BRAVELLE 75 IU powder and solvent for solution for injection.

Summary of Product Characteristics Updated 17-May-2017 | Ferring Pharmaceuticals Ltd

1. Name of the medicinal product

BRAVELLE 75 IU powder and solvent for solution for injection.

2. Qualitative and quantitative composition

Each vial of powder contains 82.5 IU of highly purified urinary follicle stimulating hormone (FSH), urofollitropin. When reconstituted with the solvent provided, each vial delivers 75 IU of FSH.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder and solvent for solution for injection.

Appearance of powder: Lyophilised, white to off-white caked mass.

Appearance of solvent: Clear colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

BRAVELLE is indicated for the treatment of female infertility in the following clinical situations:

Anovulation (including polycystic ovarian disease (PCOD)) in women who have been unresponsive to treatment with clomiphene citrate.

Controlled ovarian hyperstimulation to 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)).

4.2 Posology and method of administration

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

Posology

There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotropins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires monitoring of ovarian response by ultrasonography alone or preferably in combination with measurement of oestradiol levels. BRAVELLE can be given alone or in combination with a gonadotropin-releasing hormone (GnRH) agonist or antagonist for controlled ovarian hyperstimulation. There is no clinical trial experience with the use of BRAVELLE in combination with GnRH antagonists in this indication. Recommendations about dosage and duration of treatment may change depending on the actual treatment protocol.

Clinical trial experience with BRAVELLE is based upon one treatment cycle in both indications.

Women with anovulation (including PCOD):

The object of BRAVELLE therapy is to develop a single Graafian follicle from which the oocyte will be liberated after the administration of human chorionic gonadotropin (hCG).

BRAVELLE therapy should start within the initial 7 days of the menstrual cycle. The recommended initial dose of BRAVELLE is 75 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 4 weeks of treatment, that cycle should be abandoned.

When an optimal response is obtained a single injection of 5,000 to 10,000 IU hCG should be given 1 day following the last BRAVELLE injection. The patient is recommended to have coitus on the day of and the day following hCG administration. Alternatively intrauterine insemination may be performed. Patients should be followed closely for at least 2 weeks after hCG administration. If an excessive response to BRAVELLE 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.

Women undergoing controlled ovarian hyperstimulation for multiple follicular development for assisted reproductive technologies (ART):

In line with clinical trials with BRAVELLE that involved down regulation with GnRH agonists, BRAVELLE therapy should start approximately 2 weeks after the start of agonist treatment. The recommended initial dose of BRAVELLE 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 150 IU per adjustment. The maximum daily dose given should not be higher than 450 IU daily and in most cases dosing beyond 12 days is not recommended.

In protocols not involving down regulation, BRAVELLE therapy should start on day 2 or 3 of the menstrual cycle. It is recommended to use the dose ranges and regimen of administration suggested above for protocols with down regulation with GnRH agonists.

When an optimal response is obtained a single injection of 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 BRAVELLE 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.

Paediatric population

There is no relevant use of BRAVELLE in the paediatric population.

Method of administration

BRAVELLE is intended for subcutaneous (SC) injection after reconstitution with the solvent provided. The powder should be reconstituted immediately prior to use. In order to avoid the injection of large volumes up to 6 vials of the powder may be dissolved in the solvent provided. The solution should not be used if it contains particles or if it is not clear.

Appearance of reconstituted solution: clear solution

For instructions of reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

BRAVELLE is contraindicated in women who have:

- Tumours of the pituitary or hypothalamic glands
- Ovarian, uterine or mammary carcinoma
- Pregnancy and lactation
- Gynaecological haemorrhage of unknown aetiology
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In the following situations treatment outcome is unlikely to be favourable, and therefore BRAVELLE should not be administered:

- Primary ovarian failure
- Ovarian cysts or enlarged ovaries not due to polycystic ovarian disease.
- Malformation of sexual organs incompatible with pregnancy
- Fibroid tumours of the uterus incompatible with pregnancy

4.4 Special warnings and precautions for use

BRAVELLE is a potent gonadotropic substance capable of causing mild to severe adverse reactions, and should only be used under the supervision of physicians who are thoroughly familiar with infertility problems and their management.

Gonadotropin 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 BRAVELLE 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.

Repeated exposure to BRAVELLE has not been investigated in clinical trials.

The first injection of BRAVELLE 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 BRAVELLE 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 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 gonadotropin 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 BRAVELLE 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). 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 at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses.

If severe OHSS occurs, gonadotropin 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 gonadotropins, the incidence of multiple pregnancy 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 ovulation induction or ART 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 gonadotropins 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

Women with generally recognised risk factors for thromboembolic events, such as personal or family history, severe obesity (Body Mass Index > 30 kg/m^2) or thrombophilia, may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotropins. In these women, the benefits of gonadotropin 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.

Although there is no clinical experience, it is expected that the concomitant use of BRAVELLE and clomiphene citrate may enhance the follicular response. When using a GnRH agonist for pituitary desensitisation, a higher dose of BRAVELLE may be necessary to achieve adequate follicular response.

4.6 Pregnancy and lactation

BRAVELLE is contraindicated in women who are pregnant or lactating (see section 4.3).

To date no teratogenic risk has been reported when gonadotropins are used clinically for controlled ovarian hyperstimulation. Data on exposed pregnancies are insufficient. Animal experiments did not reveal teratogenic effects (see section 5.3).

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, BRAVELLE is unlikely to have influence on the patient's performance to drive and use machines.

4.8 Undesirable effects

The most commonly reported adverse events during treatment with BRAVELLE in clinical trials are headache and abdominal pain, both occurring in 10% of patients followed by nausea, vaginal haemorrhage, OHSS and abdominal distension, each occurring in 5 to 9% of patients. The table below displays the adverse events occurring in more than 1% of the patients treated with BRAVELLE in clinical trials according to organ class and frequency.

Organ Class	**Very common (>1/10)**	**Common (>1/100, <1/10)**
Infections and infestations	-	Urinary tract infection, nasopharyngitis
Nervous system disorders	Headache	-
Vascular disorders	-	Hot flushes
Gastrointestinal disorders	Abdominal pain	Nausea, vomiting, abdominal distension, abdominal discomfort, diarrhoea, constipation
Skin and subcutaneous tissue disorders	-	Rash
Muscoloskeletal and connective tissue disorders	-	Muscle spasms
Reproductive system and breast disorders	-	Vaginal haemorrhage, OHSS, pelvic pain, breast tenderness, vaginal discharge
General disorders and administration site disorders	-	Pain, injection site pain and reactions (redness, bruising, swelling and/or itching)

As complications of OHSS, venous thromboembolic events and ovarian torsion might occur.

Allergic, local or generalized skin reactions and delayed-type hypersensitivity have been reported with the use of gonadotropin preparations.

Repeated exposure to BRAVELLE has not been investigated in clinical trials.

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 Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotropins

ATC code: G03G A04

BRAVELLE contains a highly purified preparation of urinary FSH extracted from the urine of postmenopausal women. FSH stimulates ovarian follicular growth and development as well as gonadal steroid production in women who do not have primary ovarian failure.

The isoform composition of the highly purified FSH in BRAVELLE displays more basic isoforms than other urofollitropin preparations, and is similar to that observed for recombinant FSH preparations. According to data from clinical trials, the pharmacodynamic responses associated with BRAVELLE treatment do not differ from those associated with recombinant FSH when administered by the same route. After SC administration, similar follicle response, peak oestradiol levels, number of oocytes retrieved and number of mature oocytes have been found with BRAVELLE and recombinant FSH, without differences in total FSH dose or duration of treatment.

Treatment with BRAVELLE is usually followed by administration of hCG to induce final follicle maturation and ovulation.

5.2 Pharmacokinetic properties

Following single doses of SC administration of BRAVELLE maximum FSH concentrations were reached within 21 hours. Steady-state was observed after 4 to 5 days. After 7 days of repeated administration, the maximum FSH concentrations were attained at 10 hours after injection.

Following single doses of SC administration of BRAVELLE, mean elimination half-life of FSH was 41 hours. After 7 days of repeated administration, the mean elimination half-life of FSH was 30 hours for the SC route.

After 7 days of dosing with BRAVELLE SC, FSH C_{max} was 11.1 IU/L and steady state FSH AUC was 235 IU/L*h.

The pharmacokinetics of BRAVELLE in patients with renal or hepatic impairment has not been investigated.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of cardiovascular safety pharmacology, single and repeat dose toxicity, and local tolerance.

Impaired fertility was observed in rats which were treated with high doses of recombinant follitropin for prolonged time. Repeat dose toxicity studies in rats and dogs have demonstrated that high doses of BRAVELLE have the potential to impair fertility due to follicular atresia and cysts in the ovaries.

6. Pharmaceutical particulars

6.1 List of excipients

Powder:

Lactose monohydrate

Polysorbate 20

Sodium phosphate dibasic heptahydrate (for pH adjustment)

Phosphoric acid (for pH adjustment)

Water for injections

Solvent:

Sodium chloride

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

After reconstitution: use immediately.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze. Store in the original container in order to protect from light.

6.5 Nature and contents of container

Powder:

The powder for solution for injection is supplied in a 2 mL single dose colourless type I glass vial with a bromobutyl rubber stopper closed with an aluminium/polypropen cap.

Solvent:

The solvent for solution for injection is provided in a 1 mL single dose colourless type I glass ampoule.

BRAVELLE is supplied in the following pack sizes:

5 vials of powder + 5 ampoules of solvent

10 vials of powder + 10 ampoules of solvent

5 vials of powder + 5 ampoules of solvent,

5 syringes with needles for dissolution of the powder, 5 injection needles,

5 disposable alcohol swabs

10 vials of powder + 10 ampoules of solvent,

10 syringes with needles for dissolution of the powder, 10 injection needles,

10 disposable alcohol swabs

30 vials of powder + 30 ampoules of solvent,

15 syringes with needles for dissolution of the powder, 15 injection needles,

15 disposable alcohol swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

BRAVELLE should only be reconstituted with the solvent provided prior to use.

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 within 2 minutes to a clear solution. If not, roll the vial gently between the hands until the solution is clear. Vigorous shaking should be avoided.

After reconstitution, the solution can be mixed with Ferring's menotrophin (hMG) MENOPUR powder for solution for injection before administration. Studies have shown that co-administration of BRAVELLE and MENOPUR does not significantly alter the expected bioactivity.

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 six powder vials (450 IU) can be dissolved in 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 solution should not be used if it contains particles or if it is not clear.

BRAVELLE should be administered immediately after reconstitution. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

PL 03194/0087

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10. Date of revision of the text

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