PRODUCT MONOGRAPH

BRAVELLE™

(Urofollitropin for Injection, Purified)

Subcutaneous or Intramuscular Injection

Gonadotropin

75 IU FSH Activity per Vial

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(Urofollitropin for Injection, Purified)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous or Intramuscular Injection	75 IU FSH activity per vial	Lactose monohydrate, Polysorbate 20 (Tween 20), Phosphate buffer (sodium phosphate dibasic, heptahydrate and phosphoric acid)

INDICATIONS AND CLINICAL USE

BRAVELLE™ (Urofollitropin for injection, purified) in conjunction with hCG is indicated for:

- Multiple follicular development (controlled ovarian stimulation)
- Ovulation induction in patients who have previously received pituitary suppression. This includes patients participating in Assisted Reproductive Technology (ART) program.

Selection of Patients

General

Careful attention should be given to the diagnosis of infertility in the selection of candidates for BRAVELLE™ (Urofollitropin for Injection, Purified) therapy.

1. Before treatment with BRAVELLE™ is instituted, a thorough gynecologic and endocrinologic evaluation must be performed, except for those patients enrolled in an *In Vitro* Fertilization (IVF) program. The evaluation may include a hysterosalpingography (to rule out uterine and tubal pathology). Anovulation should be confirmed by menstrual history, observation of basal body temperature pattern, serial vaginal smears, examination of cervical mucus, and determination of serum (or urine) progesterone, urinary pregnanediol and endometrial biopsy. Patients with tubal pathology should receive urofollitropins only if enrolled in an *in vitro* fertilization program.
2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.
3. Careful examination should be made to rule out the presence of an early pregnancy.
4. Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of anovulatory disorders. Cervical dilation and curettage should always be done for

diagnosis before starting BRAVELLE™ therapy in such patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities.

5. Evaluation of the husband's fertility potential should be included in the workup.

Prior to therapy with BRAVELLE™ patients should be informed of the duration of treatment and monitoring of their condition that will be required. Possible adverse reactions (see ADVERSE REACTIONS section) and the risk of multiple births should be discussed.

Pregnant Women

BRAVELLE™ (Urofollitropin for Injection, Purified) is contraindicated in pregnant women.

Pediatric and Geriatric Populations

BRAVELLE™ (Urofollitropin for Injection, Purified) is not used in pediatric or geriatric populations.

CONTRAINDICATIONS

BRAVELLE™ (Urofollitropin for Injection, Purified) is contraindicated in women who exhibit:

1. A high circulating FSH level indicating primary ovarian failure.
2. Uncontrolled thyroid and adrenal dysfunction.
3. An organic intracranial lesion such as pituitary tumor.
4. The presence of any causes of infertility other than anovulation unless they are candidates for assisted reproductive procedures.
5. Abnormal bleeding of undetermined origin.
6. Ovarian cysts or enlargement not due to polycystic ovary syndrome.
7. Prior hypersensitivity to urofollitropins.
8. BRAVELLE ™ is not indicated in women who are pregnant or lactating. There are limited human data on the effects of BRAVELLE ™ when administered during pregnancy.

WARNINGS AND PRECAUTIONS

General

BRAVELLE™ (Urofollitropin for Injection, Purified) is a drug that should only be used by physicians who are experienced in the management of fertility disorders and only when facilities for appropriate clinical and endocrinologic evaluations are available. It is a potent gonadotropic substance capable of causing mild to severe adverse reactions in women. Urofollitropin therapy requires a certain time commitment by physicians and supportive health professionals, and its use requires the availability of

appropriate monitoring facilities (see Laboratory Tests). In female patients it must be used with a great deal of care.

The drug substance of this drug product is manufactured from human urine. Although the risk is theoretical, and no case of transmission of an infectious agent linked to the use of urine-derived gonadotropins has ever been identified, the risk of transmitting infectious agents cannot be completely excluded.

Overstimulation of the Ovary during BRAVELLE™ Therapy:

Ovarian Enlargement: Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain, occurs in approximately 20% of those treated with follitropin and hCG, and generally regresses without treatment within two or three weeks.

In order to minimize the hazard associated with the occasional abnormal ovarian enlargement which may occur with FSH - hCG therapy, the lowest dose consistent with expectation of good results should be used. Careful monitoring of ovarian response can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of BRAVELLE™ therapy, hCG should not be administered in the course of therapy; this will reduce the chance of developing the Ovarian Hyperstimulation Syndrome.

Ovarian Hyperstimulation Syndrome (OHSS):

OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS may progress rapidly to become a serious medical event. It is characterized by an apparent dramatic increase in vascular permeability, which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain. The following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see "Pulmonary and Vascular Complications" below). Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with the Ovarian Hyperstimulation Syndrome (OHSS).

In the clinical study of ovulation induction, 6 of 72 (8.33 %) BRAVELLE™ treated women developed OHSS and two were classified as severe. Cases of OHSS are more common, more severe and more protracted if pregnancy occurs. OHSS develops rapidly; therefore patients should be followed for at least two weeks after hCG administration. Most often, OHSS occurs after treatment has been discontinued and reaches its maximum at about 7 to 10 days after treatment. Usually, in cases where OHSS may be developing prior to hCG administration (see- Laboratory Tests), the hCG should be withheld.

If severe OHSS occurs, treatment must be stopped and the patient should be hospitalized.

A physician experienced in the management of the syndrome, or who is experienced in the management of fluid and electrolyte imbalances should be consulted.

Pulmonary and Vascular Complications

Serious pulmonary conditions (e.g. atelectasis, acute respiratory distress syndrome) have been reported. In addition, thromboembolic events both in association with, and separate from, the Ovarian Hyperstimulation Syndrome have been reported following urofollitropin therapy. Intravascular thrombosis and embolism, which may originate in venous or arterial vessels, can result in reduced blood flow to critical organs or the extremities. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death.

Other Reproductive Complications

Multiple ovulations with resulting multiple births occur frequently following treatment with gonadotropins and hCG. Prior to gonadotropin and hCG therapy, the patient and her partner should be informed of the possibility and risks associated with multiple births.

Multiple pregnancies have occurred following treatment with BRAVELLE™ SC and IM in a clinical trial for ovulation induction in which BRAVELLE™ SC, BRAVELLE™ IM and a recombinant FSH product were directly compared. The rates of multiple pregnancies appear in Table 1.

TABLE 1
Multiple Pregnancies-Primary Efficacy Responders in Ovulation Induction Study

	BRAVELLE SC	**BRAVELLE IM**	**Recombinant FSH SC**	**p-value**
Parameter (%)	N=26	N=28	N=35	
Total number of continuing pregnancies	9 (34.6)	7 (25.0)	10 (28.6)	0.261
Total number of multiple pregnancies	6 (23.1)	2 (7.1)	4 (11.4)	
Singlets	3 (11.5)	5 (17.9)	6 (17.1)	
Twins	4 (15.4)	0	2 (5.7)	
Triplets	2 (7.7)	0	0	
Quadruplets	0	1 (4.8)	2 (5.7)	
Quintuplets	0	0	0	
Sextuplets	0	1 (4.8)	0	

The multiple pregnancy rates for the *In Vitro* Fertilization (IVF) studies appear in Table 2.

TABLE 2
Multiple Pregnancies –Primary Efficacy Responders in *In Vitro* Fertilization Studies

	Study 1				Study 2		
Parameter (%)	**BRAVELLE™ SC**	**BRAVELLE™ IM**	**Recombinant FSH SC**	**p-value**	**BRAVELLE™ SC**	**Recombinant FSH SC**	**p-value**
	N=56	**N=55**	**N=56**		**N=57**	**N=59**	
Total number of continuing pregnancies	25 (44.6)	19 (32.2)	17 (29.3)		23 (40.3)	27 (45.8)	
Total number of multiple pregnancies	7 (12.5)	9 (16.4)	9 (16.1)	0.816	8 (14.0)	11 (18.6)	0.6179
Singlets	18 (32.1)	10 (18.2)	8 (13.2)		15 (26.3)	16 (27.1)	
Twins	5 (8.9)	7 (12.7)	7 (12.5)		5 (8.8)	10 (16.9)	
Triplets	1 (1.8)	1 (1.8)	2 (3.6)		3 (5.3)	1 (1.7)	
Quadruplets	1 (1.8)	1 (1.8)	0		0	0	

Hypersensitivity/Anaphylactic Reactions

Hypersensitivity anaphylactic reactions associated with urofollitropins administered have been reported in some patients. These reactions presented as generalized urticaria, facial edema, angioneurotic edema, and/or dyspnea suggestive of laryngeal edema. The relationship of these symptoms to uncharacterized urinary proteins is uncertain.

Renal and Hepatic

The safety and efficacy of BRAVELLE™ (Urofollitropin for Injection, Purified) in renal and hepatic insufficiency have not been studied.

Special Populations

Nursing Women

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in the nursing infant from BRAVELLE™ (Urofollitropin for Injection, Purified), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Monitoring and Laboratory Test

Laboratory Tests

The combination of both estradiol levels and ultrasonography are useful for monitoring the growth and development of follicles, timing of hCG administration, as well as minimizing the risk of the Ovarian Hyperstimulation Syndrome and multiple gestations.

The clinical confirmation of ovulation is determined by:

(a) A rise in basal body temperature;
(b) Increase in serum progesterone, and
(c) Menstruation following the shift in basal body temperature.

When used in conjunction with indices of progesterone production, sonographic visualization of the ovaries will assist in determining if ovulation has occurred. Sonographic evidence of ovulation may include the following:

(a) Fluid in the cul-de-sac;
(b) Ovarian stigmata; and
(c) Collapsed follicle.

Because of the subjectivity of the various tests for the determination of follicular maturation and ovulation, it cannot be overemphasized that the physician should choose tests with which he/she is thoroughly familiar.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of BRAVELLE™ (Urofollitropin for Injection, Purified) was examined in three clinical studies that enrolled a total of 251patients receiving BRAVELLE ™ including 72 for ovulation induction and 179 for IVF (*In Vitro* Fertilization).

Adverse events occurring with ≥ 1% incidence in the clinical study patients receiving BRAVELLE™ are listed in Table 3.

TABLE 3: INCIDENCE OF ADVERSE EVENTS ≥ 1% REPORTED IN THE CLINICAL TRIAL

ADVERSE EVENTS BODY SYSTEM/PREFERRED TERM	BRAVELLE™ SC N = 155	BRAVELLE™ IM N = 96	RECOMBINANT SC N = 157
Body as a Whole			
Abdomen Enlarged	2 (1.3%)	1 (1.0%)	4 (2.5%)
Abdominal Cramps	11 (7.1%)	5 (5.2%)	13 (8.3%)
Abdominal Fullness	7 (4.5%)	0 (0.0%)	3 (1.9%)
Abdominal Pain	7 (4.5%)	4 (4.2%)	10 (6.4%)
Accidental Injury	0 (0.0%)	1 (1.0%)	0 (0.0%)
Allergic Reaction	2 (1.3%)	1 (1.0%)	0 (0.0%)
Back Pain	2 (1.3%)	0 (0.0%)	3 (1.9%)
Fever	0 (0.0%)	1 (1.0%)	0 (0.0%)
Flu Syndrome	0 (0.0%)	1 (1.0%)	0 (0.0%)
Headache	22 (14.2%)	13 (13.5%)	18 (11.5%)
Injection Site Hemorrhage	2 (1.3%)	1 (1.0%)	0 (0.0%)
Injection Site Pain	0 (0.0%)	0 (0.0%)	2 (1.3%)
Injection Site Reaction	6 (3.9%)	1 (1.0%)	5 (3.2%)
Knee Edema	0 (0.0%)	1 (1.0%)	0 (0.0%)
Malaise	0 (0.0%)	1 (1.0%)	3 (1.9%)
Neck Pain	0 (0.0%)	2 (2.1%)	0 (0.0%)
Pain	10 (6.5%)	7 (7.3%)	3 (1.9%)
Pelvic Pain	4 (2.6%)	4 (4.2%)	5 (3.2%)
Cardiovascular			
Tachycardia	0 (0.0%)	1 (1.0%)	0 (0.0%)
Digestive			
Constipation	2 (1.3%)	3 (3.1%)	4 (2.5%)
Diarrhea	2 (1.3%)	2 (2.1%)	2 (1.3%)
Nausea	14 (9.0%)	9 (9.4%)	17 (10.8%)
Vomiting	2 (1.3%)	5 (5.2%)	7 (4.5%)
Metabolic/Nutritional			
Dehydration	0 (0.0%)	1 (1.0%)	0 (0.0%)
Musculoskeletal			
Joint Disorder	0 (0.0%)	1 (1.0%)	0 (0.0%)
Nervous			
Anxiety	2 (1.3%)	0 (0.0%)	0 (0.0%)
Depression	0 (0.0%)	1 (1.0%)	0 (0.0%)
Emotional Lability	2 (1.3%)	3 (3.1%)	2 (1.3%)
Hypertension	0 (0.0%)	1 (1.0%)	0 (0.0%)
Insomnia	0 (0.0%)	0 (0.0%)	2 (1.3%)

TABLE 3: INCIDENCE OF ADVERSE EVENTS ≥ 1% REPORTED IN THE CLINICAL TRIAL			
ADVERSE EVENTS BODY SYSTEM/PREFERRED TERM	**BRAVELLE™ SC N = 155**	**BRAVELLE™ IM N = 96**	**RECOMBINANT SC N = 157**
Respiratory			
Cough Increased	2 (1.3%)	0 (0.0%)	0 (0.0%)
Nasal Congestion	2 (1.3%)	0 (0.0%)	0 (0.0%)
Respiratory Disorder	8 (5.2%)	1 (1.0%)	6 (3.8%)
Sinusitis	3 (1.9%)	0 (0.0%)	4 (2.5%)
Skin/Appendages			
Exfoliative Dermatitis	0 (0.0%)	1 (1.0%)	0 (0.0%)
Pruritus	0 (0.0%)	2 (2.1%)	2 (1.3%)
Rash	3 (1.9%)	4 (4.2%)	5 (3.2%)
Skin Disorder	0 (0.0%)	1 (1.0%)	0 (0.0%)
Sweating	0 (0.0%)	1 (1.0%)	0 (0.0%)
Urogenital			
Abdominal Cramps	6 (3.9%)	5 (5.2%)	9 (5.7%)
Breast Tenderness	3 (1.9%)	1 (1.0%)	0 (0.0%)
Cervix Disorder	2 (1.3%)	0 (0.0%)	0 (0.0%)
Cystitis	0 (0.0%)	1 (1.0%)	0 (0.0%)
Hot Flash	7 (4.5%)	1 (1.0%)	0 (0.0%)
Infection Fungal	2 (1.3%)	1 (1.0%)	2 (1.3%)
OHSS	10 (6.5%)	5 (5.2%)	7 (4.5%)
Ovarian Disorder	3 (1.9%)	3 (3.1%)	2 (1.3%)
Pelvic Cramps	4 (2.6%)	0 (0.0%)	0 (0.0%)
Post-Retrieval Pain	12 (7.7%)	0 (0.0%)	12 (7.6%)
Pregnancy Disorder	2 (1.3%)	0 (0.0%)	0 (0.0%)
Urinary Tract Infection	5 (3.2%)	1 (1.0%)	3 (1.9%)
Uterine Disorder	0 (0.0%)	1 (1.0%)	0 (0.0%)
Uterine Spasm	4 (2.6%)	4 (4.2%)	6 (3.8%)
Vaginal Discharge	4 (2.6%)	0 (0.0%)	0 (0.0%)
Vaginal Hemorrhage	10 (6.5%)	6 (6.3%)	13 (8.3%)
Vaginal Pruritus	0 (0.0%)	2 (2.1%)	0 (0.0%)
Vaginal Spotting	4 (2.6%)	0 (0.0%)	4 (2.5%)
Vaginitis	0 (0.0%)	0 (0.0%)	3 (1.9%)

The following other adverse events occurred in BRAVELLE™ treated patients with a frequency < 1%:

- Body as a whole: allergic reaction, chest pain, fever, flu syndrome, infection, itchy throat, malaise, shingles
- Cardiovacular: thrombosis
- Digestive: abnormal stools, melena, upset stomach
- Endocrine: Endocrine disorder
- Metabolic/Nutritional: weight gain
- Musculoskeletal: leg cramps
- Nervous System: dizziness, dystonia
- Respiratory: bronchitis, rhinitis
- Skin/Appendages: acne, herpes simplex, pruritus
- Special Senses: conjunctivitis, sty
- Urogenital: abortion, dysmenorrhea, kidney calculus, urinary frequency, urinary incontinence, vaginitis

The following medical events have been reported subsequent to pregnancies resulting from gonadotropin therapy in published clinical studies:

1. Spontaneous abortion.
2. Ectopic pregnancy.
3. Premature labor.
4. Postpartum fever.
5. Congenital abnormalities.

The following adverse reactions have been previously reported during urofollitropin for injection, purified therapy:

1. Pulmonary and vascular complications (see **WARNINGS AND PRECAUTIONS**).
2. Adnexal torsion (as a complication of ovarian enlargement).
3. Mild to moderate ovarian enlargement.
4. Hemoperitoneum.
5. There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for ovulation induction; however, a causal relationship has not been established.

No local injection site reactions were observed following administration of BRAVELLE™; however, pain and irritation at the injection site were statistically significantly less frequent with BRAVELLE™ than with comparator, recombinant hFSH.

DRUG INTERACTIONS

Drug-Drug Interactions

No drug/drug interaction studies have been conducted for BRAVELLE™ (Urofollitropin for Injection, Purified) in humans.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Infertile patients with oligo-anovulation:

The dose of BRAVELLE™ (Urofollitropin for Injection, Purified) to stimulate development of ovarian follicles must be individualized for each patient. The lowest dose consistent with achieving good results based on clinical experience and reported clinical data should be used.

Recommended Dose and Dosage Adjustment

Infertile patients with oligo-anovulation/ Ovulation Induction

The recommended initial dose of BRAVELLE™ for patients who have received GnRH agonist or antagonist pituitary suppression is 150 IU daily for the first 5 days of treatment. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results), subsequent dosing should be adjusted according to individual patient response.

Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of BRAVELLE™ should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended.

If patient response to BRAVELLE™ is appropriate, hCG (5000 to 10,000 USP units) should be given one day following the last dose of BRAVELLE™. The hCG should be withheld if the serum estradiol is greater than 2000 pg/mL, if the ovaries are abnormally enlarged or if abdominal pain occurs, and the patient should be advised to refrain from intercourse. These precautions may reduce the risk of Ovarian Hyperstimulation Syndrome and multiple gestations. Patients should be followed closely for at least 2 weeks after hCG administration. If there is inadequate follicle development or ovulation without subsequent pregnancy, the course of treatment with BRAVELLE™ may be repeated. The couple should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG until ovulation becomes apparent from the indices employed for the determination of progestational activity. In the light of the foregoing indices and parameters mentioned, it should become obvious that, unless a physician is willing to devote considerable time to these patients and be familiar with and conduct the necessary laboratory studies, he/she should not use BRAVELLE™.

Assisted Reproductive Technologies (ART)/*In Vitro* Fertilization (IVF):

The recommended initial dose of BRAVELLE™ (Urofollitropin for Injection, Purified) for patients who have received GnRH agonist or antagonist pituitary suppression is 225 IU for the first 5 days of treatment. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results), subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of BRAVELLE™ given should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended.

Once adequate follicular development is evident, hCG (5000-10,000 USP units) should be administered to induce final follicular maturation in preparation for oocyte retrieval. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of therapy. This should reduce the chance of developing OHSS.

Administration

Dissolve the contents of one or more vials of BRAVELLE™ (Urofollitropin for Injection, Purified) in one mL sterile saline for injection, USP and **ADMINISTER SUBCUTANEOUSLY OR INTRAMUSCULARLY** immediately. Any unused reconstituted material should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For patients requiring a single injection from multiple vials of BRAVELLE™, up to 6 vials can be reconstituted with 1 mL of Sterile Saline for Injection, USP. This can be accomplished by reconstituting a single vial. Then draw the entire contents of the first vial into a syringe, and inject the contents into a second vial of lyophilized BRAVELLE™. Gently swirl the second vial and check to make sure that the solution is clear and free of particles. This step can be repeated with 4 additional vials for a total of up to 6 vials of lyophilized BRAVELLE™ into 1 mL of diluent.

The injection site should be swabbed with a disinfectant to remove any surface bacteria. Clean about two inches around the point where the needle will go in and let the disinfectant dry at least one minute before proceeding.

Subcutaneous administration

The recommended sites for subcutaneous injection are either side of the lower abdomen (around the navel) in alternating fashion with the actual injection site varied a little with each injection. Pinch up a large area of skin between the finger and thumb. The needle should be inserted at the base of the pinched-up skin at a 45º angle. Subcutaneous injection of BRAVELLE™ into the thigh is not recommended unless the lower abdomen is not usable because of scarring, surgical deformity or other medical conditions. Subcutaneous injection of BRAVELLE™ may be carried out by patients or their partners, provided proper instructions are given by the physician. Self-administration of BRAVELLE™ should only be performed by patients who are well motivated, adequately trained and with access to expert advice.

Intramuscular administration

The best site for intramuscular administration is the upper outer quadrant of the buttock muscle near the hip. The area contains few blood vessels and major nerves. Stretching the skin helps the needle to go in more easily and pushes the tissue beneath the skin out of the way. This helps the solution to disperse correctly. The needle should be inserted right up to the hilt at an angle of 90º to the skin surface. Pushing in with a quick thrust causes the least discomfort.

Drug Abuse and Dependence

There have been no reports of abuse or dependence with follitropins.

OVERDOSAGE

Aside from possible ovarian hyperstimulation and multiple gestations (see WARNINGS AND PRECAUTIONS), little is known concerning the consequences of acute overdosage with BRAVELLE™ (Urofollitropin for Injection, Purified).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

BRAVELLE™ (Urofollitropin for Injection, Purified) is a highly purified preparation of human follicle stimulating hormone (hFSH) extracted from the urine of postmenopausal women. Human FSH consists of two non-covalently linked glycoproteins designated as the α and β subunits. The alpha subunit has 92 amino acids of which two are modified by attachment of carbohydrates. The β subunit has 111 amino acids of which two are modified by attachment of carbohydrates. BRAVELLE™ is biologically standardized for FSH activity in terms of the Second International Reference Preparation for Human Menopausal Gonadotropins established in September 1964 by the Expert Committee on Biological Standards of the World Health Organization.

Follicle Stimulating Hormone (FSH) is essential for normal female and male gamete growth and maturation, and gonadal steroid production. Deficiencies in the endogenous production of FSH may lead to infertility. FSH is critical at the onset and duration of follicular development, and consequently for the timing and number of follicles reaching maturity in females. The primary action of follitropin in women with gonadal dysfunction is the stimulation of follicular development and steroid production. Follitropin may also be used to promote multiple follicular development in medically assisted reproduction programs. In order to induce ovulation, in the absence of an endogenous luteinizing hormone (LH) surge, human chorionic gonadotropin (hCG) must be given after follitropin administration once follicular maturation has occurred.

Pharmacokinetics

Single doses of 225 IU and multiple daily doses (7 days) of 150 IU of FSH were administered to healthy volunteer female subjects while their endogenous FSH was suppressed. Serum FSH concentrations were determined in sixteen subjects who received FSH subcutaneously (SC) and 13 who received the drug intramuscularly (IM). Based on the steady state ratio of FSH C_{max} and AUC, SC and IM administration of FSH were not bioequivalent. Multiple doses of FSH IM resulted in C_{max} and AUC of 77.7% and 81.8% compared to multiple doses of FSH SC which may result in higher dosage used in IM.

The FSH pharmacokinetic parameters for single and multiple dose BRAVELLE™, administered SC and IM are in Table 4.

Table 4
FSH Pharmacokinetic Parameters Following BRAVELLE™ Administration

	Single Dose (225 IU)		Multiple dose X 7 (150 IU)	
Pharmacokinetic Parameters	**SC**	**IM**	**SC**	**IM**
C_{max} (mIU/mL)	6.0 (1.7)	8.8 (4.5)	14.8 (2.9)	11.5 (2.9)
T_{max} (hrs)	20.5 (7.7)	17.4 (12.2)	9.6 (2.1)	11.3 (8.4)
AUC_{abs} (mIU.hr/mL)	379 (111)	331 (179)	234.7 (77.0)	192.1 (52.3)
$T_{1/2}$ (hrs)	31.8	37	20.6	15.2
K_{el} (L/min)	0.0218	0.0209	0.0336	0.0457
V (mL)	16835.6 (74.9)	29936.7 (15353.7)	21168.8 (3151.1)	16601.9 (4296.7)
K_a(hr-1)	0.0500 (0.0231)	0.1408 (0.1227)	0.0905 (0.0383)	0.0358 (0.0108)

Absorption

The maximum plasma concentration of FSH was attained at 20.5 and 17.4 hours following SC and IM single dose administration, respectively. However, following multiple dosing, it was attained at approximately 10 hours following both routes of administration.

Distribution

Human tissue or organ distribution of FSH has not been studied for BRAVELLE™ .

Metabolism

Metabolism of FSH has not been studied for BRAVELLE™ in humans.

Excretion

The mean elimination half-lives of FSH for SC and IM single dosing are 31.8 and 37 hours, respectively. However, following multiple dosing (x 7 days) they are 20.6 and 15.2 hours for SC and IM, respectively.

STORAGE AND STABILITY

Store at 15º - 25ºC. Protect from light.

Reconstituted Solutions

Use immediately after reconstitution. Discard unused material.

SPECIAL HANDLING INSTRUCTIONS

No special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Each vial of BRAVELLE™ (Urofollitropin for Injection, Purified) contains 75 International Units (IU) of follicle stimulating hormone (FSH) activity, plus 20 mg of lactose as the monohydrate and 0.005 mg tween in a sterile, lyophilized form. The final product contains sodium phosphate buffer (sodium phosphate dibasic and phosphoric acid). BRAVELLE™ contains 1-2% luteinizing hormone (LH) activity based on bioassay. Human Chorionic Gonadotropin (hCG) is not detected in BRAVELLE™. BRAVELLE™is administered by subcutaneous or intramuscular injection.

Dosage Forms/Packaging

BRAVELLE™ (Urofollitropin for Injection, Purified) 75 IU FSH activity, is available in vials as a sterile, lyophilized, white to off-white powder or pellet.

Each vial is available with an accompanying vial of sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP.

BRAVELLE™ is supplied as:

Box of 5 vials + 5 vials diluent.
Box of 100 vials + 100 vials diluent.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Purified urofollitropin
Chemical Name:	Human follicle stimulating hormone
Structural Formula:	Purified urofollitropin is a heterodimer consisting of α and β subunits, combined by non-covalent bonds
Molecular Weight:	Between 45,000 and 52,000 daltons
Physical Form:	Off-white, amorphous powder cake
Solubility:	Very soluble in water and in high concentration salt-water-ethanol solutions

CLINICAL TRIALS

Efficacy results from three randomized, active controlled, multi-center studies are summarized in Tables 5 and 6. Two studies were conducted for *In Vitro* Fertilization (IVF) and one study for Ovulation Induction (OI).

Assisted Reproductive Technologies (ART)/ In Vitro Fertilization

Two randomized, controlled IVF studies were conducted. Patients underwent pituitary suppression with GnRH agonist before being randomized to BRAVELLE™ SC, BRAVELLE™ IM or a commercial recombinant FSH product administered SC. A total of 297 were randomized of whom 179 received BRAVELLE™ starting at a dose of 225 IU daily for 5 days. This was followed by individual titration of the dose from 75 to 450 IU daily based on ultrasound and estradiol (E_2) levels. The total duration of dosing did not exceed 12 days. Results are summarized in Table 5 for the intent-to-treat population.

Study 1

BRAVELLE™ administered SC and IM in terms of the primary efficacy variable of oocytes retrieved per patient showed no statistically significant differences in either the intent-to-treat or primary efficacy responder (received hCG) populations when compared to the recombinant FSH. A strong numerical trend in favor of BRAVELLE™ SC compared to recombinant FSH SC for chemical, clinical and continuing pregnancies was demonstrated in both intent-to-treat and primary efficacy responder analyses. BRAVELLE™ IM required slightly higher doses, but this did not correlate with a different safety profile

or a clinically significant longer duration of treatment. Pregnancy rates with BRAVELLE™ SC and IM treatment groups for one cycle therapy were excellent compared to historical and published data for various follitropins. BRAVELLE™ SC and IM showed superior local tolerance at the injection site compared to recombinant FSH.

Study 2

BRAVELLE™ SC showed no statistically significant differences in either the intent-to-treat or primary efficacy responder (received hCG) in terms of the primary efficacy variable of oocytes retrieved per patient when compared to recombinant FSH SC. BRAVELLE™ SC showed similar numerical results for chemical, clinical and continuing pregnancies in both the intent-to-treat and primary responder patient populations compared to recombinant FSH. BRAVELLE™ SC showed superior local tolerance at the injection site compared to recombinant FSH SC.

TABLE 5
EFFICACY OUTCOME BY TREATMENT GROUP FOR IVF STUDIES
(one cycle of treatment)

Parameter	Study 1			Study 2	
	BRAVELLE™ SC n=60	BRAVELLE™ IM n=59	Recombinant FSH n=58	BRAVELLE™ SC n=60	Recombinant FSH SC n=60
Total oocytes retrieved per patient (SD)	13.3 (7.9)	12.2 (7.8)	13.1 (8.7)	11.8 (6.3)	11.9 (6.9)
Mature oocytes retrieved per patient (SD)	9.9 (5.7)	8.7 (5.5)	9.5 (5.6)	9.0 (5.7)	9.2 (6.0)
Patients with oocyte retrieval (%)	56 (93.3)	55 (93.2)	56 (96.6)	57 (95.0)	59 (98.3)
Patients with embryo transfer (%)	54 (90.0)	51 (86.4)	55 (94.8)	57 (95.0)	58 (96.7)
Patients with chemical pregnancy (%)	30 (50.0)	23 (39.0)	20 (34.5)	28 (46.6)	30 (50.0)
Patients with clinical pregnancy (%)	26 (43.3)	19 (32.2)	18 (31.0)	25 (41.7)	27 (45.0)
Patients with continuing pregnancy (%)	25 (41.7)	19 (32.2)	17 (29.3)	23 (38.3)	27 (45.0)

Ovulation Induction

In the one randomized, controlled ovulation induction study, patients underwent pituitary suppression with GnRH agonist before being randomized to BRAVELLE™ SC, BRAVELLE™ IM or commercial recombinant FSH product administered SC. A total of 111 oligo-anovulatory patients were randomized of whom 72 received BRAVELLE™ starting at a dose of 150 IU BRAVELLE™ daily for 5 days. This was followed by individual titration of the dose from 75 to 450 IU daily based on ultrasound and estradiol (E_2) levels. The total duration of dosing did not exceed 12 days. Results for the intent-to-treat population are summarized in Table 6.

BRAVELLE™ SC or IM were equal in effectiveness to recombinant FSH for ovulation induction in oligo-anovulatory down-regulated patients in the study. Pregnancy rates were also equivalent. There were a few significant differences favouring recombinant FSH over BRAVELLE™ SC or IM for the secondary efficacy variables of meeting hCG criteria and receiving hCG, but these pharmacological differences were small and did not translate into differences in clinical outcomes. The mean dose and duration of treatment with BRAVELLE™IM were slightly more than those for BRAVELLE™ SC and recombinant FSH SC. BRAVELLE™IM or SC demonstrated excellent and equivalent safety and local tolerance.

TABLE 6
EFFICACY OUTCOME BY TREATMENT GROUP IN OVULATION INDUCTION STUDY
(one cycle of treatment)

Parameter	BRAVELLE™ SC n=35	BRAVELLE™ IM n=37	Recombinant FSH SC n=38
Ovulation (%)	25 (69.4)	26 (70.3)	30 (78.9)
Received hCG (%)	26 (72.2)	28 (75.7)	35 (92.1)
Peak serum E_2 (pg/mL) (SD)	990.9 (696.2)	893.2 (815.2)	1109.0 (788.9)
Patients with chemical pregnancy (%)	11 (30.6)	8 (21.6)	13 (34.2)
Patients with clinical pregnancy (%)	9 (25.0)	7 (18.9)	11 (28.9)
Patients with continuing pregnancy (%)	9 (25.7)	7 (18.9)	10 (26.3)

- Chi-Square Test - significant for BRAVELLE™ SC vs. Recombinant hFSH SC

PHARMACOLOGY

No preclinical pharmacology studies were conducted with BRAVELLE™ (Urofollitropin for Injection, Purified), since the pharmacologic actions of human gonadotropins are well known. Observations made in two single-dose studies, conducted to assess the overall toxicological effects in female Sprague Dawley CD rats and female Beagles confirmed the pharmacological activity of Purified urofollitropin in showing an increase in the number and size of ovarian follicles following subcutaneous administration of the compound at doses of 4 to 400 IU/kg. In a single-dose toxicity study in Beagle dogs, subcutaneous administration of 4, 40 and 400 IU/kg of Purified urofollitropin did not elicit any effects on cardiovascular parameters such as blood pressure, heart rate or ECG readings.

TOXICOLOGY

Two studies were conducted to assess the overall toxicological effects of single doses of Purified urofollitropin administered subcutaneously to female Sprague Dawley CD rats and female Beagle dogs. Another study was conducted in conscious female Beagle dogs to determine whether Purified urofollitropin has any effects on cardiovascular parameters.

Following subcutaneous administration of 4, 40 or 400 IU/kg to Sprague Dawley rats, and 4, 40, or 100 IU/kg to female Beagle dogs, a dose-related increase in the size and number of ovarian follicles was observed. A statistically significant increase in ovarian weight was observed in the highest dose groups of both species (400 IU/kg group in rats and 100 IU/kg group in dogs). No treatment-related adverse effects were observed in either.

In the conscious dog model, no significant cardiovascular (blood pressure, heart rate, mean arterial pressure), physiological or electrophysiological effects were observed at doses up to 100 IU/kg.

Carcinogenesis and Mutagenesis

Long-term toxicity studies in animals have not been performed to evaluate the carcinogenic potential of urofollitropin.

REFERENCES

1. Fein, S.H.S., Cheng, L., Nardi, R.V. *An Open-label, Parallel Group, Single Center Pharmacokinetic Study in Normal Female Subjects Comparing Ferring hFSH™ SC and IM.* Fertility & Sterility 2001; 75(4, Suppl. 1):12S. P-8.

2. Nardi, R.V., Dickey, R.P., Thornton, M. et al. *A Randomized, Open-label, Parallel Group, Multi-center Efficacy Study Comparing Ferring hFSH™ SC, Ferring hFSH™ IM, and Follistim® SC in Female Patients Undergoing In vitro Fertilization.* Fertility & Sterility 2001; 75(4, Suppl. 1):12S. P-13.

3. Nardi, R.V., Feigenbaum, S., Miller, P. et al. *A Randomized, Open-label, Parallel Group, Multi-center Efficacy Study in Oligoanovulatory Patients Comparing Ferring hFSH™ SC and IM, and Follistim® SC for Ovulation Induction*. Fertility & Sterility 2001; 75(4, Suppl. 1):12S. P-14.

PART III: CONSUMER INFORMATION

BRAVELLE™

(Urofollitropin for Injection, Purified)

For Subcutaneous or Intramuscular Injection

This leaflet is part III of a three-part "Product Monograph" published when BRAVELLE™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BRAVELLE™.

Before administration of this medicine, please read this information carefully. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

BRAVELLE™ (Urofollitropin for Injection, Purified) is a highly purified preparation of Follicle Stimulating Hormone (FSH), collected from the urine of menopausal women.

Follicle stimulating hormone (FSH) is a hormone produced by the pituitary gland which helps to develop eggs (follicles) in women's ovaries. About 40% of female infertility disorders are caused by ovulation abnormalities.

BRAVELLE™ is used as a treatment of infertility in women who have not been able to become pregnant because of ovulation problems. It is also used by women enrolled in an assisted fertility program that uses procedures such as *in vitro* fertilization or embryo transfer.

What it does:

In women, FSH is important for the monthly ripening of the follicle, a tiny cyst in the ovary in which the egg cell develops. If the body does not produce enough FSH, infertility may result. In these cases, BRAVELLE™ can be used to make up for the shortage. To determine the right dosage, a daily check may be necessary. Follicle ripening is determined by means of ultrasound, and the amount of estrogens (female hormones) in blood or urine can be measured. When the follicle is big enough, a hormone preparation with a strong hormonal activity is given (human chorionic gonadotropin, hCG). This causes ovulation (release of the egg).

In spite of careful monitoring, often more than one egg cell is released. This increases the chance of having more than one baby.

BRAVELLE™ is only available with your physician's prescription.

When it should not be used:

BRAVELLE™ should **not** be used if you have any of the following conditions:

- Abnormal bleeding of genitals or uterus without known cause
- Uncontrolled adrenal gland or thyroid disease
- Tumours: Brain or sex-hormone-dependent
- Ovarian cyst or enlarged ovaries
- Primary ovarian failure

And/or

- If you suspect you may be pregnant
- If you are breast-feeding

Talk to your physician before taking the medication.

What the medicinal ingredient is:

BRAVELLE ™ contains Follicle Stimulating Hormone (FSH), corresponding to 75 international units (IU) per vial.

What are the important nonmedicinal ingredients:

The important nonmedicinal ingredients are: Lactose monohydrate, Polysorbate 20 (Tween 20), Sodium Phosphate buffer (sodium phosphate dibasic, heptahydrate and phosphoric acid).

What dosage form it comes in:

BRAVELLE™ is available in vials as a sterile, lyophilized, white to off-white powder or pellet.

Each vial is available with an accompanying vial of sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP.

WARNINGS AND PRECAUTIONS

BRAVELLE™ should only be prescribed by a physician who is thoroughly familiar with fertility problems.

Taking any preparation of Follicle Stimulating Hormone puts a woman at risk of producing multiple eggs, which, if fertilized, may lead to multiple births.

BRAVELLE™ is a potent gonadotropic (gonad-stimulating) compound capable of causing Ovarian Hyperstimulation Syndrome (OHSS), characterized by minor enlargement of ovaries and accumulation of fluid in the abdomen, which can cause distention and pain. In rare severe cases, the ovarian enlargement can be massive and result in loss of fluid from the blood. The fluid accumulates in the abdomen, around the lungs and/or the heart, causing pressure on these critical organs. The main symptoms are pain, difficulty breathing, vomiting and diarrhea. Patients suffering from moderate to severe OHSS may need hospitalization.

Before using BRAVELLE™

Before treatment with BRAVELLE™ is considered, the patient has to undergo a thorough gynecological and endocrinological evaluation. This may involve gynecological examination, as well as documentation of ovulation (or lack thereof) by means of daily basal body temperature measurements and other tests.

PROPER USE OF THIS MEDICATION

Usual Dose:

The dose of BRAVELLE™ will be different for each patient. Follow your doctor's directions. Generally, BRAVELLE™ is taken every day for a period of up to 12 days. Once your physician determines that your response has been sufficient to support ovulation, he/she may administer a single dose of hCG by injection.

How to Use BRAVELLE™:

BRAVELLE™ is administered as an injection. Your physician may ask you to administer BRAVELLE™ to yourself. BRAVELLE™ comes in a box containing 2 vials: The active medicine is contained in a vial as a cake of dry powder. The second vial contains a liquid, Sodium Chloride Injection, which is used to dissolve the dry powder. The injections are given slowly under the skin (for instance, the abdominal wall) or into the muscle (for instance, in the buttock near the hip).

In some instances, you or your partner may give the injections. Your doctor will tell you when and how to do this.

If you are using this drug at home:

- Understand and use the proper method of safety. Prepare the medicine, according to instruction given to you by your physician.
- Wash your hands with soap and water and use a clean work area to prepare your injection.
- Make sure you clearly understand and carefully follow your doctor's instructions on how to give yourself an injection, including the proper needle and syringe.
- Do not inject more or less of the medicine than your doctor prescribed.
- Move the site of injection to different areas to prevent skin problems.
- Throw away needles, syringes, bottles and unused medicine after the injection in a safe manner.

Tell your doctor when you use the last dose of BRAVELLE™. Usually a single dose of another hormone, human chorionic gonadotropin (hCG), is given to women taking BRAVELLE™ the day after the last dose of BRAVELLE™. Your doctor will give you this medicine or arrange for you to get it at the right time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Treatment with gonadotropic preparations may lead to unwanted over stimulation of the ovaries. The first symptoms of ovarian stimulation may be noticed as pain in the abdomen, feeling sick or diarrhea. More severe cases may have accumulation of fluid in the abdomen and/or chest, weight gain and the occurrence of blood clots. Contact your doctor without delay if you are experiencing any of these symptoms during treatment or within a few days after the last injection.

If severe abdominal pain, nausea, vomiting and rapid weight gain occur, stop taking BRAVELLE™ and get emergency help immediately.

Check with your doctor as soon as possible if any of the following side effects occur:

Abdominal bloating, diarrhea, flu-like symptoms, such as body aches or pain, coughing, fever, headache, loss of voice, runny nose, unusual tiredness or weakness, nausea, passing of excess gas, vaginal bleeding between menstrual periods, acne, breast pain or tenderness, mood swings, dizziness, painful menstrual periods, redness, pain or swelling at the injection site, sleepiness, vaginal discharge, fainting, light-headedness, migraine headache, nervousness, stomach discomfort, fast, racing heartbeat, itchy skin, loss of appetite, unusual thirst.

Once you stop taking BRAVELLE™ your body may need time to adjust. The length of time this takes depends on the amount of medicine you had used and how long you have used it for. During this period, check with your doctor immediately if you notice any of the following: Severe abdominal pain, nausea, vomiting, rapid weight gain.

HOW TO STORE IT

- This medicine has been prescribed only for your current medical problem. It should not be used for other medical conditions or by other people.
- Keep BRAVELLE™ in the original box in a safe place out of the reach of children.
- Store at 15º - 25ºC. Protect from light.
- The expiry date is printed on the label after "exp:" Do not use after this date.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 866-234-2345
Toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

For more information or help, call **1-800-263-4057**

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