Pack Insert (Pen)
Date : 12AUG22
Date : 17AUG22*
Date : 19AUG22**
Date : 18NOV22***
Date : 12DEC22****
All Country Export
Version-5

(8)

Ovarian and other reproductive system tumours:
There have been reports of ovarian and other reproductive system tumours in women who have had infertility treatment. It is not known if treatment with fertility medicines increases the risk of these tumours in infertile women.

Other medical conditions:
In addition, before starting to use this medicine, tell your doctor if you:
• Have been told by a doctor that pregnancy would be dangerous for you.

Children and adolescents:
There is no relevant use of Foligraf in children and adolescents.

Other medicines and Foligraf:
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. If Recombinant Human Follicular Stimulating Hormone is used in a combination with clomifene citrate, the effect of Recombinant Human Follicular Stimulating Hormone may be increased. If a GnRH agonist (a medicine used to prevent early ovulation) has been given, higher doses of Foligraf may be needed.

Pregnancy and breast-feeding:
Ask your doctor or pharmacist for advice before taking any medicine. You should not use Foligraf if you are already pregnant or think you might be pregnant. Foligraf may affect milk production. It is unlikely that Foligraf is passed into breast milk. If you are breast-feeding, tell your doctor before using Foligraf.

Driving and using machines:
Foligraf is unlikely to affect your ability to drive or use machines.

c. How to use Foligraf:
Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage in women:
Your doctor will decide on your starting dose. This dose may be adjusted during your treatment period. Further details on the treatment schedule are given below. There are large differences between women in the response of the ovaries to FSH, which makes it impossible to set a dosage schedule which is suitable for all patients. To find the right dosage, your doctor will check your follicle growth by means of ultrasound scanning, and measurement of the amount of oestradiol (female sex hormone) in the blood.

***Women who are not ovulating:**
A starting dose is set by your doctor. This dose is continued for at least seven days. If there is no ovarian response, the daily dose will then be gradually increased until follicle growth and/or plasma oestradiol levels indicate a proper response. The daily dose is then maintained until a follicle of proper size is present. Usually, 7 to 14 days of treatment are sufficient. Foligraf treatment is then stopped and ovulation will be induced by giving human chorionic gonadotrophin (hCG).

How are the injections given?
Foligraf solution for injection in cartridges has been developed for use in pen. The separate instructions for using the pen must be followed carefully. Do not use the Pen if the solution in cartridge contains particles or if the solution is not clear. Using the pen, injections just under the skin (in the lower stomach, for example) can be given by yourself or your partner. Your doctor will tell you when and how to do this. If you inject yourself with Foligraf, follow the instructions carefully. The very first injection of Foligraf should only be given in the presence of a doctor or nurse.

What is Foligraf Pen Injector?
Foligraf pen injector is composed of a Pen body having the dose adjustment rod and injection button, and cartridge holder with a pen cap.It does not include the liquid medicine and the Pen needle, and all the parts are not in contact with the liquid medicine.

What precaution should you take during needle installation?
Use a new, unopened, Pen needle provided in the pack for every single injection. Do no re-use the same Pen needle after injection and discard the Pen needle after use.

How is the Foligraf Pen Injector assembled?
The pen injector is used in conjunction with the 3mL cartridge and injection needle for subcutaneous injection of liquid medicine. All parts are not in direct contact with the injection site and the liquid medicine. This product is only used as an injection tool, and the contraindications are mainly related to the injected liquid medicine.

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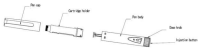
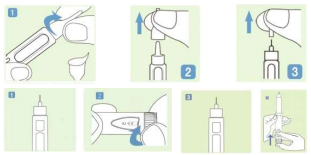
What are the warning signs to consider before needle installation?
If the needle is not fully seated, you will not get the full dose you need. If the needle is bent or damaged, the needle must be replaced immediately for injection. Do not install a new needle on the pen injector until you are ready for the next injection. Before each injection, install a new needle and make sure that the needle has been tightened.

How to adjust and check the working of needle (exhaust)?
Rotate the dose adjustment level to call up a scale (after hearing the 'click', make the scale line aligned with the centre of the window). Refer to the images 1 and 2 below.
Pick up the pen injector upright with the needle tip upward.
Press the injection button and the liquid medicine can be seen hanging on the needle tip. Refer to the images 3 and 4 below.



How is the Foligraf Pen Injector assembled?
The pen injector is used in conjunction with the USP Type 1 Glass cartridge of pack size 3ml cartridge and pen needle for subcutaneous injection of liquid medicine. All parts are not in direct contact with the injection site and the liquid medicine. This product is only used as an injection tool, and the contraindications are mainly related to the injected liquid medicine.

Instructions:
How to install the Needle?
1. Take a new needle and remove the protective sheet from the needle.
2. Combine the needle with the cartridge holder and rotate the needle until it stops.
3. Before injection, remove the inner and outer needle caps. Be careful not to bend or damage the needle. Keep the inner and outer needle caps properly.



What are the precautions to be taken while checking the needle exhaust?
Do not share pen injector and needle with others. A new needle is used for each injection. Replace a needle every injection, which can ensure sterility and prevent leakage, eliminate air bubbles, and reduce needle blockage.

What are the warning signs that show that the needle exhaust is not functioning properly?
The pen injector often needs to be vented several times when it is first used. If you still do not see the liquid medicine flowing out after exhausting several times, the needle may be blocked. If the liquid medicine is still not visible, repeat the above steps until the liquid medicine appears. Be sure to confirm that your pen injector is in a state where the liquid medicine can be seen on the tip of the needle. If there is liquid medicine flowing out after the needle is installed, this step is not necessary.

How to set the dosage?
1. Rotate the dose adjustment lever until the reading of the dose indication is the injection dose unit you need.

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2. If you accidentally overdose while adjusting the dose, turn the dose adjustment lever to indicate the correct dose. Retract to the correct dose. Refer to image 2.2 below. After you hear " click ", you must align the scale line to the centre of the window. Do not hold down the injection button when you retract). Refer to image 2.2 below.

What are the precautions to be taken while adjusting the dose?
The increment is 12.5 IU 0.0 208 mL. The maximum dose for a single injection is 0.75mL. If your injection dose is greater than 0.75mL, you should divide the entire dose into two injections. The total dose of two injections is the dose you need to inject.

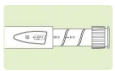
How to inject the drug?
In case the user is the patient, they should take proper training about injecting the drug regarding site of injection, method to clean the injection site and how to inject using pen from their consulting doctor or healthcare professionals.
The user selects the injection position and disinfects the skin at the selected position. After the needle is pierced vertically into the selected position, press the injection button until it stops. At this time, the dose indication is "0". Refer to image 3-1. In order to ensure that the dose you choose has been accurately injected into the body, please do not remove the needle immediately after the injection. The needle should be left under the skin for at least 10 seconds. Before pulling out the needle, you should keep pressing the injection button without releasing it. Refer to image 3-2 below.

Pull out the needle, the injection dose you have selected has been injected. After the injection is over, install the outer needle cap and unscrew the needle. Close the cap tightly. Dispose of discarded needles carefully to avoid accidental stabbing.

What are the precautions to be used while injecting?
The injection button must be pressed to inject the medicine into the body. Do not try to change the dose during the injection.

What are the warning signs while injecting?
This product is for one time use only, that is, the function becomes invalid after the liquid medicine in a cartridge finish. The liquid medicine in the cartridge can be injected in multiple times. The pushing process is irreversible. It is forbidden to use the injection button to push the push piece out of the pen body before use.

What to do when the medicine in cartridge almost used up?
When the remaining dose is less than 450IU, the highest dose that can be adjusted by the dose adjustment lever is the remaining dose.



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Problems that can be encountered while using the pen injector.
1. What should I do if I cannot see the liquid coming from the tip of the needle when exhaust?
Answer: Please confirm that the cartridge holder and the pen body have been installed in place. After confirming the installation is in place, follow the 3.2 exhaust steps until the first drop of liquid appears on the needle tip.

2. What should I do if I cannot see any fluid from the tip of the needle and the injection button cannot be pressed down when exhausting?
Answer: The needle may be clogged. Remove the needle, replace it with another needle, and then follow the exhaust steps until the first drop of liquid appears on the needle tip.

3. What should I do if I choose the wrong injection dose?
Answer: Rotate the dose adjustment lever until the reading of the dose display is the injection dose you need.

How to maintain the pen injector?
Pen injectors need to be used with care, be careful not to fall, avoid hitting hard objects, pay attention to dust and keep it clean. Before each injection, make sure that there is liquid medicine at the needle tip (see exhaust operation for details). After each injection, the needle should be removed immediately, otherwise there may be other potential risks. Do not use iodine or fluorine containing detergent to clean the pen injector, otherwise the plastic part of the pen injector will be damaged. pen injector cartridge, and needles should be stored out of the reach of children. Do not lubricate the pen injector. The pen injector is for one person only. Store the pen injector in a box as much as possible and keep it away from contamination. Wipe the pen injector with a cotton ball dipped in mild detergent, never immerse the syringe in water. When the pen injector fails, please do not repair it yourself. In the transportation process of the pen injector, avoid rain and snow splashing and mechanical collision. The syringe should be stored in a dry and well-ventilated room, away from strong sunlight and other gases that can cause corrosion.

If you forget to use Foligraf:
If you forget a dose do not use a double dose to make up for a missed dose.
• Contact your doctor.
If you have any further questions on the use of this medicine, ask your doctor.

d. Possible side effects:
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects in women:
A complication with FSH treatment is hyperstimulation of the ovaries. Ovarian overstimulation may develop into a medical condition called ovarian **hyperstimulation syndrome (OHSS)**, which can be a serious medical problem. The risk can be reduced by careful monitoring of follicular development during treatment. Your doctor will do ultrasound scans of your ovaries to carefully monitor the number of maturing follicles. Your doctor may also check blood hormone levels. Pain in the stomach, feeling sick or diarrhoea are the first symptoms. In more severe cases symptoms may include enlargement of the ovaries, accumulation of fluid in the abdomen and/or chest (which may cause sudden weight gain due to fluid build-up) and the occurrence of blood clots in the circulation.
• Contact your doctor immediately if you are experiencing stomach pains, or any of the other symptoms of ovarian hyperstimulation, also if this occurs some days after the last injection.
If you are a woman:

Common side effects (may affect up to 1 in 10 people):
• Headach.
• Injection site reactions (such as bruising, pain, redness, swelling and itching).
• Ovarian hyperstimulation syndrome (OHSS).
• Pelvic pain.
• Stomach pain and/or bloating.
Uncommon side effects (may affect up to 1 in 100 people):
• Breast complaints (including tenderness).
• Diarrhoea, constipation, or stomach discomfort.
• Enlargement of the uterus.
• Feeling sick.
• Hypersensitivity reactions (such as rash, redness, hives and itching).
• Ovarian cysts or enlargement of the ovaries.
• Ovarian torsion (twisting of the ovaries).
• Vaginal bleeding.

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Rare side effects (may affect up to 1 in 1,000 people):
• Blood clots (this may also occur in the absence of unwanted overstimulation of the ovaries
• Pregnancy outside the uterus (an ectopic pregnancy), miscarriage and multiple pregnancies have also been reported. These side effects are not considered to be related to the use of Recombinant Human Follicular Stimulating Hormone, but to Assisted Reproductive Technology (ART) or subsequent pregnancy.

e. How to store Foligraf:
Keep this medicine out of the sight and reach of children.

Storage by the patient:
Store between 2° – 8°C. Do not freeze. Protect from Light.
Keep the cartridge in the outer carton.
Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days, when store below 25°C.
Discard used needles immediately after injection.
Do not mix any other drug into the cartridges. Empty cartridges must not be refilled.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

f. Contents of the pack and other information:
What Recombinant Human Follicular Stimulating Hormone contains:
Each cartridge contains the active substance Follitropin concentrated solution (Human Recombinant) with strengths of 450 IU (33,0 µg) / 900 IU (66,0 µg) in aqueous solution.

What Foligraf looks like and contents of the pack:
Foligraf is a clear, colourless liquid solution for injection supplied in a cartridge fitted into a Pen injector device. The other contents of the pack are sterile Pen needles with pack insert.

11. Details license number:
KD-1.

12. Date of revision:
21st July 2022.

Manufactured in India by :
BSV BHARAT SERUMS AND VACCINES LIMITED
Plot No. K-27, K-27 Part and K-27/1, Anand Nagar, Jambivli Village, Additional MIDC, Ambernath (East), Thane 421506, Maharashtra State, India.
IN90435E0ACPEN

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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only
READ PACKAGE INSERT CAREFULLY BEFORE USE

Recombinant Human Follicle Stimulating Hormone Injection
IH 450 IU (33,0 µg) / 900 IU (66,0 µg)

Foligraf®
(Multidose) Prefilled Pen

Solution for injection in prefilled pen
For subcutaneous use only

1. Generic Name:
Recombinant Human Follicle Stimulating Hormone Injection IH 450 IU (33,0 µg) / 900 IU (66,0 µg).

2. Qualitative and quantitative composition:
Each Prefilled pen containing one cartridge contains:
• Recombinant Human Follicle Stimulating Hormone Injection IH (66,0 µg)/1.5ml Solution for injection in Prefilled Pen.
• Recombinant Human Follicle Stimulating Hormone Injection IH (33,0 µg)/0,75ml Solution for injection in Prefilled Pen.
• Excipients: Disodium Hydrogen Phosphate Anhydrous B.P., Mannitol B.P., Sucrose B.P., L-Methionine B.P., Tween 20 B.P., Meta-cresol B.P. Water for injection USP.

3. Dosage Form and strength:
- Foligraf 900 IU (66,0 µg)/1,5 ml Solution for Injection in Prefilled Pen:
One cartridge contains a net total dose of 900 IU (66,0 µg) Follicle-stimulating Hormone (Human Recombinant) in 1,5 ml aqueous solution. The solution for injection contains the active substance produced by genetic engineering of a Chinese hamster ovary (CHO) cell line.

-Foligraf 450 IU (33,0 µg)/0,75 ml Solution for Injection in Prefilled Pen
One cartridge contains a net total dose of 450 IU (33,0 µg) Follicle-stimulating Hormone (Human Recombinant) in 0,75 ml aqueous solution. The solution for injection contains the active substance produced by genetic Chinese hamster ovary (CHO) cell line.

4. Clinical particulars:
4.1 Therapeutic indication:
• In adult Women
• Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate.
• Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer.
• rFSH in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level ~ 1.2 IU/L.

• In adult men
• rFSH is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy.

4.2 Posology and method of administration:
Treatment with Foligraf 450 IU (33,0 µg) /900 IU (66,0 µg) Solution for Injection in Prefilled Pen should be initiated under the supervision of a physician experienced in the treatment of fertility problems. Foligraf 450 IU (33,0 µg) /900 IU (66,0 µg) Solution for Injection in prefilled pen is intended for subcutaneous administration. The dosage recommendations given for 450 IU (33,0 µg) /900 IU (66,0 µg) Solution for injection in prefilled pen are those in use for urinary FSH.

Clinical assessment of indicates that its daily doses, regimens of administration, and treatment monitoring procedures should not be different from those currently used for urinary FSH-containing preparations. However, the study reports conclude that, Foligraf is more efective than urinary FSH in terms of a lower total dose and a shorter treatment period needed to achieve pre-ovulatory conditions. It is advised to adhere to the recommended starting doses indicated below.

1. Women with anovulation (including PCOD):
The object of 450 IU (33,0 µg) /900 IU (66,0 µg) cartridge in Prefilled multidose Pen therapy is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of HCG. Foligraf 450 IU (33,0 µg) / 900 IU (66,0 µg) Solution for injection in prefilled pen may be given as a course of daily injections. In menstruating patients' treatment should commence within the first 7 days of the menstrual cycle. Treatment should be tailored to the individual patient's response as

Size : L x H = 450mm x 200mm

Black Colour | **Light Green Colour** | **Light Blue Colour**
Light Blue Colour | **Dark Blue Colour** | **CMYK**

Paper : 60 gsm, Maplitho White
Outline & Cutting marks not to print
Artwork Code No. : IN90435E0ACPEN
Back to Back Printing
3 Vertical Folds (Center Creasing Folds)
Final Folding Size : 75 x 200mm

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assessed by measuring follicle size by ultrasound and/or oestrogen secretion. A commonly used regimen commences at 75 - 150 IU. FSH daily and is increased preferably by 37.5 or 75 IU. at 7 or preferably 14-day intervals if necessary, to obtain an adequate, but not excessive, response. The maximal daily dose is usually not higher than 225 IU of FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned, and the patient should recommence treatment at a higher starting dose than in the abandoned cycle. When an optimal response is obtained, a single injection of 5 000 IU., up to 10 000 IU. HCG should be administered 24 - 48 hours after the last Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for Injection in prefilled pen. The patient is recommended to have coitus on the day of, and the day following, HCG administration. Alternatively, intrauterine insemination (IUI) may be performed. If an excessive response is obtained, treatment should be stopped, and HCG withheld (please see warnings). Treatment should recommence in the next cycle at a dosage lower than that of the previous cycle.

2. Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other assisted reproductive technologies:
A commonly used regimen for superovulation involves the administration of 150-225 IU of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen daily, commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum oestrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450 IU daily. In general, adequate follicular development is achieved on average by the tenth day of treatment (range 5 to 20 days).
A single injection of 250 micrograms (6500 IU) r-hCG or 5,000 IU up to 10,000 IU hCG is administered 24-48 hours after the last Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen injection to induce final follicular maturation.
Down-regulation with a gonadotropin-releasing hormone (GnRH) agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. In a commonly used protocol, Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks of treatment with an agonist, 150-225 IU Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen are administered for the first 7 days. The dose is then adjusted according to the ovarian response.
Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

3. Women with anovulation resulting from severe LH and FSH deficiency:
In LH and FSH deficient women (hypogonadotrophic hypogonadism), the objective of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen therapy in association with lutropin alfa is to develop a single mature Graafian follicle from which the oocyte will be liberated after the administration of human chorionic gonadotropin (hCG). Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen should be given as a course of daily injections simultaneously with lutropin alfa. Since these patients are amenorrhoeic and have low endogenous oestrogen secretion, treatment can commence at any time.
A recommended regimen commences at 75 IU of recombinant LH (rLH) daily with 75-150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and oestrogen response.
If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7-14 day intervals and preferably by 37.5-75 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks.
When an optimal response is obtained, a single injection of 250 micrograms r-hCG or 5,000 IU up to 10,000 IU hCG should be administered 24-48 hours after the last Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen and rLH injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, IUI may be performed.
Luteal phase support may be considered since lack of substances with luteotrophic activity (LH/hCG) after ovulation may lead to premature failure of the corpus luteum. If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle.

4. Men with hypogonadotrophic hypogonadism:
Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen should be given at a dose of 150 IU three times a week, concomitantly with hCG, for a minimum of 4 months.

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If after this period, the patient has not responded, the combination treatment may be continued; current clinical experience indicates that treatment for at least 18 months may be necessary to achieve spermatogenesis.

Special populations:
Elderly:
There is no relevant use of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen in the elderly population. Safety and effectiveness of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen in elderly patients have not been established.

Renal or hepatic impairment:
Safety, efficacy and pharmacokinetics of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen in patients with renal or hepatic impairment have not been established.

Pediatric population:
There is no relevant use of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen in the pediatric population.

4.3 Contraindications
Foligraf must not be used in:
- Hypersensitivity to Foligraf, FSH or to any of the excipients
- Case of tumors of the hypothalamus and pituitary gland
- Ovarian enlargement or cyst not due to polycystic ovarian disease
- Gynecological hemorrhages of unknown aetiology
- Ovarian, uterine or mammary carcinoma.

Foligraf should not be used when an effective response cannot be obtained in conditions, such as:
- Primary ovarian failure
- Malformations of sexual organs incompatible with pregnancy
- Fibroid tumors of the uterus incompatible with pregnancy

4.4 Special warnings and precautions for use:
Recombinant Human Follicle Stimulating Hormone for Injection is a potent gonadotrophic substance capable of causing mild to severe adverse reactions and should only be used by physicians who are thoroughly familiar with infertility problems and their management.
Gonadotrophin therapy requires a certain time commitment by physicians and supportive health professionals, as well as the availability of appropriate monitoring facilities. In women, safe and effective use of Foligraf calls for monitoring of ovarian response with ultrasound, alone or preferably in combination with measurement of serum oestradiol levels, on a regular basis. There may be a degree of interpatient variability in response to FSH administration, with a poor response to FSH in some patients.
The lowest effective dose in relation to the treatment objective should be used. Self-administration of Foligraf should only be performed by patients who are well motivated, adequately trained and with access to expert advice. The first injection of Foligraf should be performed under direct medical supervision. Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and pituitary or hypothalamic tumors, and appropriate specific treatment given. Patients undergoing stimulation of follicular growth, whether in the frame of a treatment for anovulatory infertility or ART procedures, may experience ovarian enlargement or develop hyper stimulation. Adherence to recommended 'Foligraf dosage and regimen of administration, and careful monitoring of therapy will minimize the incidence of such events. Acute interpretation of the indices of follicle development and maturation require a physician who is experienced in the interpretation of the relevant tests. If an FSH dose increase is deemed appropriate, dose adaptation should preferably be at 7 to 14-day intervals and preferably with 37.5-75 IU increments.

Ovarian Hyperstimulation Syndrome (OHSS):
OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS is a syndrome that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities. The following symptomatology may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events. Excessive ovarian response to gonadotrophin treatment seldom gives rise to OHSS unless HCG is administered to trigger ovulation. Therefore, in cases of ovarian

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hyperstimulation it is prudent to withhold HCG and advise the patient to refrain from coitus or to use barrier methods for at least 4 days.OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event, therefore patients should be followed for at least two weeks after HCG administration.
To minimize the risk of OHSS or of multiple pregnancy, ultrasound scans as well as oestradiol measurements are recommended. In anovulation the risk of OHSS and multiple pregnancy is increased by a serum oestradiol > 900 pg/mL (3300 pmol/l) and more than 3 follicles of 14 mm or more in diameter. In ART there is an increased risk of OHSS with a serum oestradiol > 3000 pg/mL (11000 pmol/l) and 20 or more follicles of 12 mm or more in diameter. When the oestradiol level is > 5500 pg/mL (20200 pmol/l) and where there are 40 or more follicles in total, it may be necessary to withhold HCG administration. Adherence to recommended 'Foligraf dosage, regimen of administration and careful monitoring of therapy will minimize the incidence of ovarian hyper stimulation and multiple pregnancy. In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyper stimulation. OHSS may be more severe and more protracted if pregnancy occurs. Most often, OHSS occurs after hormonal treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Usually, OHSS Resolves spontaneously with the onset of menses. If severe OHSS occurs, gonadotrophin treatment should be stopped if still ongoing, the patient hospitalized and specific therapy for OHSS started. This syndrome occurs with higher incidence in patients with polycystic ovarian disease.

Multiple pregnancies:
Multiple pregnancies, especially high order, carries an increase risk in adverse maternal and perinatal outcomes. In patients undergoing ovulation induction with 'Foligraf, the incidence of multiple pregnancies is increased as compared with natural conception. The majority of multiple conceptions are twins. To minimize the risk of multiple pregnancies, careful monitoring of ovarian response is recommended. In patients undergoing ART procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient age. The patients should be advised of the potential risk of multiple births before starting treatment.

Pregnancy wastage:
The incidence of pregnancy wastage by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than following natural conception. in the normal population.

Ectopic pregnancy:
Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after ART, was reported to be higher than in the general population.

Reproductive system 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. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumors in infertile women.

Congenital malformation:
The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and multiple pregnancies.

Thromboembolic events:
In women with generally recognized risk factors for thrombo-embolic events, such as personal or family history, treatment with gonadotrophins may further increase the risk. In these women, the benefits of gonadotrophin administration need to be weighed against the risks. It should be noted however, that pregnancy itself also carries an increased risk of thromboembolism.

Treatment in men:
Elevated endogenous FSH levels are indicative of primary testicular failure. Such patients are unresponsive to r FSH/hCG therapy. Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen should not be used when an effective response cannot be obtained. Semen analysis is recommended 4 to 6 months after the beginning of treatment as part of the assessment of the response.

4.5 Drugs interactions:
Concomitant use of Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) with other agents used to stimulate ovulation (e.g. HCG, clomiphene citrate) may potentiate the follicular response, whereas concurrent use of a GnRH agonist to induce pituitary

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desensitization may increase the dosage of Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) 'needed to elicit an adequate ovarian response. No other clinically significant drug interaction has been reported during Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH)

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
Use during pregnancy: There is no indication for use of Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotrophins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant human follicular stimulating hormone. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Use during lactation:
Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) is not indicated during lactation. During lactation, the secretion of prolactin can entail a poor prognosis to ovarian stimulation.

4.7 Effects on ability to drive and use machines:
- No studies on the effects on ability to drive and use machines have been performed

4.8 Undesirable effects:
Treatment in women:
Very Common (> 1/10):
- Ovarian cysts;
- Mild to severe injection site reaction (pain, redness, bruising, swelling and/or irritation at the site of injection);
- Headache.

Common ((≥ 1/100 to < 1/10):
- Mild to moderate OHSS;
- Abdominal pain and gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal cramps and bloating.
- Gynaecomastia, varicocele.

Uncommon (≥ 1/1,000 to < 1/100):
- Severe OHSS.

Rare (≥ 1/10, 000 to < 1/1,000):
- Ovarian torsion, a complication of OHSS.

Very rare (< 1/10 000):
- Thromboembolism usually associated with severe OHSS;
- Mild systemic allergic reactions (erythema, rash or facial swelling).
- Exacerbation or aggravation of asthma.

4.9 Overdose:
The effects of an overdose of r-hFSH are unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur, which is further described in Special Warnings and Special Precautions for Use.

5. Pharmacological properties:
5.1 Mechanism of Action:
FSH is indispensable in normal follicular growth and maturation, and gonadal steroid production. In the female the level of FSH is critical for the onset and duration of follicular development, and consequently for the timing and number of follicles reaching maturity. Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function.

5.2 Pharmacodynamic properties:
Pharmacotherapeutic group: gonadotrophins.
'Foligraf Solution for injection in prefilled multidose pen is a preparation of follicle stimulating hormone produced by genetically engineered Chinese Hamster Ovary (CHO) cells. In women, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles.

5.3 Pharmacokinetic properties:
Following subcutaneous administration, Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) is distributed to the extra cellular fluid space with an initial half-life of around 2 hours and eliminated from the body with a terminal half-life of about one day. The steady state volume of distribution and total clearance are 10 L and 0.6 L/h, respectively. One eighth of the Recombinant Human Stimulating hormone dose is excreted in the urine. Following subcutaneous administration, the absolute bioavailability is about 70%. Following repeated administration, Recombinant Human Stimulating Hormone accumulates 3-fold achieving a steady state within 3-4 days.

6. Nonclinical properties:
6.1 Animal Toxicology or Pharmacology:
In an extensive range of animal toxicity studies studied in laboratory animal models (mice, rats, rabbits), no significant findings were observed.

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7. Description:
Foligraf consist of a prefilled cartridge in a multidose Pen injector device containing Follicle Stimulating Hormone Injection (Human Recombinant) (r-hFSH) drug product. Each cartridge containing clear and colorless solution of r-hFSH drug product is designed to be used in conjunction with pen injector. The dosage recommendations given above are general guidelines and therapy should be individualized. The objective of the therapy is to develop mature graafian follicles for assisted reproductive techniques or in women with anovulation.

8. Pharmaceutical particulars:
8.1 Incompatibilities:
This medicinal product must not be mixed with other medicinal products except those mentioned.

8.2 Packaging information:
8.2.1 Foligraf 900 IU (66.0 µg) / 1.5ml Solution for Injection in Prefilled Pen:
Each Carton contains:
1 Foligraf multi-dose prefilled pen.
14 sterile Pen needles.

8.2.2 Foligraf 450 IU (33.0 µg) / 0.75ml ml Solution for Injection in Prefilled Pen
Each Carton contains:
1 Foligraf multi-dose prefilled pen.
7 sterile Pen needles.

8.3 Storage and Handling instructions:
Keep out of reach of children.
Store between 2°C - 8°C. Do not freeze. Protect from light.
Store in the original package.
Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen should be used within 28 days after first dose, if the drug is stored below 25°C.

8.4 Shelf-life:
24 months when stored between 2°C to 8°C.

9. Patient Counselling Information:
a. What is Foligraf? and in Which case this medicine should be used?
Foligraf solution for injection in Prefilled Pen contains Recombinant Human Follicle Stimulating Hormone E.P. is a hormone known as follitropin concentrated solution (Human Recombinant) E.P. FSH belongs to the group of gonadotrophins, which play an important role in human fertility and reproduction. In women, FSH is needed for the growth and development of follicles in the ovaries. Follicles are small round sacs that contain the egg cells.

Foligraf is used to treat infertility in any of the following situations:

Women:
- In women who do not ovulate and do not respond to treatment with clomifene citrate, Foligraf can be used to cause ovulation.
- Together with rLH to help release egg from the ovary (ovulation) in women that are not ovulating because their body is producing very little gonadotropins (FSH and LH).
- To help develop several follicles (each containing an egg) in women undergoing assisted reproductive technology procedures (procedures that may help you to become pregnant) such as "in vitro fertilisation", "gamete intra-fallopian transfer" or "zygote intra-fallopian transfer".

Men:
- Together with another medicine called "human Chorionic Gonadotropin" (hCG) to help produce sperm in men that are infertile due to a low level of certain hormones.

b. What you need to know before you use Foligraf?
Do not use Foligraf If you:
- are allergic to Recombinant Human Follicle Stimulating Hormone E.P. or any of the other ingredients of Recombinant Human Follicular Stimulating Hormone
- Have a tumour of the ovary, breast, uterus, testis or brain (pituitary gland or hypothalamus) Have heavy or irregular vaginal bleeding where the cause is unknown.
- Have ovaries that do not work because of a condition called primary ovarian failure.
- Have ovarian cysts or enlarged ovaries not caused by polycystic ovarian syndrome (PCOS)
- Have malformations of the sexual organs which make a normal pregnancy impossible.
- Have fibroid tumours in the uterus which make a normal pregnancy impossible.

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if you are a man:
- with damaged testicles that cannot be healed.

Warnings and precautions:
Please talk to your doctor before using Foligraf if you:
- Have had an allergic reaction to certain antibiotics (neomycin and/or streptomycin)
- Have uncontrolled pituitary gland or hypothalamic problems
- Have an underactive thyroid gland (hypothyroidism)
- Have adrenal glands that are not working properly (adrenocortical insufficiency)
- Have high prolactin levels in the blood (hyperprolactinemia)
- Have any other medical conditions (for example, diabetes, heart disease, or any other long-term disease).

If you are a woman:
Ovarian hyperstimulation syndrome (OHSS):
Your doctor will check the effects of the treatment regularly to be able to choose the correct dose of Foligraf from day to day. You may regularly have ultrasound scans of the ovaries. Your doctor may also check blood hormone levels. This is very important since too high a dose of FSH may lead to rare but serious complications in which the ovaries are overly stimulated, and the growing follicles become larger than normal. This serious medical condition is called ovarian hyperstimulation syndrome (OHSS). In rare cases, severe OHSS may be life-threatening. OHSS causes fluid to build-up suddenly in your stomach and chest areas with formation of blood clots. Call your doctor right away if you notice severe abdominal swelling, pain in the stomach area (abdomen), feeling sick (nausea), vomiting, sudden weight gain due to fluid build-up, diarrhoea, decreased urine output or trouble breathing (see also section 4 on Possible side effects). Regular monitoring of the response to FSH treatment helps to prevent ovarian overstimulation. Contact your doctor immediately if you are experiencing stomach pains, also if this occurs some days after the last injection has been given.

Multiple pregnancy or birth defects:
After treatment with gonadotrophin preparations, there is an increased chance of having multiple pregnancies, even when only one embryo is transferred into the uterus. Multiple pregnancies carry an increased health risk for both the mother and her babies around the time of birth. Furthermore, multiple pregnancies and characteristics of the patients undergoing fertility treatment (e.g. age of the female, sperm characteristics, genetic background of both parents) may be associated with an increased risk of birth defects.

Pregnancy complications:
There is a slightly increased risk of a pregnancy outside the uterus (an ectopic pregnancy). Therefore, your doctor should perform an early ultrasound examination to exclude the possibility of pregnancy outside the uterus. In women undergoing fertility treatment there may be a slightly higher chance of a miscarriage.

Blood clot (Thrombosis):
Treatment with Foligraf, just as pregnancy itself, may increase the risk of having a blood clot (thrombosis). Thrombosis is the formation of a blood clot in a blood vessel. Blood clots can lead to serious medical conditions, such as:
- blockage in your lungs (pulmonary embolus)
- stroke
- heart attack
- blood vessel problems (thrombophlebitis)
- a lack of blood flow (deep venous thrombosis) that may result in a loss of your arm or leg.

Please discuss this with your doctor, before starting treatment, especially:
- if you already know you have an increased chance of having thrombosis.
- if you, or anyone in your immediate family, have ever had a thrombosis.
- if you are severely overweight.

Ovarian torsion:
Ovarian torsion has occurred after treatment with gonadotropins including Foligraf. Ovarian torsion is the twisting of an ovary.
Twisting of the ovary could cause the blood flow to the ovary to be cut off.

Before starting to use this medicine, tell your doctor if you:
- Have ever had ovarian hyperstimulation syndrome OHSS.
- are pregnant or think that you may be pregnant.
- Have ever had stomach (abdominal) surgery.
- Have ever had a twisting of an ovary.
- have past or current cysts in your ovary or ovaries.

Size : L x H = 450mm x 200mm

Black Colour | Light Green Colour | Light Blue Colour
Light Blue Colour | Dark Blue Colour | CMYK

Paper : 60 gsm, Maplitho White
Outline & Cutting marks not to print
Artwork Code No. : IN90435E0ACPEN
Back to Back Printing
3 Vertical Folds (Center Creasing Folds)
Final Folding Size : 75 x 200mm