. This dose should allow the patient to have an erection at home, which should not last longer than one hour. If he experiences prolonged erections beyond 2 hours but less than 4 hours, the patient is recommended to contact his physician to re-establish the dose of the drug. Maximum injection frequency recommended is 2 or 3 times a week with an interval of at least 24 hours between the injections.

Follow-up
After the first injections and at regular intervals, e.g. every three months, the physician should re-evaluate the patient. Any local adverse reaction, e.g. haematoma, fibrosis or nodules should be noted and controlled. Following discussion with the patient, an adjustment of dosage may be necessary.

Paediatric population
The safety and efficacy of Viridal Duo in children under 18 years of age has not yet been established. No data are available.

Elderly
The safety and efficacy of Viridal Duo in patients over 80 years of age has not yet been established. No data are available.

Method of preparation and administration
The drug solution should be prepared shortly before the injection.

Administration cartridges

Prior to injection the needle should be screwed onto the tip of the injector. After disinfecting the tip of the cartridge with one of the alcohol swabs, the cartridge should then be inserted into the injector.

Duoject device (cartridge)
Screwing the thread part clockwise, the cartridge is fixed in the applicator. While holding the device in a vertical position with the needle upwards, the dry substance inside the front chamber of the cartridge is reconstituted with 1 ml sterile sodium chloride solution 0.9 % in the back chamber by screwing the thread part slowly until it will not go any further.

Easy Duo device (cartridge)
Put the cartridge into the Easy Duo device. Screw the syringe and plunger together. Hold the device in a vertical position and push the plunger upwards. The solvent will by-pass the upper stopper into the front chamber and dissolve the dry substance within a few seconds.

Administration

As soon as the dry substance is reconstituted, the larger external and the smaller inner protective cap have to be removed from the needle. The device is still held in a vertical position and the air has to be expelled out of the cartridge by tapping against the cartridge and by carefully pushing the plunger until the air is pressed out. The plunger is pushed up until the grey stopper reaches the prescribed dose.

Viridal Duo is injected into either the right or the left cavernous body of the penile shaft. Once the needle is in the cavernous body, the injection should be done within 5 to 10 seconds and is very easy without much resistance if the needle is in the correct position. If bleeding occurs at the injection site, apply manual pressure for 2 – 3 minutes.

The development of an erection will start approximately 5 – 15 minutes after the injection.
Unused solution must be discarded immediately.

Notes
For patients who require a starting dose of 1.25 mcg, the dose of the reconstituted injection solution can be extracted from the carpoule using a syringe with a needle size 29 G x1/2 (0.33 mm x 12.7 mm) and appropriately graduated to extract and administer 0.125 ml injection volume from the carpoule containing 10 mcg Viridal Duo. Under aseptic conditions the solution can be extracted from the carpoule through the rubber seal. Unused injection solution must be discarded.

4.3 Contraindications

Viridal Duo 20 micrograms/ml must not be used:
- in patients with hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- in patients with diseases causing priapism e.g. sickle-cell anaemia or trait, multiple myeloma or leukaemia.
- in patients with anatomical deformation of the penis such as angulation, cavernosal fibrosis or Peyronie's disease.
- in patients with penis implants.
- in men for whom sexual activity is contraindicated (e.g. patients suffering from severe heart disease).

4.4 Special warnings and precautions for use

The physician should carefully select patients suitable for self-injection therapy. Underlying treatable medical causes of erectile dysfunction should be diagnosed and treated prior to initiation of therapy with Viridal Duo.

Sexual stimulation and intercourse can lead to cardiac and/or pulmonary events in patients with coronary heart disease, congestive heart failure or pulmonary disease. These patients when using Viridal Duo should engage in sexual activity with caution and patients should be examined and cleared for stress resistance by a cardiologist before treatment.

Viridal Duo should be used with caution in patients with cardiovascular and cerebrovascular risk factors.

Priapism (erection lasting over six hours) may occur following intracavernosal administration of Viridal Duo. Prolonged erections of more than four hours can be dangerous. Treatment of priapism should not be delayed more than six hours (see section 4.9).

To minimise the risk, select the lowest effective dose and instruct the patient to immediately report to his prescribing physician, or, if unavailable, seek immediate medical assistance for any erection that persist longer than 4 hours. Treatment of priapism should be according to established medical practice.

Therefore it is recommended that the patient has an emergency telephone number of his attending physician or of a clinic experienced in therapy of erectile dysfunction. Prolonged erection may damage penile erectile tissue and lead to irreversible erectile dysfunction.

Painful erection is more likely to occur in patients with anatomical deformations of the penis, such as angulation, phimosis, cavernosal fibrosis, Peyronie's disease or plaques. Penile fibrosis, including angulation, cavernal fibrosis, fibrotic nodules and Peyronie's disease may occur following the intracavernosal administration of Viridal Duo. The occurrence of fibrosis may increase with increased duration of use. Regular follow-up of patients, with careful examination of the penis, is strongly recommended to detect signs of penile fibrosis or Peyronie's disease. Treatment with Viridal Duo should be discontinued in patients who develop penile angulation, cavernosal fibrosis, or Peyronie's disease.

Patients who have to be treated with alpha-adrenergic drugs due to prolonged erections (see: overdose) may in the case of concomitant therapy with monoamino-oxidase-inhibitors, develop a hypertensive crisis.

Other intracavernous drugs e.g. smooth muscle relaxing agents or alpha-adrenergic blocking agents may lead to prolonged erection and must not be used concomitantly.

Viridal Duo is not intended for co-administration with any other agent for the treatment of erectile dysfunction (see Section 4.5).

In some patients, injection of Viridal Duo can induce a small amount of bleeding at the site of injection. In patients infected with blood borne diseases, this could increase the transmission of such diseases to their partner.

Patients with blood clotting disorders or patients on therapy influencing blood clotting parameters should be carefully selected for treatment by the treating physician and treated with special care, e.g. monitoring of the clotting parameters.

Patients should be thoroughly educated by their physician about the risks and the patients should be advised to compress the site of injection with a swab for a sufficiently long period after the intracavernous injection (see section 4.5). Patients on anticoagulants such as warfarin or heparin may have increased propensity for bleeding after the intracavernous injection.

To prevent abuse, self-injection therapy with Viridal Duo should not be used by patients with drug addiction and/or disturbances of psychological or intellectual development.

In cases of excessive use, e.g. higher frequencies than recommended, an increased risk of penile scarring cannot be excluded.

Use of intracavernous alprostadil offers no protection from the transmission of sexually transmitted diseases. Individuals who use alprostadil should be counselled about the protective measures that are necessary to guard against the spread of sexually transmitted diseases, including the human immunodeficiency virus (HIV). For this reason we recommend that a condom is used for intercourse after injecting Viridal Duo.

Viridal Duo is for intracavernous injection. Subcutaneous injection or injections at areas of the penis other than the cavernous body should be avoided.

The injection should be performed under hygienic conditions to avoid infections. In any condition that precludes safe self-injection like poor manual dexterity, poor visual acuity or morbid obesity, the partner should be trained in the injection technique and should perform the injection.

Up to now, there is no clinical experience in patients under 18 and over 80 years of age.

Reconstituted solutions of Viridal Duo are intended for single use only. The injection delivery system/syringe and any remaining solution should be properly discarded.

Human semen contains PGE_1, but additional amounts may be present due to the Viridal Duo administration. This way, an appropriate contraception is recommended if the partner is a woman of child-bearing age (see section 4.6). Also, Viridal Duo must not be used for sexual intercourse with a pregnant woman without a condom.

4.5 Interaction with other medicinal products and other forms of interaction

The effects of combinations of alprostadil with other treatments for erectile dysfunction (e.g. sildenafil) or other drugs inducing erection (e.g. papaverine) have not been formally studied. Such agents should not be used in combination with Viridal Duo due to the potential for inducing prolonged erections.

Risks exist when using alpha-adrenergic drugs to terminate prolonged erections in patients with cardiovascular disorders or receiving MAO inhibitors.

Sympathomimetics may reduce the effect of alprostadil. Alprostadil may enhance the effects of antihypertensives, vasodilative agents, anticoagulants and platelet aggregation inhibitors.

Patients with impaired coagulation, thrombocytic function-disorder or those being treated with anticoagulative therapy, anti-platelet therapy or with thrombolytic agents are at higher risk of bleeding. These patients should be carefully selected by the treating physician. Clotting parameters should be monitored closely. Patients should be thoroughly educated by their physician about the risks and should be advised to compress the site of injection with a swab for a sufficiently long period after the intracavernous injection (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

The natural amount of PGE_1 present in the sperm may be increased by the PGE_1 present in Viridal Duo.

In case the partner is pregnant, a condom should be used in order to avoid irritation of the vagina and a risk for either preterm delivery or for the foetus.

Fertility
Alprostadil does not interfere with ejaculation and fertility.

4.7 Effects on ability to drive and use machines

In single cases, Viridal Duo may induce transient drop of blood pressure with subsequent impairment of reactivity.

4.8 Undesirable effects

Summary of the safety profile:
The most frequent adverse effects following an intracavernous injection are pain in the penis. Thirty percent of patients reported pain at least once. Pain was associated with 11% of the injections administered. In most cases pain was assessed as mild or moderate. Three per cent of patients discontinued treatment because of pain.

Penile fibrosis, including angulation, fibrotic nodules, and Peyronie's disease, was reported in 3% of clinical trial patients overall. In one self-injection study in which the duration of use was up to 18 months, the incidence of penile fibrosis was higher, approximately 8%.

Haematoma and ecchymosis at the injection site, which is related with the injection technique rather than the effect of alprostadil, was reported by 3% and 2% of patients, respectively.

Prolonged erection (an erection for 4 - 6 h) developed in 4% of patients. Priapism (a painful erection for more than 6 hours) occurred in 0.4%. In most cases it disappeared spontaneously.

Adverse drug reactions reported during clinical trials and post marketing experience are presented in the table below.

Tabulate list of adverse reactions:
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, < 1/1,000);
Very rare (<1/10,000):
Not known (cannot be estimated from the available data)
During administration of Viridal Duo the following undesirable effects may be observed:

SOC	**Frequency**					
	Very common:	**Common:**	**Uncommon:**	**Rare:**	**Very rare:**	**Not known:**
Infections and infestations			Fungal infection Common cold			
Blood and lymphatic system disorders					Isolated cases of thrombocytopenia.	
Immune system disorders				Hypersensitivity ranging from dermatitis allergic, urticaria to anaphylactic/anaphylactoid reaction.		
Nervous system disorders			Headache**.** Hypoaesthesia Hyperaesthesia Presyncope	Vertigo, dizziness.		Amnesia, cerebro-vascular accident.
Eye disorders			Mydriasis			

Cardiac disorders			Supraventricular extrasystoles	Circulatory effects such as short periods of hypotension		Myocardial ischemia, myocardial infarction.
Vascular disorders		Haematoma	Vein disorder Hypotension Peripheral vascular disorder Vasodilatation			
Gastrointestinal disorders			Nausea Dry mouth			
Skin and subcutaneous tissue disorders			Hyperhidrosis Erythema Rash Pruritus	urticaria		
Musculoskeletal and Connective Tissue Disorders		Muscle spasm				
Renal and urinary disorders			Dysuria Haematuria Micturition urgency Pollakiuria Urethral haemorrhage			
Reproductive system and breast disorders	Penile pain	Injection site fibrosis (e.g. fibrotic nodules, plaques at the site of injection) can occur during long-term treatment Erection increased Peyronie's disease Penis disorder	Fibrotic alterations associated with penis deviation, Erectile dysfunction, Ejaculation disorder, Balanitis, Painful erection, Phimosis, Priapism (prolonged erection of more than 4 hours' duration, mainly seen during dose titration), Testicular pain, Scrotal disorder, Scrotal erythema, Scrotal pain, Spermatocele, Scrotal oedema, Testicular disorder, Testicular swelling, Testicular oedema, Testicular mass, Pelvic pain	Fibrosis of the corpora cavernosa during a long-term treatment lasting up to 4 years.		
General disorders and administration site condition		Burning sensation during and after the injection, injection site pain of mostly mild intensity. Injection site haematoma Haematoma Ecchymosis	Haemosiderin deposits, spotlike haemorrhage, spotlike bruises at the site of puncture, injection site erythema, injection site swelling, Asthenia Injection site inflammation Injection site hemorrhage Injection site pruritus, Injection site oedema Injection site warmth Injection site irritation Haemorrhage Inflammation Oedema peripheral Oedema Injection site anaesthesia			Penile oedema
Investigations			Blood pressure decreased Heart rate increased Blood creatinine increased			

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms include:
Full rigid erection lasting more than four hours.

Overdosage was not observed in clinical trials with alprostadil. If intracavernous overdose of Viridal Duo occurs, the patient should be placed under medical supervision until any systemic effects have resolved and/or until penile detumescence has occurred. Symptomatic treatment of any systemic symptoms would be appropriate.

The treatment of priapism (prolonged erection) should not be delayed more than 6 hours.

Initial therapy should be by penile aspiration. Using aseptic technique, insert a 19-21 gauge butterfly needle into the corpus cavernosum and aspirate 20-50 ml of blood. This may detumesce the penis. If necessary, the procedure may be repeated on the opposite side of the penis until a total of up to 100 ml blood has been aspirated.

If still unsuccessful, intracavernous injection of alpha-adrenergic medication is recommended. Although the usual contra-indication to intrapenile administration of a vasoconstrictor does not apply in the treatment of priapism, caution is advised when this option is exercised. Blood pressure and pulse should be continuously monitored during the procedure. Extreme caution is required in patients with coronary heart disease, uncontrolled hypertension, cerebral ischaemia, and in subjects taking monoamine oxidase inhibitors. In the latter case, facilities should be available to manage a hypertensive crisis. A 200 microgram/ml solution of phenylephrine should be prepared, and 0.5 to 1.0 ml of the solution injected every 5 to 10 minutes. Alternatively, a 20 microgram/ml solution of epinephrine should be used. If necessary, this may be followed by further aspiration of blood through the same butterfly needle. The maximum dose of phenylephrine should be 1 mg, or epinephrine 100 micrograms (5 ml of the solution). As an alternative metaraminol may be used, but it should be noted that fatal hypertensive crises have been reported. If this still fails to resolve the priapism, urgent surgical referral for further management, which may include a shunt procedure is required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in erectile dysfunction,

ATC Code: Other urologicals G04BE01

Mechanism of action

Alprostadil [Prostaglandin E_1 (PGE_1)], the active ingredient of Viridal Duo, is an endogenous compound derived from the essential fatty acid dihomogammalinolenic acid.

Alprostadil is a potent smooth muscle relaxant that produces vasodilation and occurs in high concentrations in the human seminal fluid. Pre-contracted isolated preparations of the human corpus cavernosum, corpus spongiosum and cavernous artery were relaxed by alprostadil, while other prostanoids were less effective. Alprostadil has been shown to bind to specific receptors in the cavernous tissue of human and non-human primates.

The binding of alprostadil to its receptors is accompanied by an increase in intracellular cAMP levels. Human cavernosal smooth muscle cells respond to alprostadil by releasing intracellular calcium. Since relaxation of smooth muscle is associated with a reduction of the cytoplasmic free calcium concentration, this effect may contribute to the relaxing activity of this prostanoid.

Pharmacodynamic effects
Intracavernous injection of alprostadil in healthy monkeys resulted in penile elongation and tumescence without rigidity. The cavernous arterial blood flow was increased for a mean duration of 20 min. In contrast, intracavernous application of alprostadil to rabbits and dogs caused no erectile response.

Systemic intravascular administration of alprostadil leads to a vasodilation and reduction of systemic peripheral vascular resistance. A decrease in blood pressure can be observed after administration of high doses. Alprostadil has also been shown in animal and *in vitro* tests to reduce platelet reactivity and neutrophil activation. Additional alprostadil activity has been reported: increase in fibrinolytic activity of fibroblasts, improvement of erythrocyte deformability and inhibition of erythrocyte aggregation; inhibition of the proliferative and mitotic activity of non-striated myocytes; inhibition of cholesterol synthesis and LDL-receptor activity; and an increase in the supply of oxygen and glucose to ischaemic tissue along with improved tissue utilisation of these substrates.

5.2 Pharmacokinetic properties

Absorption
After reconstitution, alprostadil (PGE_1) dissociates from the α-cyclodextrin clathrate, and the two components have independent fates.

In symptomatic volunteers, systemic mean endogenous PGE_1 venous plasma concentrations measured before intracavernous injection are approximately 1pg/ml. After injection of 20 mcg of alprostadil, the PGE_1 venous plasma concentrations increase rapidly to concentrations of about 10-20 pg/ml. The PGE_1 plasma concentrations return to concentrations close to the baseline within 2 hours.

Distribution
Approximately 90% of PGE1 found in plasma is protein-bound.

Biotransformation

Enzymatic oxidation of the C15-hydroxy group and reduction of the C13,14 double bond produce the primary metabolites, 15-keto-PGE_1, PGE_o (13,14-dihydro-PGE_1) and 15-keto-PGE_o. Only PGE_o and 15-keto-PGE_o have been detected in human plasma. Unlike the 15-keto metabolites, which are less pharmacologically active than the parent compound, PGE_o has a potency similar to that of PGE_1 in most respects.

In symptomatic volunteers, the mean endogenous PGE_o venous plasma concentrations measured before an intracavernous injection are approximately 1 pg/ml. After the injection of 20 mcg of alprostadil, the PGE_o plasma concentrations increase to concentrations of about 5 pg/ml within 20 minutes followed by a return to concentrations close to baseline. The terminal half-life of PGE_0 is about 30 minutes.

Elimination

After further degradation of the primary metabolites by beta and omega oxidation, the resulting, more polar metabolites are excreted primarily with the urine (88%) and the faeces (12%) and there is no evidence of tissue retention of PGE_1 or its metabolites.

5.3 Preclinical safety data

Studies on local tolerance following single and repeated intracavernous injections of alprostadil or alprostadil alfadex in rabbits and/or monkeys, in monkeys up to 6 months with daily injection revealed in general good local tolerance. Possible adverse effects like haematomas and inflammations are more likely related to the injection procedure.

Within the 6 months study in male monkeys, there were no adverse effects of alprostadil alfadex on male reproductive organs.

Alprostadil did not cause any adverse effects on fertility or general reproductive performance in male and female rats treated with 40-200 mcg/kg/day. The high dose of 200 mcg/kg/day is about 300 times the maximum recommended human dose on a body weight basis (MHRD < 1 mcg/kg).

Alprostadil was not fetotoxic or teratogenic at doses up to 5000 mcg/kg/day (7500 times the MHRD) in rats, 200 mcg/kg/day (300 times the MHRD) in rabbits and doses up to 20 mcg/kg/day (30 times the MHRD) in guinea pigs or monkeys.

Being an endogenous substance, PGE1 is considered harmless as to mutagenic or carcinogenic effects.

Different mutagenicity studies with alprostadil alfadex revealed no risk of mutagenicity.

Chronic toxicity studies in dogs (6 months, daily intravenous infusion) and monkeys (6 months, daily intracavernous injection) indicate that systemic side effects are unlikely to occur following intracavernous injection of 5 to 60 mcg alprostadil (used as clathrate complex with alfadex) in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for injection:
Lactose monohydrate
Alfadex

Diluent
Sodium chloride
Water for injection

6.2 Incompatibilities

It is not intended that this medicinal product be mixed with other medicinal products, therefore in the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Shelf life for the product as packaged for sale:	36 months
Shelf life after reconstitution:	for immediate use only

Discard any unused solution immediately after use.

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

1. Cartons containing one colourless Type I glass double-chamber cartridge, one injection needle 29 G x ½ (0.33 mm x 12.7 mm) and one reusable injector (starter kit).
2. Cartons containing two colourless Type I glass double-chamber cartridges, two injection needles 29 G x ½ (0.33 mm x 12.7 mm) and one reusable injector (starter kit).
3. Cartons containing one, two or six colourless Type I glass double-chamber cartridges and corresponding number of injection needles 29 G x ½ (0.33 mm x 12.7 mm) without reusable injector.

Not all pack sizes may be marketed.

Administration devices

1 reusable injector (starter kit)
1 double chamber cartridge with dry substance and 1 ml 0.9% sterile sodium chloride solution
1 injection needle 29G x ½ (0.33 mm x 12.7 mm)

1 alcohol swab to be obtained for each injection

6.6 Special precautions for disposal and other handling

Advice

For instructions on reconstitution of the medicinal product before administration, see section 4.2.

There is a white, dry powder cake which forms a compact layer in a height of approx. 8 mm in the cartridge.

In case of damage to the cartridge, the usually dry content of the front chamber becomes moist and sticky and extensively loses volume. Viridal must not be used in this case.

The dry substance dissolves immediately after addition of the sodium chloride solution. Initially after reconstitution the solution may appear slightly opaque due to the presence of bubbles. This is of no relevance and disappears within a short time to give a clear solution.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

UCB (Pharma) Ireland Limited
United Drug House
Magna Drive
Magna Business Park
Citywest Road
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0891/015/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 14 November 2007

10 DATE OF REVISION OF THE TEXT

March 2017