Summary of Product Characteristics

1. Name of the medicinal product
GYNOGEN HP 75 IU (Menotrophin 75 G/G) Lyophilized Injection.

2. Qualitative and quantitative composition
Active ingredient
Each vial of powder contains highly purified menotrophin (human menopausal gonadotrophin, HMG) corresponding to 75 IU human follicle stimulating hormone (FSH) and 75 IU human luteinising hormone (LH) activity.

Human Chorionic Gonadotrophin (hCG), a naturally occurring hormone in postmenopausal urine, is present in GYNOGEN HP and contributes to the overall luteinizing hormone activity.

Menotrophin is produced from human urine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Lyophilized Injection.

An almost white or slightly yellowish freeze-dried product

4. Clinical particulars
4.1 Therapeutic indications

Treatment of female and male infertility in the following groups of patients:

Anovulation, including polycystic ovarian disease (PCOD) in women who have been unresponsive to treatment with clomiphene citrate:
- Women undergoing controlled ovarian hyperstimulation: GYNOGEN HP can induce the development of multiple follicles for assisted reproductive technologies (ART) (e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)).
- Hypogonadotrophic hypogonadism in men: GYNOGEN HP may be given in combination with human chorionic gonadotrophin (e.g. Choragon) for the stimulation of spermatogenesis. Patients with primary testicular failure are usually unresponsive.

4.2 Posology and method of administration

Treatment with GYNOGEN HP should be initiated under the supervision of a physician experienced in the treatment of fertility problems.

Posology
For intramuscular or subcutaneous use. The dosage regimens described below are identical for both forms of administration.

There are great inter-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. Recommendations about dosage and duration of treatment may change depending on the actual treatment protocol.

Anovulatory infertility:
Menotrophin is administered to induce follicular maturation and is followed by treatment with chorionic gonadotrophin to stimulate ovulation and corpus luteum formation.

GYNOGEN HP therapy should start within the initial 7 days of the menstrual cycle. The recommended initial dose of GYNOGEN HP is 75-150 IU daily, which should be maintained for at least 7 days. Based on clinical monitoring (including ovarian ultrasound alone or in combination with measurement of oestradiol levels) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than every 7 days. The recommended dose increment is 37.5 IU per adjustment and should not exceed 75 IU. The maximum daily dose should not be higher than 225 IU. If a patient fails to respond adequately after 3 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, administration of GYNOGEN HP 75 IU s stopped. A single injection of 5,000 IU to 10,000 IU of hCG should be given 1 day after the last GYNOGEN HP 75 IU injection. 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 to GYNOGEN HP 75 IU is obtained, treatment should be stopped and hCG withheld (see section 4.4), and the patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started. Treatment should recommence in the next treatment cycle at a dose lower than in the previous cycle.

Women undergoing controlled ovarian hyperstimulation for multiple follicular development for assisted reproductive technologies (ART):
In a protocol using down-regulation with a GnRH agonist, GYNOGEN HP 75 IU therapy should start approximately 2 weeks after the start of agonist treatment. In a protocol using down-regulation with a GnRH antagonist, GYNOGEN HP 75 IU therapy should start on day 2 or 3 of the menstrual cycle.

The recommended initial dose of GYNOGEN HP 75 IU is 150-225 IU daily for at least the first 5 days of treatment. Based on clinical monitoring (including ovarian ultrasound alone or in combination with measurement of oestradiol levels) subsequent dosing should be adjusted according to individual patient response and should not exceed more than 150 IU per adjustment. The maximum daily dose given should not be higher than 450 IU daily and, in most cases, dosing beyond 20 days is not recommended.

When a suitable number of follicles have reached an appropriate size a single injection of 5,000 IU up to 10,000 IU hCG should be administered to induce final follicular maturation in preparation

for oocyte retrieval. Patients should be followed closely for at least 2 weeks after hCG administration. If an excessive response to GYNOGEN HP 75 IU is obtained treatment should be stopped and hCG withheld (see section 4.4) and the patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started.

Male infertility:
Spermatogenesis is stimulated with chorionic gonadotrophin (1000 – 2000 IU two to three times a week) and then menotrophin is given in a dose of 75 or 150 IU units of FSH with 75 or 150 IU units of LH two or three times weekly. Treatment should be continued for at least 3 or 4 months.

Paediatric population:
There is no relevant use of GYNOGEN HP 75 IU in the paediatric population.

Elderly:
There is no relevant use of GYNOGEN HP 75 IU in the elderly population.

Method of Administration:
By intramuscular or subcutaneous use.
The powder must be reconstituted immediately with the solvent provided prior to use (see section 6.6). In order to avoid the injection of large volumes up to 3 vials of the powder may be dissolved in 1 ml of the solvent provided.

Shaking should be avoided. The solution should not be used if it contains particles or if it is not clear.

4.3 Contraindications

Women and Men
GYNOGEN HP 75 IU is contraindicated in women and men with:
- Tumours of the pituitary gland or hypothalamus
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Women
- Ovarian, uterine or mammary carcinoma
- Pregnancy and lactation
- Gynaecological haemorrhage of unknown aetiology
- Ovarian cysts or enlarged ovaries not due to polycystic ovarian disease.

In the following situations treatment outcome is unlikely to be favourable, and therefore GYNOGEN HP 75 IU should not be administered:
- Primary ovarian failure
- Malformation of sexual organs incompatible with pregnancy
- Fibroid tumours of the uterus incompatible with pregnancy

- Structural abnormalities in which a satisfactory outcome cannot be expected, for example, tubal occlusion (unless superovulation is to be induced for IVF), ovarian dysgenesis, absent uterus or premature menopause.

Men

- Tumours in the testes
- Prostate carcinoma

4.4 Special warnings and precautions for use

GYNOGEN HP 75 IU is a potent gonadotropic 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, and calls for monitoring of ovarian response with ultrasound, alone or in combination with measurement of serum oestradiol levels, on a regular basis. There is considerable inter-patient variability in response to menotrophin administration, with a poor response to menotrophin in some patients. The lowest effective dose in relation to the treatment objective should be used.

The first injection of GYNOGEN HP 75 IU 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 tumours, 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 hyperstimulation. Adherence to recommended GYNOGEN HP 75 IU dosage and regimen of administration, and careful monitoring of therapy will minimise the incidence of such events. Acute interpretation of the indices of follicle development and maturation requires a physician who is experienced in the interpretation of the relevant tests.

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 symptoms may be observed in 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.

If urinary oestrogen levels exceed 540 nmol (150 micrograms)/24 hours, or if plasma 17 beta-oestradiol levels exceed 3000 pmol/L (800 picograms/ml), or if there is any steep rise in values, there is an increased risk of hyperstimulation and GYNOGEN HP 75 IU treatment should be immediately discontinued and human chorionic gonadotrophin withheld. Ultrasound will reveal any excessive follicular development and unintentional hyperstimulation.

The severe form OHSS may be life-threatening and is characterised by large ovarian cysts (prone to rupture), acute abdominal pain, ascites, very often hydrothorax and occasionally thromboembolic phenomena. Other symptoms that may be observed include: 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, haemoperitoneum, pleural effusions and acute pulmonary distress.

Excessive ovarian response to gonadotrophin treatment seldom gives rise to OHSS unless hCG is administered to trigger ovulation. Therefore, in cases of ovarian 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 the hCG administration. Adherence to recommended GYNOGEN HP 75 IU dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and multiple pregnancy (see sections 4.2 and 4.8). Patients undergoing controlled ovarian hyperstimulation may be at an increased risk of developing hyperstimulation in view of the excessive oestrogen response and multiple follicular development. In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyperstimulation.

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 severity 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 hospitalised and specific therapy for OHSS started.

This syndrome occurs with higher incidence in patients with polycystic ovarian disease.

Multiple pregnancy
Multiple pregnancy, especially high order, carries an increased risk of adverse maternal and perinatal outcomes.

In patients undergoing ovulation induction with gonadotrophins, the incidence of multiple pregnancies is increased compared with natural conception. The majority of multiple conceptions are twins. To minimise the risk of multiple pregnancy, 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 age of the patient.

The patient 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 ART procedures than 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 treatment. The prevalence of ectopic pregnancy after IVF has been reported to be 2 to 5%, as compared to 1 to 1.5% 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 if treatment with gonadotrophins increases the baseline risk of these tumours 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
Women with generally recognised risk factors for thromboembolic events, such as personal or family history, severe obesity (Body Mass Index > 30kg/m^2) 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 gonadotrophin administration need to be weighed against the risks. It should be noted however, that pregnancy itself also carries an increased risk of thromboembolic events.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with GYNOGEN HP 75 IU in humans.
Although there is no controlled clinical experience, it is expected that the concomitant use of GYNOGEN HP 75 IU and clomiphene citrate may enhance the follicular response. When using GnRH agonist for pituitary desensitization, a higher dose of GYNOGEN HP 75 IU may be necessary to achieve adequate follicular response.

4.6 Fertility, pregnancy and lactation

Fertility
GYNOGEN HP 75 IU is indicated for use in infertility (see section 4.1).

Pregnancy
GYNOGEN HP 75 IU is contraindicated in women who are pregnant (see section 4.3).

There are no or limited amount of data from the use of menotrophins in pregnant women. No animal studies have been carried out to evaluate the effects of GYNOGEN HP 75 IU during pregnancy (see section 5.3).

Breast-feeding
GYNOGEN HP 75 IU is contraindicated in women who are breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, GYNOGEN HP 75 IU is unlikely to have influence on the patient's ability to drive and use machines.

4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADR) during treatment with GYNOGEN HP 75 IU in clinical trials are Ovarian Hyperstimulation Syndrome OHSS, abdominal pain, headache, abdominal distension, and injection site pain. None of these ADRs have been reported with an incidence rate of more than 5%.

The table below displays the main ADR in women treated with GYNOGEN HP 75 IU in clinical trials distributed by system organ classes (SOCs) and frequency. ADRs seen during post-marketing experience are mentioned with unknown frequency.

System Organ Class	**Common (> 1/100 to < 1/10)**	**Uncommon (> 1/1,000 to < 1/100)**	**Rare (> 1/10,000 to < 1/1,000)**	**Unknown**
Eye disorders				Visual disorders
Gastrointestinal disorders	Abdominal pain, Abdominal distension, Nausea	Vomiting, Abdominal discomfort, Diarrhoea		
General disorders and administration site condition	Injection site reactions [a]	Fatigue		
Immune system disorders				Hypersensitivity reactions [b]

Investigations				
Musculoskeletal & connective tissue disorders				Musculoskeletal pain [c]
Nervous system disorders	Headache	Dizziness		
Reproductive system disorders	OHSS [d], Pelvic pain[e]	Ovarian cyst, Breast complaints [f]		Ovarian torsion [d]
Skin and subcutaneous tissue disorders			Acne, Rash	Pruritus, Urticaria
Vascular Disorders		Hot flush		

[a] Most frequently reported injection site reaction was injection site pain.
[b] Cases of localised or generalised allergic reactions , including anaphylactic reaction, along with associated symptomatology have been reported rarely.
[c] Musculoskeletal pain includes arthralgia, back pain, neck pain and pain in extremities.
[d] Gastrointestinal symptoms associated with OHSS such as abdominal distension and discomfort, nausea, vomiting, diarrhoea have been reported with GYNOGEN HP 75 IU in clinical trials. In cases of severe OHSS ascites and pelvic fluid collection, pleural effusion, dyspnoea, oliguria, thromboembolic events and ovarian torsion have been reported as rare complications.
[e] Pelvic pain includes ovarian pain and adnexa uteri pain.
[f] Breast complaints include breast pain, breast tenderness, breast discomfort, nipple pain and breast swelling.

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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system (see details below).

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*

4.9 Overdose

The effects of an overdose is unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur (see section 4.4).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophins
ATC code: G03G A02

Menotrophin (Human Menopausal Gonadotrophin, HMG) is a gonadotrophin extracted from the urine of postmenopausal women. It has both luteinising hormone and follicle stimulating hormone activity in a 1:1 ratio. Human Chorionic Gonadotrophin (hCG), a naturally occurring hormone in postmenopausal urine, is present in GYNOGEN HP 75 IU and is the main contributor of the LH activity.
Menotrophin (HMG) directly affects the ovaries and the testes. HMG has a gametropic and steroidogenic effect.

In the ovaries, the FSH-component in HMG induces an increase in the number of growing follicles and stimulates their development. FSH increases the production of oestradiol in the granulosa cells by aromatising androgens that originate in the Theca cells under the influence of the LH-component.

Follicular growth can be stimulated by FSH in the total absence of LH, but the resulting follicles develop abnormally and are associated with low oestradiol levels and inability to luteinize to a normal ovulatory stimulus.

In line with the action of LH activity in enhancing steroidogenesis, oestradiol levels associated with treatment with GYNOGEN HP 75 IU are higher than with recombinant FSH preparations in downregulated IVF/ICSI cycles. This issue should be considered when monitoring patient's response based on oestradiol levels.

In the testes, FSH induces the transformation of premature to mature Sertoli cells. It mainly causes the maturation of the seminal canals and the development of the spermatozoa. However, a high concentration of androgens within the testes is necessary and can be attained by a prior treatment using hCG.

5.2 Pharmacokinetic properties

The pharmacokinetics of menotrophin following intramuscular or subcutaneous administration shows great interindividual variability. After 7 days of repeated dosing with 150 IU GYNOGEN HP 75 IU in downregulated healthy female volunteers, plasma FSH concentrations Cmax (baseline-corrected) (mean ± SD) were 8.9 ± 3.5 IU/L and 8.4 ± 3.2 IU/L for the SC and IM administration, respectively. The area under the curve (AUC_τ) of FSH concentration was (mean ± SD) 180 ± 77 h.IU/L and 166 ± 67 h.IU/L for SC and IM administration, respectively. Maximum FSH concentrations were reached (Tmax) within 7 hours for both routes of administration. After repeated administration, FSH was eliminated with a half-life (T1/2) (mean ± SD) of 30 ± 11 hours and 27 ± 9 hours for the SC and IM administration, respectively. Although the individual LH concentration versus time curves show an increase in the LH concentration after dosing with

GYNOGEN HP 75 IU, the data available were too sparse to be subjected to a pharmacokinetic analysis.
Menotrophin is excreted primarily via the kidneys.

The pharmacokinetics of GYNOGEN HP 75 IU in patients with renal or hepatic impairment has not been investigated.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans, which is not known from the extensive clinical experience.

Reproduction toxicity studies have not been carried out to evaluate the effects of GYNOGEN HP 75 IU during pregnancy or post-partum as GYNOGEN HP 75 IU is not indicated during these periods.

GYNOGEN HP 75 IU consist of naturally occurring hormones and should be expected to be non-genotoxic.
Carcinogenicity studies have not been carried out as the indication is for short term treatment.

6. Pharmaceutical particulars

6.1 List of excipients

Powder:
NNN

Solvent:
NNN

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

36 months.

The reconstituted product should be used immediately, and any remaining solution should be discarded.

For immediate and single use following reconstitution.

6.4 Special precautions for storage

Store in a refrigerator 2 - 8°C, protect from light.

6.5 Nature and contents of container

GLASS (TYPE I) VIAL OF 1 X 2 ML.

6.6 Special precautions for disposal and other handling

The powder should only be reconstituted with the solvent provided in the package.
Attach the reconstitution needle to the syringe. Withdraw the entire content from the ampoule with solvent and inject the total contents into the vial containing the powder. The powder should dissolve quickly to a clear solution. If not, roll the vial gently between the hands until the solution is clear. Shaking should be avoided.

If needed, the solution can be drawn up into the syringe again to transfer it to the next vial with powder until the prescribed dose has been reached. Up to three powder vials can be dissolved with one ampoule of solvent.

When the prescribed dose has been reached, draw up the mixed solution from the vial into the syringe, change to the hypodermic needle and administer immediately.

The reconstituted solution should not be administered if it contains particles or is not clear.

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

7. Marketing authorisation holder
SANZYME (P) LIMITED
PLOT NO. 08 SY.NO. 542, KOLTUR VILLAGE, SHAMIRPET MANDAL,
MEDCHAL-MALKAJGIRI (DISTRICT)
PINCODE: 500101,
JIANDE
INDIA

8. Marketing authorisation number(s)
TZ 19 H 0198

9. Date of first authorisation/renewal of the authorisation
August 02, 2019

10. Date of revision of the text
October 10, 2023