SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Zivafert PFS 5000 IU powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains:

Human chorionic gonadotropin 5000 IU, produced from human urine

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder in vial: white to almost white lyophilized powder

Solvent in pre-filled syringe (0.9% sodium chloride): clear and colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In anovulatory or oligo-ovulatory women to trigger ovulation and luteinisation induction after stimulation of follicle growth.

For Assisted Reproductive Technology (ART) program such as in vitro fertilisation: triggering of final follicular maturation and luteinisation after stimulation of follicle growth.

4.2 Posology and method of administration

The treatment should only be initiated by a physician experienced in treating infertility.

Posology

Anovulatory or oligo-ovulatory women: One vial (5000 IU) or two vials (10000 IU) of Zivafert PFS are administered 24 to 48 hours after optimal stimulation of follicular growth are achieved. The patient is recommended to have coitus on the day of, and the day after, Zivafert PFS injection.

For Assisted Reproductive Technology program such as in vitro fertilisation (IVF): One vial (5 000 IU) or two vials (10000 IU) of Zivafert PFS are administered 24 to 48 hours after the last administration of an FSH- or hMG preparation, i.e. when optimal stimulation of follicular growth is achieved.

Paediatric population

The product is not intended for paediatric use.

Method of administration

After reconstitution of the powder with the solvent, the final solution should be given immediately by intramuscular or subcutaneous injection. Any unused solution should be discarded.

4.3 Contraindications

Hypersensitivity to active substance or any of the excipients listed in section 6.1 (see section 4.4).

Uncontrolled non-gonadal endocrinopathies (e.g. thyroid, adrenal or pituitary disorders).

Breast, uterine, ovarian tumours.

Abnormal (not menstrual) vaginal bleeding of unknown aetiology.

Zivafert PFS should not be used when an effective response cannot be obtained, such as in case of primary ovarian failure.

Malformations of the reproductive organs incompatible with pregnancy.

Fibroid tumours of the uterus incompatible with pregnancy.

4.4 Special warnings and precautions for use

Interference with serum or urinary testing

Following administration, Zivafert PFS may interfere for up to ten days with the immunological determination of serum or urinary hCG, potentially leading

to a false positive pregnancy test.

Hypersensitivity reactions:

Hypersensitivity reactions, both generalised and local; anaphylaxis; and angioedema have been reported. If a hypersensitivity reaction is suspected, discontinue Zivafert PFS and assess for other potential causes for the event (see section 4.3).

Ectopic pregnancy:

Infertile women undergoing Assisted Reproductive Technologies (ART) have an increased incidence of ectopic pregnancy. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important. Prior to treating patients for inadequate endogenous stimulation of the gonads, an examination should be performed to exclude anatomical abnormalities of the genital organs or nongonadal endocrinopathies (e.g. thyroid or adrenal disorders, diabetes). Primary ovarian failure should be excluded by the determination of gonadotrophin levels.

Multi-foetal gestation and birth and abortion:

In the pregnancies occurring after induction of ovulation with gonadotrophic preparations, there is an increased risk of abortion and multiple pregnancies. Multiple pregnancy, especially high order, carries an increased risk in adverse maternal and perinatal outcomes. The parents should be advised of the potential risks of multiple pregnancies before starting treatment.

Congenital Malformations:

The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be higher than after spontaneous conceptions. This is thought to be due to factors contributing to infertility (e.g. maternal age, sperm characteristics) and an increased incidence of multiple gestations.

Vascular Complications:

Thromboembolic events, both in association with and separate from Ovarian Hyperstimulation Syndrome (OHSS), have been reported following treatment with gonadotropins, including Zivafert PFS. Intravascular thrombosis, which may originate in venous or arterial vessels, can result in reduced blood flow to vital organs or the extremities. Women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity or thrombophilia, may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotrophins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.

Benign and malignant neoplasms:

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. The effect of gonadotrophins on the development of benign and malignant neoplasms in infertile women has not yet been established.

Medical examinations:

For up to ten days after administration of Zivafert PFS, a pregnancy test may give a false-positive result.

Ovarian Hyperstimulation Syndrome (OHSS):

OHSS is a medical condition different from uncomplicated ovarian enlargement. Clinical signs and symptoms of mild and moderate OHSS are abdominal pain, nausea, diarrhoea, mild to moderate enlargement of ovaries and ovarian cysts. Severe OHSS may be life-threatening. Clinical signs and symptoms of severe OHSS are large ovarian cysts, acute abdominal pain, ascites, pleural effusion, hydrothorax, dyspnoea, oliguria, haematological abnormalities and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS. Transient liver function test abnormalities suggestive of hepatic dysfunction with or without morphologic changes on liver biopsy have also been reported in association with OHSS.

OHSS may be caused by administration of human Chorionic Gonadotropin (hCG) and by pregnancy (endogenous hCG). Early OHSS usually occurs within 10 days after hCG administration and may be associated with an excessive ovarian response to gonadotropin stimulation. Late OHSS occurs more than 10 days after hCG administration, as a consequence of the hormonal changes with pregnancy. Because of the risk of developing OHSS, patients should be monitored for at least two weeks after hCG administration.

Women with known risk factors for a high ovarian response may be especially prone to the development of OHSS during or following treatment with Zivafert PFS. For women having their first cycle of ovarian stimulation, for whom risk factors are only partially known, close observation for early signs and symptoms of OHSS is recommended.

To reduce the risk of OHSS, ultrasonographic assessments of follicular development should be performed prior to treatment and at regular intervals during treatment. The concurrent determination of serum oestradiol levels may also be useful. In ART, there is an increased risk of OHSS with 18 or more follicles of 11 mm or more in diameter. When there are 30 or more follicles in total, it is advised to withhold hCG administration.

Adherence to the recommended Zivafert PFS dose and treatment regimen and careful monitoring of ovarian response is important to reduce the risk of OHSS. If OHSS develops, standard and appropriate management of OHSS should be implemented and followed

Ovarian torsion:

Ovarian torsion has been reported after treatment with gonadotropins, including Zivafert PFS. Ovarian torsion may be related to other conditions, such as OHSS, pregnancy, previous abdominal surgery, past history of ovarian torsion, and previous or current ovarian cysts. Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded

Additional information:

This medicine contains less than 1 mmol of sodium (23 mg) per reconstituted solution, that it is essentially “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies with Zivafert PFS have been performed; however no clinically significant medicinal product interactions have been reported.

HCG can crossreact in the radioimmunoassay of gonadotropins, especially luteinizing hormone. Physicians should make the laboratory aware of patients on HCG if gonadotropin levels are requested.

For up to 10 days after administration of TRADE NAME, a pregnancy test may give a false-positive result.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no indication for the use of Zivafert PFS during pregnancy. No clinical data on exposed pregnancies are available. The potential risk for humans is unknown.

Breast-feeding

Zivafert PFS is not indicated during breastfeeding. There are no data on the excretion of human chorionic gonadotropin in milk.

Fertility

Zivafert PFS is indicated for use in infertility (see section 4.1).

4.7 Effects on ability to drive and use machines

Zivafert PFS has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Zivafert PFS may cause reactions at the site of injection which are usually mild and transient. The most serious adverse reaction is ovarian

hyperstimulation syndrome (OHSS) which in most cases can be successfully managed if promptly recognised and treated (see section 4.4).

The undesirable effects are listed below according to MedDRA frequency convention and system organ class database.
Within each system organ class, the ADRs are ranked under headings of frequency, most frequent reactions first, using the following convention:

Very common (1/10); common (1/100 to 1/10); uncommon (1/1,000 to 1/100); rare (1/10,000 to 1/1,000); very rare (1/10,000), not known (cannot be estimated form the available data).

<u>Immune system disorders</u>	
Common	Local hypersensitivity reaction
Rare	Generalised rash or fever, general hypersensitivity reaction, anaphylactic reaction
<u>Gastrointestinal disorders</u>	
Common	Abdominal pain, nausea, vomiting and diarrhoea
Uncommon	Ascites
<u>General disorders and administrative site conditions</u>	
Common	Bruising, pain, redness, swelling and itching at the injection site, oedema
Uncommon	Tiredness
<u>Nervous system disorders</u>	
Common	Headache
<u>Psychiatric disorders</u>	
Common	Mood changes
Uncommon	Agitation
<u>Reproductive system and breast disorders</u>	
Common	Mild or moderate OHSS, painful breasts, ovarian cysts
Uncommon	Severe OHSS
Rare	Ovarian cyst rupture
<u>Respiratory, thoracic and mediastinal disorders</u>	
Uncommon	Pleural effusion associated with severe OHSS
<u>Skin and subcutaneous tissue disorders</u>	
Rare	angioedema
<u>Investigations</u>	
Uncommon	Weight gain associated with severe OHSS

Vascular disorders

Rare Thromboembolism associated with OHSS

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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The toxicity of human chorionic gonadotrophic hormone is very low. However, a too high dose may lead to hyperstimulation of the ovaries (see OHSS, section 4.4).

Management:

In case of overdose women should be evaluated by a clinician for symptoms suggestive of OHSS (see section 4.4). Women with mild or moderate OHSS may require fluid intake and output monitoring. Paracentesis of ascitic fluid may be needed. Women with severe OHSS should also have fluid intake and output monitoring, further should thromboprophylaxis with low molecular weight heparin (LMWH) be considered. Haematocrit is a useful guide to the degree of intravascular volume depletion. Vital parameters should be monitored and hospital admission should be considered for women unable to achieve satisfactory pain control or maintain adequate fluid intake due to nausea or have critical OHSS.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system, gonadotropins ATC code: G03GA01

Zivafert PFS is a preparation of human chorionic gonadotrophin obtained from the urine of pregnant women.

Zivafert PFS stimulates steroidogenesis in the gonads, a biological effect similar to LH (Luteinizing hormone). Zivafert PFS promotes the production of oestrogens and progesterone after ovulation.

In a comparative clinical trial, involving 147 infertile women, aged 18–39 years whose BMI was between 18 and 30 kg/m2, basal FSH <10 mIU/mL, regular menstrual cycles and both ovaries present, undergoing controlled ovarian stimulation with a standard long GnRH-agonist protocol, the administration of a dose of 10000 IU of Zivafert PFS was as effective as 250 □g of recombinant hCG in inducing final follicular maturation and early luteinisation. The number of retrieved oocytes was not inferior when HP-hCG was used as compared to r-hCG: the mean number was 13.3

(6.8) in HP-hCG and 12.5 (5.8) in the r-hCG group (p = 0.49) with a 95% CI (−1.34, 2.77).

HCG is of human origin and therefore, no antibody formation is to be expected.

5.2 Pharmacokinetic properties

The pharmacokinetics of Zivafert PFS following subcutaneous administration shows great inter-individual variability. After a single subcutaneous injection of 10000 IU, the maximum serum level of hCG is reached approximately 16 hours after the injection. hCG peak concentrations (Cmax) reached 338 ±100 IU/L with an AUC0-t of 22989 ±4802 IUxh/L. After that, the serum level decreases by a half-life of approximately 37 hours. Excretion of hCG, following administration, is predominantly renal.

No pharmacokinetic studies were performed in patients with impaired hepatic or renal function.

5.3 Preclinical safety data

No non-clinical studies have been performed with Zivafert PFS.

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients in the:

Vial of powder: lactose monohydrate

Prefilled syringe with solvent: sodium chloride, water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this product must not be mixed with other medicinal products. This is particularly important for drugs that stimulate ovulation (e.g. hMG) or contain cortisone, especially high doses.

6.3 Shelf life

3 years

After reconstitution, the product must be used immediately.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the vial and solvent in the prefilled syringe in the original package to protect the medicine from the light.

6.5 Nature and contents of container

1 pack contains:

Powder in a vial (type I glass), sealed with a rubber closure and held in place with a flip-off cap.

1 ml of solvent in a prefilled syringe (type I glass), 1 long needle for the reconstitution and for the intramuscular injection and 1 short needle for the subcutaneous injection.

Multipack containing 2 packs of 5 vials + 5 prefilled syringes of solvent, as described above.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The solution must be prepared just before injection.

Each vial is for single use only. The medicinal product must be reconstituted under aseptic conditions.

Zivafert PFS must only be reconstituted with the solvent provided in the package.

Use a clean surface and wash your hands before the solution reconstituted.

Set out all the following items on the clean surface:

- two cotton-wool alcohol swabs (not provided)
- one vial containing Zivafert PFS powder
- one solvent in a prefilled syringe
- one long needle for the reconstitution and for the intramuscular injection
- one short needle for the subcutaneous injection

<u>Reconstitution of the solution for injection</u>

Prepare the solution for injection:

Remove only the cap from the prefilled syringe, insert the reconstitution needle (long needle) on the syringe and check if the needle is well allocatedin order to avoid leaking of solution.In case of leaking of solution please try to fix better the needle with a slight rotation.

1. Remove the coloured plastic cap cover from the vial containing Zivafert PFS powder and disinfect the rubber area of the cap with a cotton-wool swab moistened with alcohol

2. Take the syringe and slowly inject the solvent into the powder vial through the rubber stopper.

3. **DO NOT SHAKE,** gently roll the vial between the hands until the powder is completely dissolved, taking care to avoid creating foam.

4. Once the powder is dissolved (which, in general, occurs immediately), slowly draw the solution into the syringe.

- With the needle still inserted, turn the vial upside down.
- Make sure the needle tip is underneath the level of the liquid.
- Gently pull the plunger to draw all the solution up into the syringe.
- Check that the reconstituted solution is clear and colourless.

Preparation of higher doses

- A higher dose of 10000 IU can be achieved by using two vials of powder. At the end of step 4 above, draw back the reconstituted contents of the first vial into the syringe and slowly inject into a second vial of powder. Repeat steps 2 to 4 for the second vial.
- If multiple vials of powder are used, the amount of human chorionic gonadotrophin contained in 1 ml of reconstituted solution will be as follows:

Zivafert PFS 5000 IU **powder and solvent for solution for injection**	
Number of vials used	Total amount of human chorionic gonadotropin in 1 ml of solution
1	5000 IU
2	10000 IU

The solution must be clear and colourless.

Dispose of all used items.

Any unused product or waste material should be disposed of in accordance with local requirements (once the injection is ended, all the needles and empty syringes should be disposed of in an appropriate container).

7 MARKETING AUTHORISATION HOLDER

IBSA Farmaceutici Italia srl
Via Martiri di Cefalonia, 2
26900 Lodi – Italy

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 21039/0072

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/08/2022

10 DATE OF REVISION OF THE TEXT

17/08/2022