# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Invicorp 25 micrograms / 2 mg solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Invicorp 25 micrograms / 2 mg: 1 dose (ampoule 0.35 ml) contains 25 micrograms of aviptadil and 2 mg of phentolamine mesilate.

Excipients with known effect: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium- free’.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection.

Appearance: Colorless to pale yellow solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Invicorp is indicated for the symptomatic treatment of erectile dysfunction in adult males due to neurogenic, vasculogenic, psychogenic, or mixed aetiology.

### 4.2 Posology and method of administration

Posology

Invicorp 25 micrograms / 2 mg.

The injection should provide the patient with an erection that is satisfactory for sexual intercourse. It is recommended that the duration of the erection does not exceed one hour.

Injection frequency should not exceed once daily or 3 times weekly.

Paediatric population: Invicorp is not recommended in children.

Elderly: No formal studies have been performed in patients above 75 years of age.

Impaired renal or hepatic function: No formal studies have been performed in patients with impaired renal or hepatic function.

Method of administration

The ampoule can be brought to room temperature before use, or it can be used directly from the refrigerator (see section 6.6).

The intracavernosal injection must be done under sterile conditions. Invicorp should be administered by direct intracavernous injection. The usual site of injection is along the dorsolateral aspect of the proximal third of the penis. Visible veins should be avoided. Both the side of the penis and the site of injection must be altered between injections.

The initial injections of Invicorp must be administered by medically trained personnel, and after proper training, Invicorp may be injected at home. It is recommended that the patient is regularly monitored (e.g. every 3 months) particularly in the initial stages of self-injection therapy.

## 4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Men for whom sexual activity is not advisable or is contraindicated due to organic disease.

Men with either of the following should not be treated with Invicorp:
- Conditions that might predispose to priapism, such as sickle cell anaemia or trait, multiple myeloma, or leukemia.
- Anatomical deformation of the penis, such as angulation, cavernosal fibrosis, or Peyronie's disease.
- Penile implants.

## 4.4 Special warnings and precautions for use

Underlying treatable medical causes of erectile dysfunction should be diagnosed and treated prior to initiation of therapy with Invicorp.

Prolonged erection and/or priapism may occur following intracavernosal administration of Invicorp (see section 4.8). Patients should be instructed to immediately report to a physician any erection lasting for a prolonged period, such as 4 hours or longer. Treatment of priapism should not be delayed more than 6 hours. Treatment of priapism should be according to established medical practice (please refer to section 4.9).

Penile fibrosis, including angulation, cavernosal fibrosis, fibrotic nodules and Peyronie's disease may occur following the intracavernosal administration of Invicorp. The occurrence of fibrosis may increase with increased duration of use(see section 4.8). Regular follow-up of patients, with careful examination of the penis, is strongly recommended to detect signs of penile fibrosis or Peyronie's disease. Whilst not so far observed onInvicorp, the attending doctor should be aware of the possibility of an association. Treatment with Invicorp should be discontinued in patients who develop penile angulation, cavernosal fibrosis, or Peyronie's disease.

Mild transient flushing of the face or trunk occurs commonly (see section 4.8). This is rarely associated with discomfort and palpitations or tachycardia (see section 4.8). In these cases patients may be withdrawn from treatment. See also section 4.8.

Invicorp must be used with caution in patients with severe cardiovascular or cerebrovascular conditions.

Sexual stimulation and intercourse can lead to cardiac and pulmonary events in patients with coronary heart disease, congestive heart failure and pulmonary disease. The potential risks in connection with intercourse in patients on multi-drug treatment for cardiovascular symptoms may be increased by the treatment itself or by the patient’s underlying heart disease. These patients when using Invicorp should engage in sexual activity with caution. If tachycardia occurs, treatment with Invicorp should be discontinued.

Invicorp is not suitable for concomitant use with other treatments of erectile dysfunction (see section 4.5).

The potential for abuse of Invicorp should be considered in patients with a history of psychiatric disorder or addiction.

Correct injection technique is important and Invicorp should not be prescribed without adequate instruction and training in its use (see section 4.2).

Invicorp contains 0.05 mmol sodium per dose which means it is essentially sodium-free.

## 4.5 Interaction with other medicinal products and other forms of interaction

Invicorp should be used with caution in combination with anticoagulants such as heparins and warfarin, including oral anticoagulants such as dabigatran, rivaroxaban or apixaban.

No clinical interaction has been observed in the use of Invicorp with concomitant intake of anti-hypertensive or other cardiovascular medication.

## 4.6 Fertility, pregnancy and lactation

Not relevant. Invicorp is only indicated in men.

No reproduction studies have been carried out on animals using a combination of aviptadil and phentolamine mesilate.

The effect of concomitant treatment with Invicorp and other treatments for erectile dysfunction (eg sildenafil) or with other drugs that induce erection (eg papaverine) has not been formally studied. Such medicinal substances should not be used with Invicorp because of the potential for prolonged duration of erections.

## 4.7 Effects on ability to drive and use machines

No trials on the effect on the ability to drive a car or use machines have been carried out.

## 4.8 Undesirable effects

Approximately 10% of patients experience adverse reactions. Flushing is often observed but is rarely problematic and may be difficult to distinguish from the flushing associated with intercourse.

Haematoma and bruise may occur at the injection site. This will become less of a problem when patients become more experienced in the injection technique itself.

| | |
|---|---|
| **Nervous system disorders**<br>Uncommon (≥1/1,000 to <1/100) | Headache, dizziness. |
| **Cardiac disorders**<br>Uncommon (≥1/1,000 to <1/100) | Tachycardia, palpitations. |
| Very rare (<1/10,000) | Myocardial infarction, angina pectoris. |

| | |
|---|---|
| **Vascular disorders**<br>Common (≥1/100 to <1/10) | Flushing. |
| **Reproductive system and breast disorders**<br>Rare (≥1/10,000 to <1/1,000) | Priapism, prolonged erection. Penile nodules/fibrosis following multiple injections. |
| **General disorders and administration site conditions**<br>Common (≥1/100 to <1/10)<br>Uncommon (≥1/1,000 to <1/100)<br>Rare (≥1/10,000 to <1/1,000) | Bruising.<br>Haematoma.<br>Pain post injection. |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the internet at www.mhra.gov.uk/yellowcard alternatively you can call Freephone 0808 100 3352 (available between 10am-2pm Monday-Friday) or fill in a paper form available from your local pharmacy.

## 4.9 Overdose

Long-term erections and/or priapism may occur with vasoactive substances following intracavernous injection.

Treatment of long-term erection (priapism) should not be delayed for more than a maximum of 6 hours. Initial treatment should be penile aspiration. Aseptic technique is used, a 19 - 21 gauge butterfly needle being introduced into the corpus cavernosum, after which 20 – 50 ml of blood is withdrawn. This may cause relaxation of the penis. If necessary, the procedure can be repeated on the other side of the penis. If this is ineffective, an intracavernous injection of an alpha-adrenergic agent is recommended. Blood pressure and pulse are to be monitored during this procedure. Extreme caution is required in patients with coronary diseases, non-controlled hypertension, cerebral ischaemia, and in patients receiving monoamine oxidase inhibitors. In the latter, facilities should be available to control a hypertensive crisis.

A 200 microgram/ml solution of phenylephrine should be prepared, and 0.5 - 1.0 ml of the solution injected every 5 to 10 minutes. Alternatively, a 20 microgram/ml adrenaline solution may be administered with further aspiration of blood. The maximum dose should be 1 mg phenylephrine, or 100 microgram of adrenaline (5 ml solution), respectively. If the priapism still does not disappear, imperative surgical intervention will be required for further control, which may include a shunt procedure.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combined medicinal products in erectile dysfunction.

ATC code: G 04 BE 30.

Phentolamine is a short-acting alpha-adrenoceptor antagonist. It causes vasodilatation and a decrease in blood pressure, as a result of the blockade of both post-junction vascular alpha 1 and alpha 2 adrenoceptors with almost the same effect. It has a directly relaxing effect on smooth muscles that is independent of alpha blockade.

Following the discovery of nerves in the male genital canal that possess VIP-immunoactivity, consideration was given to whether aviptadil (vasoactive intestinal polypeptide) had a possible role in relation to local nerve control of smooth musculature activity in the male urogenital canal. The venous occlusion caused by the relaxation of the smooth musculature seems to be under VIP control. In smooth muscle preparations for the human corpus cavernosa it has been found that VIP has a relaxing effect, both on spontaneous activity and electrically pre-contracted tissue.

Effect of Invicorp in patients with predominantly non-psychogenic erectile dysfunction:

| Study | No. patients | No. injections | | No. of Grade 3 Responders* (%) | |
|---|---|---|---|---|---|
| | | Active** | Placebo | Active** | Placebo |
| VP004 | 238 | 2272 | 451 | 1674 (74%) | 53 (12%) |
| VP005 | 105 | 1017 | 207 | 747 (73%) | 26 (13%) |

*Patients with erection suitable for vaginal penetration (as judged in clinic) or sexual intercourse in the home environment.

**25 micrograms VIP and 1.0 mg phentolamine or 25 micrograms VIP and 2.0 mg phentolamine.

## 5.2 Pharmacokinetic properties

| *Pharmacokinetic parameters of VIP after administration of Invicorp 25 microgram / 2 mg (Baseline adjusted) | | |
|---|---|---|
| Pharmacokinetic parameter | Intravenous injection | Intracavernosal injection |
| Cmax (pmoles/L) | 396,6 | 37,2 |
| Tmax (minutes) | 1,4 | 4,3 |
| AUC0-∞ (pmoles.h/L) | 10,4 | 6,1 |
| Half life (minutes) | 1,7 | 5,3 |
| Clearance (L/hr) | 987,1 | |
| Volume of distribution (L) | 50,4 | |

| *Pharmacokinetic parameters of Phentolamine after administration of Invicorp 25 microgram / 2 mg | | |
|---|---|---|
| Pharmacokinetic parameter | Intravenous injection | Intracavernosal injection |
| Cmax (ng/ml) | 79,5 | 12,4 |
| Tmax (minutes) | 1,5 | 2,0 |
| AUC (ng/h/ml) | 1,9 | 0,2 |
| Half life (minutes) | 1,2 | |
| Clearance (L/min) | 14,4 | |

* Study VP001 – A two-way crossover pharmacokinetic study of vasopotin 2 in healthy male volunteers

Endogenous catecholamines displace phentolamine from the alpha-receptors and accounts for the short observed duration of action.

The biological response of VIP is terminated by enzymatic degradation of the peptide after its binding to the receptor.

## 5.3 Preclinical safety data

No evidence of genotoxic potential of Invicorp has been found in *in vitro* and *in vivo* studies.

In a 6-month study in male Cynomolgus monkeys given twice-weekly intracavernosal injections of Invicorp 25 micrograms / 2 mg, there were no drug-related toxicities and no local reactions that could not be attributed to mechanical damage associated with repeated injections.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium chloride

Disodium edetate

Phosphoric acid

Sodium hydroxide (for pH-adjustment)

Hydrochloric acid (for pH-adjustment)

Water for injections

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

9 months.

## 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

## 6.5 Nature and contents of container

Ampoule:

Light brown glass ampoule.

Syringe:

Sterile hypodermic three piece syringe without needle, and for single use.

Barrel: Polypropylene

Plunger: Polystyrene

Piston seal: Synthetic polyisoprene rubber

Needle:

Sterile, disposable hypodermic needle manufactured from stainless steel, and intended for single use.

Gauge x length: 30G x ½ (diameter x length: 0.30 x 13.0 mm).

Gauge x length: 21G x 1½ (diameter x length 0.80 x 40.0mm).

The ampoule(s) are packed into cardboard box(es). The ampoule(s) are co-packed with a seperate box containing syringe(s) and needles.

Pack sizes:

Glass ampoule 1 x 0.35 ml with 1 syringe, 1 30G needle and 1 21G needle

Glass ampoules 2 x 0.35 ml with 2 syringes, 2 30G needles and 2 21G needles

Glass ampoules 3 x 0.35 ml with 3 syringes, 3 30G needles and 3 21G needles

Glass ampoules 4 x 0.35 ml with 4 syringes, 4 30G needles and 4 21G needles

Glass ampoules 5 x 0.35 ml with 5 syringes, 5 30G needles and 5 21G needles

Glass ampoules 10 x 0.35 ml with 10 syringes, 10 30G needles and 10 21G needles

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

The ampoule can be brought to room temperature before use, or it can be used directly from the refrigerator.

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

## 7 MARKETING AUTHORISATION HOLDER

Evolan Pharma AB
Box 120
SE-182 12 Danderyd
Sweden

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 44616/0001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/03/2022

## 10 DATE OF REVISION OF THE TEXT

29/08/2023