SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vitaros 2 mg/g cream
Vitaros 3 mg/g cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single use container contains 200 micrograms of alprostadil in 100 mg of cream (2 mg/g).
Each single use container contains 300 micrograms of alprostadil in 100 mg of cream (3 mg/g).
For a full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Cream
Vitaros is a white to off-white cream supplied in AccuDose, a single dose container. AccuDose is a container consisting of a plunger, barrel, and protective cap provided in a protective sachet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of men ≥ 18 years of age with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

4.2 Posology and method of administration

Vitaros is applied to the tip of the penis.
Vitaros is available in two dosage strengths of 200 and 300 mcg alprostadil in 100 mg of cream. Vitaros should be used as needed to achieve an erection. Each Vitaros AccuDose container is for single use only and should be properly discarded after use. The onset of effect is within 5 to 30 minutes after administration. The duration of effect is approximately 1 to 2 hours. However, the actual duration will vary from patient to patient. Each patient should be instructed by a medical professional on proper technique for administration of Vitaros prior to self-administration. The maximum frequency of use is no more than 2-3 times per week and only once per 24-hour period.

The initial dose should be recommended by a physician. A starting dose with the 300 mcg dose can be considered especially in patients with serious ED, co-morbidity or failure to PDE-5 inhibitors. Those patients that do not tolerate the 300 mcg dose due to local side effects can be titrated to the lower 200 mcg dose.
Patients should be given instruction on proper administration technique, information on possible side effects (e.g., dizziness, fainting) and the need to avoid operating machinery until one is aware of their tolerance to the drug. In the clinical trial there was a higher withdrawal rate in the 300 mcg treated group compared to the 200 mcg group, 30% compared to 20% respectively.

Method of administration:
It is recommended to urinate before applying the drug. After removing the cap, apply all the contents of Vitaros into the opening at the tip of the penis (meatus) 5 to 30 minutes before attempting intercourse by following the instructions below:
1) Wash your hands before applying Vitaros. Remove the AccuDose container (see Fig. 1) from the sachet by tearing fully down the seal from the middle of the top edge. Save the sachet for discarding the used AccuDose container later.
2) Bring the contents of the single-dose container to room temperature by rolling the container between your hands (see Fig. 2). This step can be avoided if the sachet was removed from the refrigerator earlier (within the time limits stated in

Section 6.4 Special precautions for storage) and the contents have already reached room temperature.
3) Twist the plunger several times to make sure it will glide easily (see Fig. 3). Then remove the cap from the tip of the AccuDose container.

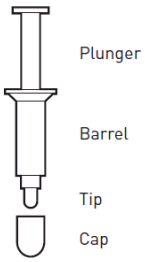

Fig. 1

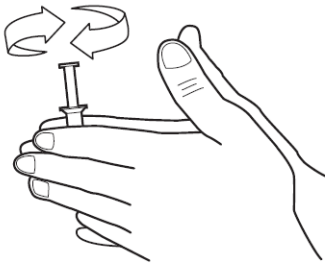

Fig. 2

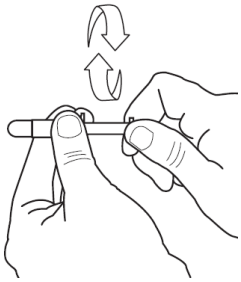

Fig. 3

4) Grasp the tip of the penis with one hand and gently squeeze to widen the opening at the tip of the penis while holding it in an upright vertical position (see Fig 4) (Note, if you are not circumcised, first retract and hold the foreskin back prior to widening the opening at the tip of the penis).
5) Hold the barrel of the AccuDose container between your fingers and **without inserting it inside the penis** (see Fig. 5), place the tip of the container as close as possible to the opening at the tip of the penis for the cream to go down the urethra (the tube that leads from the bladder and transports and discharges urine and semen outside the body). Remember to push out all the cream from the AccuDose container. Slowly, but firmly, push down the plunger with your thumb or finger until all the cream is expelled into the opening at the tip of the penis and down the urethra.
Note: While it is important that all the cream goes down the urethra, take care **not to insert the tip of the AccuDose container into the opening at the tip of the penis.**
6) Hold the penis in an upright position for approximately 30 seconds in order to allow the cream to penetrate. There will likely be some cream that does not initially fit into the opening at the tip of the penis. Any excess cream covering the opening at the tip of the penis should be gently moved into the opening with the tip of a finger (see Fig. 6). Do not use a second AccuDose to compensate for cream not expelled into the opening at the tip of the penis. Do not urinate immediately after application, due to the risk that drug could come out before the effect takes place.
7) Remember, each Vitaros dose is suitable for a single administration only. Replace the cap on the tip of the AccuDose container and place in the opened sachet, fold and discard in accordance with local requirements.
8) Vitaros may be irritating to the eyes. Wash your hands after applying Vitaros.

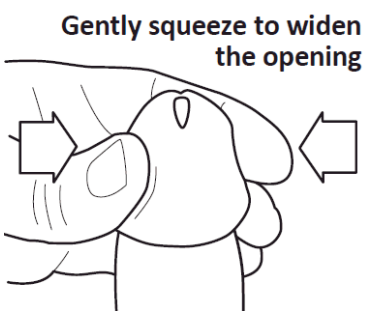

Fig. 4

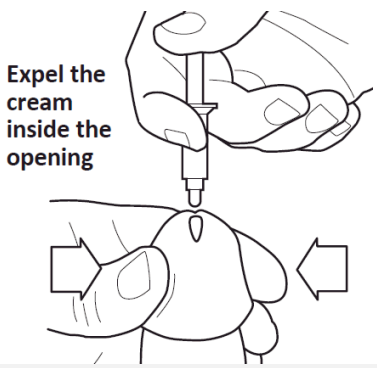

Fig. 5

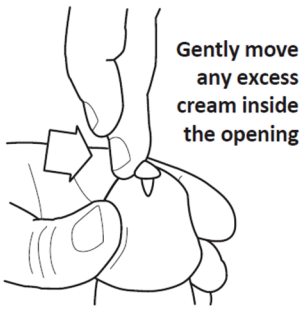

Fig. 6

4.3 Contraindications

Vitaros should not be used in patients with any of the following:

- Underlying disorders such as orthostatic hypotension, myocardial infarction and syncope.
- Known hypersensitivity to alprostadil or any of the ingredients in Vitaros.
- Conditions that might predispose them to priapism, such as sickle cell anaemia or trait, thrombocythemia, polycythemia or multiple myeloma or leukaemia.
- Abnormal penile anatomy such as severe hypospadias, in patients with anatomical deformation of the penis, such as curvature, and in patients with urethritis and balanitis (inflammation/infection of the glans of the penis).
- Prone to venous thrombosis or who have a hyperviscosity syndrome and are therefore at increased risk of priapism (rigid erection lasting 4 or more hours).
- Vitaros should not be used in patients for whom sexual activity is inadvisable as in men with unstable cardiovascular or unstable cerebrovascular conditions.
- Vitaros should not be used for sexual intercourse with a woman with child-bearing potential unless the couple uses a condom barrier.

4.4 Special warnings and precautions for use

Local effects:
Prolonged erections lasting > 4 hours (priapism), although rare, were observed with the use of Vitaros. Priapism was observed in the two 3-month studies in 1 patient (0.06%) and in the > 6-month study in 5 (0.4%) patients, including 4 (0.3%) in the 200 mcg and 1 (0.1%) in the 300 mcg groups. If priapism occurs, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

Symptomatic hypotension (dizziness) and syncope occurred in a small percent of patients (2/459 (0.4%), 6/1591 (0.4%), and 6/1280 (0.5%) at the 100, 200 and 300 mcg alprostadil doses, respectively, during dosing in the Phase 3 studies. Patients should be cautioned to avoid activities, such as driving or hazardous tasks, where injury could result if hypotension or syncope occurs after Vitaros administration.

Before initiation of treatment with Vitaros, causes of erectile dysfunction, that are treatable, should be excluded by appropriate diagnostic methods.

In addition, patients with underlying disorders, such as orthostatic hypotension, myocardial infarction and syncope, should not use Vitaros (see CONTRAINDICATIONS, section 4.3).

Clinical studies have not been conducted in patients with a history of neurological disease or spinal injury.

The pharmacokinetics of Vitaros have not been formally studied in patients with hepatic and /or renal insufficiency. The dose may need to be lowered in these populations due to impaired metabolism.

General Precautions:
Vitaros should be applied according to the instructions above. Inadvertent

intraurethral exposure may result in penile burning or tingling sensation and pain. Repeated longer term intraurethral exposure of Vitaros is unknown.

Patients should be informed that Vitaros offers no protection from the transmission of sexually transmitted diseases. Patients and partners who use Vitaros need to be counselled about the protective measures that are necessary to guard against the spread of sexually transmitted agents, including the human immunodeficiency virus (HIV). Health care professionals should encourage their patients to inform their sexual partners that they are using Vitaros. Partners of Vitaros users can experience adverse events, most commonly vaginal irritation. A condom barrier is therefore recommended.

The effects of Vitaros on the oral or anal mucosa has not been studied. A condom barrier should be used for oral sex (fellatio) or anal sex.

Vitaros has no contraceptive properties. It is recommended that couples using Vitaros use adequate contraception if the female partner is of childbearing potential.

There is no information on the effects on early pregnancy of alprostadil at the levels received by the female partners. A condom barrier should be used for sexual intercourse with women of childbearing age, pregnant or lactating women.

Only latex material based condoms have been investigated together with its use and other materials may not exclude possible risk for occurrence of damage to the condom.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic or pharmacodynamic interaction studies with Vitaros were not done. Based on the nature of metabolism (see “Pharmacokinetics”) drug-drug interactions are considered unlikely.

Effect of Interaction

The safety and efficacy for Vitaros in combination with other treatments for erectile dysfunction, especially for the treatment with Phosphodiesterase-5 inhibitors (PDE-5) or sildenafil, tadalafil and vardenafil , has not been studied. Therefore, Vitaros should not be used in combination with PDE5 inhibitors. As both Vitaros and PDE5 inhibitors have cardiovascular effects, an additive increased cardiovascular risk cannot be excluded.

No interaction studies have been performed for Vitaros in combination with penile implants or smooth muscle relaxants such as papaverine; drugs used to induce erections such as alpha blocking drugs (e.g. intracavernosal phentolamine, thymoxamine). There is a risk of priapism (painful prolonged abnormal erection) when used in combination.

No interaction studies have been performed for Vitaros in combination with sympathomimetics, decongestants and appetite suppressants. When used in combination there may be a reduced effect of alprostadil (drug interaction inhibition).

No interaction studies have been performed for Vitaros in combinationwith anticoagulants and platelet aggregation inhibitors. When used in combination there may be an increased risk of urethral bleeding, haematuria.

Patients concomitantly treated with antihypertensive drugs and vasoactive medications may show an increased risk for hypotension, especially in elderly patients.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no data on the use of Vitaros in pregnant women. The indirect exposure to alprostadil in women is likely to be low.

Animal data on higher doses of alprostadil show reproductive toxicity (see section 5.3).

Pregnant women should not be exposed to Vitaros.

Breastfeeding

It is not known if indirect exposure to alprostadil via Vitaros will lead to significant excretion in breastmilk. It is not recommended to use Vitaros while breastfeeding.

Fertility

In male rabbits, atrophy of the seminiferous tubules of the testes was observed after repeated dosing. It is not known whether Vitaros has an effect on human male fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of the ability to drive and use machines have been performed. As dizziness and syncope (fainting) have been reported rarely in clinical trials with Vitaros, patients should avoid activities, such as driving or hazardous tasks, where injury could result if syncope occurs within 1 to 2 hours after administration of Vitaros.

4.8 Undesirable effects

Tabulated list of adverse reactions

The most frequently reported adverse events in treatment with Vitaros are presented in the table below. (Very common ≥ 1/10; Common ≥ 1/100, <1/10; Uncommon ≥1/1000, <1/100; Rare ≥1/10000, <1/1000; Very rare <1/10000)

Priapism (an erection lasting longer than 4 hours) is a serious condition that requires prompt treatment by a physician.

Table 1 Adverse Reactions

System Organ Class (MedDRA)	Frequency	Adverse Reaction
Nervous System Disorders	Uncommon	Hyperesthesia
Vascular Systems Disorders*	Uncommon	Dizziness Syncope Hypotension

Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal and Connective Tissue Disorders	Uncommon	Pain in Extremity
Renal and Urinary Disorders	Common	Urethral pain
	Uncommon	Urethral Stenosis Urinary Tract Inflammation
Reproductive system and breast disorders	Common	Penile Burning Penile Pain Penile Erythema Genital Pain Penile Erythema Genital Discomfort Genital Erythema Erection Increased Pruritus Genital Penile Oedema Balanitis Penile Tingling Penile throbbing Penile numbness <u>In women partners</u>: Vulvovaginal Burning Sensation Vaginitis
	Uncommon	Penile Itching Genital Rash Scrotal Pain Fullness genital Excessive rigidity Lack of sensation to Penis Prolonged erection/priapism <u>In women partners</u>: Vulvovaginal Pruritus
General Disorders and Administration Site Conditions	Uncommon	Application Site Pain

<u>Special populations</u>

* There is no clear indication that alprostadil increases the risk of cardiovascular events, other than the vasodilative effects, but it cannot be excluded that patients with underlying disease/risk factors are at increased risk in combination with increased sexual/physical activity that is associated with alprostadil use (see 4.3 and 4.4)

<u>Reporting of suspected adverse reactions</u>

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 <<To be completed during the National Phase>>.

4.9 Overdose

Overdosage requiring treatment has not been reported with Vitaros. Overdosage with Vitaros may result in hypotension, syncope, dizziness, penile pain and possible priapism (rigid erection lasting > 4 hours). Priapism can result in permanent worsening of erectile function. Patients suspected of overdose who develop these symptoms should be under medical supervision until systemic or local symptoms have been resolved.

Should a prolonged erection lasting 4 or more hours occur, the patient should be advised to seek medical help. The following actions can be taken:

• The patient should be supine or lying on his side. Apply an ice pack alternately for two minutes to each upper inner thigh (this may cause a reflex opening of the venous valves). If there is no response after 10 minutes, discontinue treatment.

• If this treatment is ineffective and a rigid erection has lasted for more than 6 hours, penile aspiration should be performed. 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.

• If still unsuccessful, intracavernous injection of α-adrenergic medication is recommended. Although the usual contraindication 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 5-10 minutes. Alternatively, a 20 microgram/ml solution of adrenaline 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 adrenaline 100 micrograms (5ml 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, the patient should immediately be referred for surgical management.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Drugs used in erectile dysfunction

ATC Code: G04BE01

Mechanism of Action:

Alprostadil is chemically identical to prostaglandin E_1, the actions of which include vasodilatation of blood vessels in the erectile tissues of the corpora cavernosa and increase in cavernosal artery blood flow, causing penile rigidity.

After application of Vitaros the onset of erection is within 5 to 30 minutes. Alprostadil has a short half-life in man and improvement of erections may last from 1 to 2 hours after dosing.

Efficacy: Two Pivotal Phase 3 studies evaluated the efficacy of Vitaros in patients with Erectile Dysfunction. Relative to placebo, a statistically significant overall improvement was observed in the 100, 200 and 300 mcg alprostadil treatment groups in each of the primary efficacy endpoints; i.e., the erectile function (EF) domain of the IIEF (International Index of Erectile Function) score and increased success in vaginal penetration and ejaculation. Additionally, there were also overall improvements and statistical significance of the treatment groups compared to placebo in several of the secondary efficacy variables, including the other IIEF domain scores (orgasmic function, intercourse satisfaction, and overall satisfaction), Patient Self-Assessment of Erection (PSAE), and Global Assessment Questionnaire (GAQ).

Subpopulation Efficacy: Similar improvements to those of all patients were generally observed within the subpopulations (diabetic, cardiac, prostatectomy, hypertensive patients, and patients who failed previous therapy with Viagra) and two age groups (< 65 and > 65 years) in the IIEF EF domain scores.

5.2 Pharmacokinetic properties

Absorption: Absolute bioavailability by the topical route was not determined. In a pharmacokinetic study, patients with erectile dysfunction were treated with 100 mg of Vitaros Cream at doses of 100, 200 and 300 mcg of alprostadil. Plasma levels of PGE1, and its metabolite, PGE0 were low or undetectable in most subjects at most of the post-dose blood sampling times and pharmacokinetic parameters could not be estimated. C_{max} values and AUC values of 15-keto-PGE0 were low and showed a less than dose proportional increase over the 100 – 300 mcg dose range. The maximum plasma concentrations of 15-keto-PGE0 were achieved within one hour after administration.

Table 2

Mean (SD) Pharmacokinetic Parameters for 15-keto-PGE_0

Parameter	Placebo (N=5)	Vitaros 100 mcg (N=5)	Vitaros 200 mcg (N=5)	Vitaros 300 mcg (N=5)
AUC[a] (pg*hr/mL)	388 (256)	439 (107)	504 (247)	960 (544)
C_{max} (pg/mL)	23 (19)	202 (229)	120 (103)	332 (224)
T_{max} (hr)	6 (8)	0.6 (0.4)	1 (0.7)	0.7 (0.3)
$T_{1/2}$ (hr)	4 (--)[b]	5 (3)	3 (1)[c]	6 (6)

[a] AUC is the area under the plasma concentration curve from time zero to hour 24

[b] Only 1 subject had sufficient data for estimation of half-life.

[c] Only 3 subjects had sufficient data for estimation of half-life.

SD = standard deviation

Distribution: After alprostadil administration to the meatus and glans of the penis,

alprostadil is rapidly absorbed into the corpus spongiosum and corpora cavernosa through collateral vessels. The remainder passes into the pelvic venous circulation through veins draining the corpus spongiosum.

Metabolism: Following topical administration, PGE1 is rapidly metabolized locally by enzymatic oxidation of the 15-hydroxyl group to 15-keto-PGE1. 15-keto-PGE1 retains only 1-2% of the biological activity of PGE1 and is rapidly reduced to form the most abundant inactive metabolite, 13, 14-dihydro, 15-keto-PGE which is cleared primarily by the kidney and liver.

Excretion: After intravenous administration of tritium-labelled alprostadil in man, labelled drug disappears rapidly from the blood in the first 10 minutes and only low-level radioactivity remains in the blood after 1 hour. The metabolites of alprostadil are excreted primarily by the kidney with approximately 90% of the administered intravenous dose excreted in the urine within 24 hours after administration. The remainder is excreted in the faeces. There is no evidence of tissue retention of alprostadil or its metabolites following intravenous administration.

Pharmacokinetics in Special Populations:

Pulmonary Disease: Patients with pulmonary disease may have a reduced capacity to clear the drug. In patients with adult respiratory distress syndrome, pulmonary extraction of intravenously administered PGE1 was reduced by approximately 15% compared to a control group of patients with normal respiratory function.

Gender: The effects of gender on the pharmacokinetics of the Vitaros have not been studied and pharmacokinetic studies have not been conducted in female partners.

Geriatric, Paediatric: The effects of age on the pharmacokinetics of topical alprostadil have not been studied. The Vitaros is not indicated for use in children or in individuals below 18 years of age.

5.3 Preclinical safety data

Alprostadil, DDAIP and Vitaros (including DDAIP) have not shown genotoxic potential.

Carcinogenicity studies with alprostadil or Vitaros have not been conducted. Carcinogenicity assessments of the excipient, DDAIP, found no tumor formation with topical administration to mice and subcutaneously in rats. In the Tg.AC transgenic mouse model administration of DDAIP at a concentration of 1.0% and 2.5% induced papillomas in females and males respectively. This effect is not likely to be relevant for humans, as it likely caused by irritation.

Alprostadil has no effect on sperm count or morphology. However, the excipient DDAIP caused atrophy of the seminiferous tubules of the testes in rabbits when administered locally at a concentration of 5%. A direct spermatotoxic effect of DDAIP could not be tested, and the relevance for a possible reduced male fertility in humans is therefore unknown. DDAIP administered subcutaneously to rats had no effect on fertility.

Alprostadil has been shown to be embryotoxic (decreased foetal weight) when administered as a subcutaneous bolus to pregnant rats at low doses Higher doses resulted in increased resorptions, reduced numbers of live foetuses, increased incidences of visceral and skeletal variation and malformations, and maternal

toxicity. Intravaginal administration of PGE1 to pregnant rabbits resulted in no harm to the foetus.

Reproductive toxicity studies for DDAIP were performed after subcutaneous administration to rats and rabbits. No effects were seen in rats, but in rabbits foetotoxicity including increased malformations were seen at high doses, which was probably due to maternal toxicity. No effects on post-natal development were evident in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water
Ethanol, anhydrous
Ethyl laurate
Hydroxypropyl guar gum
Dodecyl-2-N,N-dimethylaminopropionate hydrochloride
Potassium dihydrogen phosphate
Sodium hydroxide, for pH adjustment
Phosphoric acid, for pH adjustment

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

9 months for Vitaros 2 mg/g cream
14 months for Vitaros 3 mg/g cream
Once opened, use immediately, discard any unused portion.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Unopened sachets may be kept out of the refrigerator by the patient, at a temperature below 25 °C for up to 3 days prior to use.

At the end of this period, the product should be discarded if not used.

Store in the original sachet in order to protect from light.

6.5 Nature and contents of container

Vitaros is supplied in individual sachets containing one (1) AccuDose container. Each single container contains 100 mg cream. Vitaros is available in unit cartons containing four (4) containers. The sachets are composed of aluminium foil/laminate. The container components are composed of polypropylene and polyethylene.

6.6 Special precautions for disposal

Each container is for single use only.

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

7 MARKETING AUTHORISATION HOLDER
To be completed nationally

8 MARKETING AUTHORISATION NUMBER(S)
To be completed nationally

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
To be completed nationally

10 DATE OF REVISION OF THE TEXT