NEW ZEALAND DATA SHEET

1 PRODUCT NAME

OVIDREL® 250 microgram/0.5 mL solution for injection pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OVIDREL is a preparation of chorionic gonadotrophin hormone produced by genetically engineered Chinese hamster ovary (CHO) cells. Each pre-filled pen contains choriogonadotropin alfa (rch) (recombinant human chorionic gonadotrophin hormone) 250 microgram in 0.5 mL.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.

OVIDREL is presented as a sterile liquid, single dose pre-filled pen. Contains no antimicrobial preservative.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OVIDREL is indicated in the treatment of

(i) *Women undergoing superovulation prior to assisted reproductive techniques such as in vitro fertilisation (IVF)*: OVIDREL is administered to trigger final follicular maturation and luteinisation after stimulation of follicular growth.

(ii) *Anovulatory or oligo-ovulatory women*: OVIDREL is administered to trigger ovulation and luteinisation in anovulatory or oligo-ovulatory patients after stimulation of follicular growth.

4.2 DOSE AND METHOD OF ADMINISTRATION

OVIDREL is intended for subcutaneous administration.

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

In comparative clinical trials, administration of a dose of 250 microgram of OVIDREL was as effective as 5000 IU or 10,000 IU of urinary-derived hCG for the Assisted Reproductive Technologies (ART) endpoint of number of oocytes retrieved per patient treated. In an Ovulation Induction (OI) study, 250 microgram of OVIDREL was as effective as 5000 IU of urinary hCG in inducing final follicular maturation and ovulation. Consequently, the following dosing regimen should be applied:

(i) *Women undergoing superovulation prior to assisted reproductive techniques such as in vitro fertilisation (IVF)*:

Initially one pre-filled pen of OVIDREL (250 microgram in 0.5 mL) should be administered 24 to 48 hours after the last administration of an FSH or hMG preparation, i.e. optimal stimulation of follicular growth is achieved.

(ii) *Anovulatory or oligo-ovulatory women*:

Initially one pre-filled pen of OVIDREL (250 microgram in 0.5 mL) should be administered 24 to 48 hours after optimal stimulation of follicular growth is achieved. The patient is recommended to have intercourse on the day of and the day after OVIDREL injection.

OVIDREL 250 microgram is equivalent to approximately 6500 IU of Profasi and adjustment to dosage should be in accord with clinical and biochemical monitoring.

OVIDREL is given as an injection under the skin (subcutaneously), usually near your stomach. OVIDREL is intended to be injected by the patient or their partner.

The patient should be instructed and assisted in learning the procedure and technique of self-injection. Prescribers and dispensors should ensure the patient or their partner have a good understanding of the principles of sterile techniques and have been assessed in their adequacy of injection technique prior to use.

OVIDREL is for single use in one patient only. Discard any residue.

Prescribers and dispensors should take the patient and their partner through the directions on 'How do I use Ovidrel' found in the Consumer Medicine Information.

4.3 CONTRAINDICATIONS

OVIDREL is contraindicated in women who exhibit:

- Prior hypersensitivity to hCG preparations or one of their excipients
- Primary ovarian failure
- Uncontrolled thyroid or adrenal dysfunction
- Uncontrolled tumours of the hypothalamus and pituitary gland
- Ovarian enlargement or cyst due to reasons other than polycystic ovarian disease
- Sex hormone dependent tumours of the reproductive tract and accessory organs
- Fibroid tumours of the uterus incompatible with pregnancy
- Postmenopausal women
- Ovarian, uterine or mammary carcinoma
- Extrauterine pregnancy in the previous 3 months
- Active thromboembolic disorders
- Gynaecological haemorrhages of unknown aetiology.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

To date, there is no clinical experience with OVIDREL in other indications commonly treated with urine derived human chorionic gonadotrophin.

Gonadotrophins, including OVIDREL, should only be used by physicians who are thoroughly familiar with infertility problems and their management.

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, hyperprolactinaemia and pituitary or hypothalamic tumours and appropriate specific treatment given.

Special precautions should be taken before administering OVIDREL to patients with clinically significant systemic disease where pregnancy could lead to a worsening of the condition.

Like other hCG products, OVIDREL is a potent gonadotrophic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) in women with or without pulmonary or vascular complications. Gonadotrophin therapy requires a certain time commitment by physicians and supportive healthcare professionals and requires the availability of appropriate monitoring facilities (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Effects on laboratory tests).

Careful attention should be given to the diagnosis of infertility in candidates for hCG therapy. Prior to therapy with hCG, patients should be informed of the duration of treatment and monitoring of their condition that will be required. The risks of OHSS and multiple births in women and other possible adverse reactions (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) should also be discussed.

Overstimulation of the ovary following hCG therapy

Ovarian enlargement:

Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain may occur in patients treated with FSH and hCG, and generally regresses without treatment within two or three weeks. Careful monitoring of the ovarian response can minimise the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of FSH therapy, choriogonadotropin alfa should not be administered in this course of therapy. This will reduce the risk of development of OHSS.

Ovarian Hyperstimulation Syndrome (OHSS):

OHSS is a medical event distinct from an uncomplicated ovarian enlargement. Severe OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event. It is characterised 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.

Mild manifestations of OHSS include abdominal pain, abdominal discomfort and distension, and enlarged ovaried. Moderate OHSS may traditionally present with nausea, vomiting, diarrhoea, ultrasound evidence of ascites and marked ovarian enlargement. Severe OHSS further includes

symptoms such as severe ovarian enlargement, weight gain, dyspnoea and oliguria. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress and thromboembolic events (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Pulmonary and vascular complications). Very rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events, such as pulmonary embolism, ischaemic stroke or myocardial infarction. 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 OHSS.

OHSS occurred in 4 of 236 (1.7%) patients treated with OVIDREL 250 microgram during clinical trials of ART and 3 of 99 (3.0%) patients in the OI trial. OHSS occurred in 8 of 89 (9.0%) patients who received OVIDREL 500 microgram. Two patients treated with OVIDREL 500 microgram developed severe OHSS.

OVIDREL has not been tested in women considered to be at risk of OHSS, who were withdrawn from the clinical studies prior to hCG administration. Because of this and because 250 microgram OVIDREL may correspond to a dose greater than 5000 IU urinary hCG, OVIDREL should be used with particular caution in women with higher order follicle numbers.

Independent risk factors for developing OHSS include young age, lean body mass, polycystic ovarian syndrome, higher doses of exogenous gonadotrophins, high absolute or rapidly increasing serum oestradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in ART cycles.

In anovulation, the risk of OHSS is increased by a serum oestradiol level > 1500 pg/mL (5400 pmol/L) and more than 3 follicles of 14 mm or more in diameter. In ART, there is an increased risk of OHSS with a serum oestradiol > 3000 pg/mL (11000 pmol/L) and 20 or more follicles of 12 mm or more in diameter. When the oestradiol level is > 5500 pg/mL (20000 pmol/L), and when there are 40 or more follicles in total, it may be necessary to withhold hCG administration.

Adherence to recommended OVIDREL dosage and regimen of administration can minimise the risk of ovarian hyperstimulation. Monitoring of stimulation cycles by ultrasound scans as well as oestradiol measurements are recommended to early identify risk factors.

OHSS may be more severe and more protracted if pregnancy occurs. Therefore, if signs of ovarian hyperstimulation occur, it is recommended that hCG is withheld and the patient is advised to refrain from coitus or use barrier contraceptive methods for at least 4 days.

OHSS develops rapidly; therefore, patients should be followed up for at least two weeks after hCG administration. Most often, OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. If there is evidence that OHSS may be developing prior to hCG administration (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Effects on laboratory tests), the hCG must be withheld.

Embryo transfer should be deferred, and embryos cryopreserved for later transfer if possible, if OHSS is developing.

Mild or moderate OHSS usually resolved spontaneously. If severe OHSS occurs, treatment with gonadotrophins must be stopped, the patient should be hospitalised and appropriate therapy should be started.

Multiple births

As with other hCG products, reports of multiple births have been associated with OVIDREL treatment. In Assisted Reproductive Technologies (ART), the risk of multiple births is related to the number of embryos transferred. In patients undergoing Ovulation Induction (OI), the incidence of multiple pregnancies and births (mostly twins) is increased compared with natural conception. The patient should be advised of the potential risk of multiple births before starting treatment.

To minimise the risk of higher order multiple pregnancy, careful monitoring of ovarian response and adherence to OVIDREL dosage and regimen of administration are recommended. If the size and number of follicles suggest a substantial risk of multiple pregnancy with triplets or more, hCG should be withheld and contraception advised.

Miscarriage

The rate of miscarriage, in both anovulatory patients and women undergoing ART, is higher than that found in the normal population but comparable with the rates observed in women with other fertility problems.

Congenital malformation

The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This could be due to parental factors (e.g. maternal age, genetics), ART procedures and multiple pregnancies.

Pulmonary and vascular complications

As with other hCG products, a potential for the occurrence of arterial thromboembolism exists.

Thromboembolic events

In women with generally recognised risk factors for thromboembolic events, such as personal or family history, treatment with gonadotrophins may further increase the risk. In these women, the benefits of gonadotrophin administration need to be weighed against the risks. It should be noted however, that pregnancy itself as well as OHSS also carry an increased risk of thromboembolic events.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

In most instances, treatment of women with FSH results only in follicular recruitment and development. In the absence of an endogenous LH surge, hCG is given when monitoring of the

patient indicates that sufficient follicular development has occurred. This may be estimated by ultrasound alone or in combination with measurement of serum oestradiol levels. The combination of both ultrasound and serum oestradiol measurement are useful for monitoring the development of follicles, for timing of the ovulatory trigger, as well as for detecting ovarian enlargement and minimising the risk of the OHSS and multiple gestation. It is recommended that the number of growing follicles be confirmed using ultrasonography because serum estrogens do not give an indication of the size or number of follicles.

Human chorionic gonadotrophins can cross react in the radioimmunoassay of gonadotrophins, especially luteinising hormone. Each individual laboratory should establish the degree of cross reactivity with their gonadotrophin assay. Physicians should make the laboratory aware of patients on hCG if gonadotrophin levels are requested.

The clinical confirmation of ovulation, with the exception of pregnancy, is obtained by direct and indirect indices of progesterone production. The indices most generally used are as follows:

1. A rise in basal body temperature
2. Increase in serum progesterone
3. Menstruation following a shift in basal body temperature

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

1. Fluid in the cul-de-sac
2. Ovarian stigmata
3. Collapsed follicle
4. Secretory endometrium

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinically significant drug interactions have been reported during hCG therapy. Following administration, OVIDREL may interfere with the immunological determination of serum / urinary hCG for up to ten days, leading to a false positive pregnancy test.

During OVIDREL therapy, minor thyroid stimulation is possible, of which the clinical relevance is unknown.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Refer to Section 4.1 THERAPEUTIC INDICATIONS.

Use in pregnancy – Pregnancy Category B3

No reproduction studies with recombinant human choriogonadotropin alfa in animals have been performed. No clinical data on exposed pregnancies are available. The potential risk for humans is unknown. OVIDREL should not be used during pregnancy.

Use in lactation.

The potential effects of choriogonadotropin alfa in lactating animals have not been studied. There are no data on the excretion of choriogonadotropin alfa in breast milk. Because many drugs are excreted in human milk, OVIDREL should not be administered to breast feeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

OVIDREL is used to trigger final follicular maturation and early luteinisation after use of ovulation induction drugs. In this context, it is difficult to attribute undesirable effects to any one of the medications used.

In comparative trials with different doses of OVIDREL, the most common side effect was application site disorder, occurring in 14.6% of patients receiving OVIDREL 250 microgram subcutaneously, compared to 28% of patients receiving u-hCG subcutaneously.

All adverse events reported with an incidence of 2% or greater are included for studies 9073, 7927, 7648 and 8209 and all adverse events for study 23286 in the following tables.

Table 1. Adverse Events for Study 9073

System class	250 µg r-hCG (OVIDREL) (n = 44)		5000 IU (Profasi) (n = 40)	
	Number of Patients	Percent Patients (%)	Number of Patients	Percent Patients (%)
Body as a whole	9	20.5	17	42.5
Injection site inflammation	0	0	2	5
Injection site pain	7	15.9	13	32.5
Injection site reaction	2	4.6	4	10.0
Haemic and lymphatic systems				
Ecchymosis	3	6.8	2	5.0
Nervous system	0	0	2	5.0
Hypersthesia	0	0	1	2.5
Twitching	0	0	1	2.5

Table 2. Adverse Events for Study GF 7927

Body System	hCG-treated Patients					
	250 mg r-hCG (n=95)		500 mg r-hCG (n=89)		Profasi (n=96)	
	Patients	Events	Patients	Events	Patients	Events
Gastro-intestinal system disorders	17 (17.9%)	30 (32.3%)	19 (21.3%)	34 (33.7%)	16 (16.7%)	27 (37.5%)
Nausea	8 (8.4%)	8 (8.6%)	13 (14.6%)	15 (14.9%)	8 (8.3%)	8 (11.1%)
Abdominal pain	8 (8.4%)	12 (12.9%)	10 (11.2%)	11 (10.9%)	8 (8.3%)	8 (11.1%)
Vomiting	5 (5.3%)	5 (5.4%)	7 (7.9%)	8 (7.9%)	5 (5.2%)	5 (6.9%)
Reproductive disorders, female	11 (11.6%)	13 (14%)	17 (19.1%)	18 (17.8%)	11 (11.5%)	12 (16.7%)
Ovarian hyperstimulation	3 (3.2%)	4 (4.3%)	8 (9.0%)	8 (7.9%)	3 (3.1%)	3 (4.2%)
Intermenstrual bleeding	2 (2.1%)	2 (2.2%)	4 (4.5%)	4 (4.0%)	4 (4.2%)	4 (5.6%)
Secondary terms post-operative pain	11 (11.6%)	11 (11.8%)	14 (15.7%)	14 (13.9%)	9 (9.4%)	9 (12.5%)
Body as a whole-general disorders	7 (7.4%)	9 (9.7%)	6 (6.7%)	7 (6.9%)	9 (9.4%)	9 (12.4%)
Pain	4 (4.2%)	4 (4.3%)	2 (2.2%)	2 (2.0%)	4 (4.2%)	4 (5.60%)
Central and peripheral nervous system disorders	6 (6.3%)	6 (6.5%)	5 (5.6%)	5 (5.0%)	4 (4.2%)	4 (5.6%)
Headache	3 (3.2%)	3 (3.2%)	3 (3.4%)	3 (3.0%)	1 (1.0%)	1 (1.4%)
Skin and appendage disorders	3 (3.2%)	3 (3.2%)	2 (2.2%)	2 (2.0%)	4 (4.2%)	4 (5.6%)
Rash	3 (3.2%)	3 (3.2%)	1 (1.1%)	1 (1.0%)	1 (1.0%)	1 (1.4%)

Table 3. Adverse Events for Study 7648

System class	250 mg r-hCG (OVIDREL) (n = 97)	5000 IU (Profasi) (n = 93)
	# AEs (# Patients - % Patients)	# AEs (# Patients - % Patients)
Application disorders		

Injection site bruising	7 (7 – 7.2%)	7 (7 – 7.5%)
Injection site inflammation	4 (3 – 3.1%)	19 (19 – 20.4%)
Injection site pain	7 (7 – 7.2%)	26 (22 – 23.7%)

Table 4. Adverse Events for Study 8209

System class	**250 mg r-hCG (OVIDREL) (n = 99)**	**5000 IU (Profasi) (n = 99)**
	# AEs (# Patients - % Patients)	**# AEs (# Patients - % Patients)**
Application disorders		
Injection site bruising	4 (3 – 7.3%)	7 (7 – 14%)
Injection site inflammation	2 (2 – 4.9%)	15 (15 – 30.0%)
Injection site pain	9 (8 – 19.5%)	20 (17 – 34%)
Injection site reaction	3 (3 – 7.3%)	8 (7 – 14%)
Gastrointestinal disorders		
Abdominal pain	2 (2 – 4.9%)	3 (3 - 3.6%)
Abdominal pain lower	-	3 (3 – 6%)
Reproductive disorders - female		
Ovarian cyst	3 (3 – 7.3%)	4 (4 – 8.0%)
OHSS	3 (3 – 7.3%)	-

Table 5. Adverse Events for Study 23286

Body System	**250 mg r-hCG freeze-dried (n=22)**	**250 mg r-hCG liquid (n=23)**
Gastro-intestinal system disorders	4 (18%)	4 (17%)
Mouth ulceration	1 (5%)	1 (4%)
Nausea	3 (14%)	3 (13%)
General disorders and administration site conditions	1 (5%)	3 (13%)
Injection site bruising	0 (0%)	1 (4%)
Pyrexia	0 (0%)	1 (4%)
Rigors	0 (0%)	1 (4%)

Body System	250 mg r-hCG freeze-dried (n=22)	250 mg r-hCG liquid (n=23)
Vessel puncture site haemorrhage	1 (5%)	1 (4%)
Infections and infestations	0 (0%)	2 (9%)
Pyelonephritis nos	0 (0%)	1 (4%)
Upper respiratory tract infections nos	0 (0%)	1 (4%)
Musculoskeletal and connective tissue disorders	1 (5%)	1 (4%)
Groin pain	0 (0%)	1 (4%)
Peripheral swelling	1 (5%)	0 (0%)
Nervous system disorders	4 (18%)	3 (13%)
Headache nos	4 (18%)	3 (13%)
Psychiatric disorders	1 (5%)	1 (4%)
Emotional disturbance nos	1 (5%)	1(4%)
Renal and urinary disorders	1 (5%)	1 (4%)
Loin pain	1 (5%)	1 (4%)
Reproductive system and breast disorders	0 (0%)	2 (9%)
Dysmenorrhoea	0 (0%)	2 (9%)
Respiratory, thoracic and mediastinal disorders	2 (9%)	0 (0%)
Pharyngolaryngeal pain	1 (5%)	0 (0%)
Rhinorrhoea	1 (5%)	0 (0%)

The following complications have been reported after treatment with FSH/choriogonadotropin alfa: ectopic pregnancy, spontaneous abortion, missed abortion, placenta previa, premature birth, ovarian torsion and congenital anomalies including Down's syndrome with atrial septal defect, chromosomal abnormality (47, XXX) and cranial malformation. These complications have previously been reported in patients undergoing infertility treatment with gonadotrophins. Ovarian Hyperstimulation Syndrome (OHSS) was observed in approximately 4% of patients treated with OVIDREL. Severe OHSS was reported in less than 0.5% of patients. Severe OHSS could be complicated in rare cases by haemoperitoneum, acute pulmonary distress, ovarian torsion and thromboembolism.

The following complications have also been reported to occur after treatment with menotropins/hCG: pulmonary and vascular complications (e.g. Thromboembolism), adnexal torsion as a complication of ovarian enlargement, mild to moderate ovarian enlargement and haematoperitoneum. Although these adverse events were not observed, there is the possibility that they may also occur with menotropins/r-hCG.

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter:

Very Common	≥ 1/10
Common	≥ 1/100 to <1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥ 1/10,000 to < 1/1,000
Very Rare	< 1/10,000

Immune system disorders

Very rare: Mild to severe hypersensitivity reactions including rash, anaphylactic reactions and shock

Nervous system disorders

Common: Headache

Vascular disorders

Very rare: Thromboembolism

Gastrointestinal disorders

Common: Abdominal pain, abdominal distension, nausea, vomiting

Uncommon: Abdominal discomfort, diarrhoea

Reproductive system and breast disorders

Common: Mild or moderate OHSS (including associated symptomatology) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Uncommon: Severe OHSS (including associated symptomatology) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

General disorders and administration site conditions

Common: Injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at https://pophealth.my.site.com/carmreportnz/s/

4.9 OVERDOSE

No case of overdosage has been reported. Nevertheless, there is a possibility that Ovarian Hyperstimulation Syndrome (OHSS) may result from an overdosage of OVIDREL (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

For risk assessment and advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Chemical structure

Choriogonadotropin alfa is a water soluble glycoprotein consisting of two non-covalently linked subunits – designated alfa (α) and beta (β) consisting of 92 and 145 amino acids residues, respectively, with carbohydrate moieties linked to ASN-52 and ASN-78 (on alfa subunits) and ASN-13, ASN-30, SER-121, SER- 127, SER-132 and SER-138 (on beta subunit). The chemical formula of the proteins are $C_{437}H_{682}N_{122}O_{134}S_{13}$ [alfa subunit] and $C_{668}H_{1090}N_{196}O_{203}S_{13}$ [beta subunit]. Molecular weight is 70kDa.

The primary structure of the α-subunit of the recombinant human chorionic gonadotrophin (r hCG) is identical to that of the α-subunit of the human chorionic gonadotrophin (hCG), follicle stimulating hormone (FSH) and luteinising hormone (LH). The glycoform pattern of the α subunit of r-hCG is closely comparable to the urinary derived hCG (u-hCG), the differences mainly being due to the branching and sialylation extent of oligosaccharides.

The β-subunit has both O- and N-glycosylation sites and its structure and glycosylation pattern are also very similar to that of u-hCG.

CAS number

CAS number 177073-44-8

Alfa subunit-(CAS-56832-30-5)

Beta subunit-(CAS-56832-34-9)

Mechanism of action

The physicochemical, immunological and biological activities of recombinant hCG are comparable to those of placental and human pregnancy urine-derived hCG. Choriogonadotropin alfa stimulates late follicular maturation and resumption of oocytes meiosis and initiates rupture of the pre-ovulatory ovarian follicle.

Choriogonadotropin alfa, the active component of OVIDREL, is an analogue of LH and binds to the LH/hCG receptor of the granulosa and the theca cells of the ovary to effect these changes in the absence of an endogenous LH surge. In pregnancy, hCG, secreted by the placenta, maintains the corpus luteum after LH secretion decreases and supports continued secretion of oestrogen and

progesterone necessary to support the first trimester of pregnancy. OVIDREL is administered when monitoring of the patient indicates that sufficient follicular development has occurred in response to FSH treatment for ovulation induction.

Clinical trials

The safety and efficacy of OVIDREL have been evaluated in four well-controlled clinical studies in women; three studies for Assisted Reproductive Technologies (ART) and one study for Ovulation Induction (OI).

(a) Assisted Reproductive Technologies (ART)

Study 9073

The safety and efficacy of OVIDREL 250 microgram administered subcutaneously and 5000 IU of an approved urinary-derived hCG product administered intramuscularly were assessed in a randomised, controlled, double-blind, double-dummy, phase III study in infertile women undergoing *in vitro* fertilisation and embryo transfer. Randomisation occurred at the time of hCG administration.

The primary efficacy parameter in this study was the number of oocytes retrieved per patient. 90 patients entered the study, of whom 44 were randomised to receive OVIDREL 250 microgram. The number of oocytes retrieved was similar in all treatment groups. The efficacy of OVIDREL 250 microgram was found to be clinically and statistically equivalent to the urinary derived hCG product for the primary endpoint of the study. The efficacy results (both primary and secondary) for the patients who received OVIDREL 250 microgram are summarised below in Table 6:

Table 6. Efficacy Outcomes of r-hCG and u-hCG in ART (Study 9073)

Parameter	**OVIDREL 250 mg (n=43)**	**u-hCG 5000 IU (n=38)**
Mean number of oocytes retrieved per patient	10.86	10.45
Mean number of mature oocytes retrieved per patient*	9.0	8.27

* Secondary efficacy outcome

The outcomes of the pregnancies are presented below in Table 7.

Table 7. Pregnancy Outcomes of r-hCG and u-hCG in ART (Study 9073)

Parameter	**OVIDREL 250** mg **(n=39)**	**u-hCG 5000 IU (n=36)**
Clinical pregnancies not reaching full term	0 (0%)	3 (42.9%)
*Live births	6 (100%)	4 (57.1%)
Singletons	5 (83.33%)	7 (100%)
Multiple births	1 (16.66%)	1 (14.3%)

* Secondary efficacy outcome

12 of the 44 patients who received hCG reported 13 adverse events after hCG administration. Of the 84 patients, 44 had received 250 microgram of r-hCG and 40 received u-hCG. There was no report of OHSS in this study. Overall, the pattern of adverse events was similar between treatment groups and was consistent with the profile of events reported in this indication. Local tolerance to study drug was also similar and no patient developed antibodies to hCG.

Study 7927

The safety and efficacy of OVIDREL 250 microgram and OVIDREL 500 microgram administered subcutaneously and 10,000 USP Units of an approved urinary-derived hCG product administered intramuscularly were assessed in a randomised, open label, multicentre study in infertile women undergoing *in vitro* fertilisation and embryo transfer. Randomisation occurred at the time of hCG administration.

The primary efficacy parameter in this single cycle study was the number of oocytes retrieved per patient. 297 patients entered the study, of whom 94 were randomised to receive OVIDREL 250 microgram. The number of oocytes retrieved was similar in all treatment groups. The efficacy of OVIDREL 250 microgram and 500 microgram were both found to be clinically and statistically equivalent to the urinary derived hCG product and to each other for the primary endpoint of the study. The efficacy results (both primary and secondary) for the patients who received OVIDREL 250 microgram are summarised below in Table 8:

Table 8. Efficacy Outcomes of r-hCG and u-hCG in ART (Study 7927)

Parameter	**OVIDREL 250 mg (n=94)**	**u-hCG 10000 IU (n=92)**
Mean number of oocytes retrieved per patient	13.60	14.64
*Mean number of mature oocytes retrieved per patient	7.6	9.4

* Secondary efficacy outcome

The outcomes of the pregnancies are presented below in Table 9.

Table 9. Pregnancy Outcomes of r-hCG and u-hCG in ART (Study 7927)

Parameter	**OVIDREL 250 mg (n=33)**	**u-hCG 10000 IU (n=34)**
Clinical pregnancies not reaching full term	4 (12.1%)	5 (15.2%)
*Live births	29 (87.9%)	28 (84.8%)
Singletons	20 (69.0%)	14 (50.0%)
Multiple births	9 (31.0%)	14 (50%)

* Secondary efficacy outcome

132 of the 280 patients who received hCG reported 266 adverse events after hCG administration, including 27 serious adverse events. Of the 132 patients, 44 had received 250 mg of r-hCG, 51 received 500 mg of r-hCG and 37 had received u-hCG. 12 of the serious events occurring after hCG occurred before study completion and 12 occurred during pregnancy resulting from treatment.

Overall, the pattern of adverse events was similar between treatment groups and was consistent with the profile of events reported in this indication. Local tolerance to study drug was also similar and no patient developed antibodies to hCG.

Study 7648

The safety and efficacy of OVIDREL 250 microgram administered subcutaneously versus 5000 IU of an approved urinary derived hCG product administered subcutaneously were assessed in a second, double blind, randomised, multicentre study in infertile women undergoing *in vitro* fertilisation and embryo transfer.

The primary efficacy parameter in this single-cycle study was the number of oocytes retrieved per patient. 205 patients entered the study, of whom 97 received OVIDREL 250 microgram. The efficacy of OVIDREL was found to be clinically and statistically equivalent to that of the approved urinary derived hCG. The efficacy results (both primary and secondary) for the 97 patients who received OVIDREL 250 microgram are summarised below in Table 10.

Table 10. Efficacy Outcomes of r-hCG and u-hCG in ART (Study 7648)

Parameter	**OVIDREL 250 mg (n=97)**	**u-hCG 5000 IU (n=93)**
Mean number of oocytes retrieved per patient	11.4	10.7
*Mean number of mature oocytes retrieved per patient	9.8	7.8

* Secondary efficacy outcome

The outcomes of the pregnancies are presented below in Table 11.

Table 11. Pregnancy Outcomes of r-hCG and u-hCG in ART (Study 7648)

Parameter	**OVIDREL 250 mg (n=32)**	**u-hCG 5000 IU (n=23)**
Clinical pregnancies not reaching term	6 (18.8%)	2 (8.7%)
*Live births	26 (81.2%)	21 (91.3%)
Singletons	18 (69.2%)	13 (61.9%)
Multiple births	8 (30.8%)	8 (38.1%)

* Secondary efficacy outcome

64 of the 190 patients who received hCG reported 97 adverse events after hCG administration, 32 (33%) in the r-hCG group and 65 (67%) in the u-hCG group. There were 11 serious adverse events reported following hCG administration, 5 up to study completion and 6 during pregnancy resulting

from treatment. Overall, the pattern of adverse events was similar between treatment groups and was consistent with the profile of events reported in this indication. Local tolerance to study drug was statistically different between treatment groups (p = 0.0001) in favour of the r-hCG treatment group and no patient developed antibodies to hCG.

(b) Ovulation Induction (OI)

Study 8209

The safety and efficacy of OVIDREL 250 microgram administered subcutaneously versus 5000 IU of an approved urinary derived hCG administered subcutaneously were assessed in a double blind, randomised, multicentre study in anovulatory infertile women.

The primary efficacy endpoint in this single cycle study was the patient ovulation rate. 242 patients entered the study, of whom 99 received OVIDREL 250 microgram. The efficacy of OVIDREL 250 microgram was found to be clinically and statistically equivalent to the approved urinary derived hCG. The efficacy results (both primary and secondary) of those patients who received OVIDREL are summarised below in Table 12.

Table 12. Efficacy Outcomes of r-hCG and u-hCG in OI (Study 8209)

Parameter	**OVIDREL 250 mg (n=99)**	**u-hCG 5000 IU (n=99)**
Ovulation rate	91 (91.9%)	85 (85.9%)
*Clinical pregnancy rate[1]	22 (22.2%)	29 (29.3%)

* Secondary efficacy outcome

[1] Clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heartbeat activity) was detected by ultrasound on day 35-42 after hCG administration

The outcomes of the pregnancies are presented below in Table 13.

Table 13. Pregnancy Outcomes of r-hCG and u-hCG in OI (Study 8209)

Parameter	**OVIDREL 250 ug (n=22)**	**u-hCG 5000 IU (n=29)**
Clinical pregnancies not reaching term	7 (31.8%)	5 (17.2%)
*Live births	15 (68.2%)	20 (68.9%)
Singletons	13 (86.7%)	17 (85%)
Multiple births	2 (13.3%)	3 (15%)

* Secondary efficacy outcome

65 of the 198 patients who received hCG reported 100 adverse events after hCG administration. Of the 100 events, 34 (34%) occurred in 26 patients who had received 250 microgram of r-hCG and 66 (66%) occurred in 39 patients who had received u-hCG. 9 serious adverse events occurred in 7 patients after study completion during pregnancy resulting from treatment. Overall, the pattern of adverse events was similar between treatment groups and was consistent with the profile of events reported in this indication. Local tolerance to study drug was statistically different between treatment groups (p = 0.0015) in favour of the r-hCG treatment group.

Primary Outcomes

Primary Efficacy endpoints of ART studies are shown in Table 14 below.

Table 14. Studies GF 7648, GF 7927, and GF 9073: Number of oocytes retrieved per patient, by study and hCG treatment group.

Statistics	Study GF 7648(a)		Study GF 7927(b)			Study GF 9073	
	hCG Treatment Group		hCG Treatment Group			hCG Treatment Group	
	250 mg r-hCG	5000 IU u-hCG	250 mg r-hCG	500 mg r-hCG	10000 IU u-hCG	250 mg r-hCG	5000 IU u-hCG
n	97	93	94	89	92	43	38
Mean(SEM)	11.6 (0.533)	10.6 (0.558)	13.60 (0.75)	14.64 (0.77)	13.66 (0.77)	10.86 (0.603)	10.4 (0.642)
Median	11.0	10.0	12.5	14.0	13.5	10.0	10.0
Range	(0, 27)	(0, 35)	(3, 37)	(4, 38)	(3,29)	(1,24)	(3,26)
	Treatment Equivalence		Treatment Equivalence			Treatment Equivalence	
	250 mg r-hCG *vs.* u-hCG		500 mg r-hCG *vs.* u-hCG	500 mg r-hCG *vs.* 250mg r-hCG		250 mg r-hCG *vs.* U-hCG	
Mean Difference (SEM)	-0.01 (0.72)		0.98 (1.06)	1.04 (1.06)		0.95 (1.90)	
90% CI for the Mean Difference	(-1.206, 1.183)		(-0.775, 2.729)	(-0.706, 2.781)		(-0.517,2.424)	

(a) A two-way ANCOVA model with treatment and centre effects and number of follicles > 10mm as the covariate was used for all estimates.

(b) A two-way ANCOVA model with treatment and centre effects was used for all estimates.

The studies clearly demonstrate equivalence between 250 microgram r-hCG and 5000 IU u-hCG (studies GF 7648 and GF 9073), and between 250 microgram r-hCG, 500 microgram r-hCG, and 10000 IU u-hCG (study GF 7927) with respect to this end-point.

Primary efficacy end-point of Ovulation Induction study (GF 8209) are shown in Tables 15a and 15b below.

Table 15a. Summary statistics for ovulation: Per Protocol data set

250 mg r-hCG			5000 IU u-hCG			All			
Success (%)	Failure (%)	n	Success (%)	Failure (%)	n	Success (%)	Failure (%)	n	p_r-p_u%
81 (95.3)	4 (4.7)	85	81 (88.0)	11 (12.0)	92	162 (91.5)	15 (8.5)	177	73
Lower limit of one-sided 95% CI -1.9									

Table 15b. Summary statistics for ovulation: All Patients Data set

250 mg r-hCG			5000 IU u-hCG			All			
Success (%)	**Failure (%)**	**n**	**Success (%)**	**Failure (%)**	**n**	**Success (%)**	**Failure (%)**	**n**	**p_r-p_u%**
91 (91.9)	8 (8.1)	99	85 (85.9)	14 (14.1)	99	176 (88.9)	22 (11.1)	198	6.1
Lower limit of one-sided 95% CI			-3.7						

5.2 PHARMACOKINETIC PROPERTIES

Following intravenous administration, choriogonadotropin alfa is distributed to the extra cellular fluid space within a few hours of its injection. There are no indications that choriogonadotropin alfa is metabolised and excreted differently than endogenous hCG. The terminal half-life is slightly longer after subcutaneous injection as compared to intravenous results.

Absorption

Following subcutaneous administration of OVIDREL 250 microgram, maximum serum concentration (121 ± 44 IU/L) is reached after approximately 12 to 24 hours. The mean absolute bioavailability of OVIDREL after subcutaneous injection to healthy female volunteers is about 40%.

Distribution

Following intravenous administration of OVIDREL 250 microgram to healthy down-regulated female volunteers, the serum profile of hCG is described by a two-compartment model with an initial half-life of 4.5 ± 0.5 hours. The volume of the central compartment is 3.0 ± 0.5 L and the steady state volume of distribution is 5.9 ± 1.0 L.

Metabolism/excretion

After intravenous administration of OVIDREL 250 microgram to healthy down-regulated females, the mean terminal half-life is 26.5 ± 2.5 hours and the total body clearance is 0.29 ± 0.04 L/h. One-tenth of the dose is excreted in the urine.

Following subcutaneous administration of OVIDREL, hCG is eliminated from the body with a mean terminal half-life of about 38 hours (37.9 ± 3.6 hours for the freeze-dried preparation and 38.2 ± 5.0 for the liquid formulation).

Bioequivalence of formulations

OVIDREL liquid has been determined to be bioequivalent to OVIDREL freeze-dried formulation based on the statistical evaluation of AUC and C_{max}. A summary of the OVIDREL freeze-dried and liquid pharmacokinetic parameters is presented in Table 16, and a summary of treatment ratios (test/reference) and 90% confidence intervals calculated from the ANOVA is presented in Table 17.

Table 16. Summary of OVIDREL Freeze-Dried and Liquid Pharmacokinetic Parameters

Parameter	C_{max} (mIU/mL)	AUC_{last} (mIU.h/mL)	AUC (mIU.h/mL)	AUC extrapolated (%)	t_{max} (h)
Reference r-hCG Freeze-dried formulation (n=22)					
Mean	129	10210	10480	2.67	24.0
(Min-Max)	(66.0 - 279)	(5627 - 20070)	(5751 - 20460)	(1.13 - 6.31)	(9.00 - 48.0)
Test r-hCG Liquid formulation (n=23)					
Mean	125	10050	10350	2.85	20.0
(Min-Max)	(68.0 - 294)	(5646 - 14850)	(5800 - 15100)	(1.08 - 6.27)	(9.00 - 48.0)

Table 17. Summary of Treatment Ratios (Test/Reference) and 90% Confidence Intervals Calculated from the ANOVA

N=22	Estimated Ratio T/R	Intrasubject CV (%)	90% CI (0.8 - 1.25)
C_{max}	0.9820	27.48	0.8529 -1.1305
AUC_{last}	0.9811	15.18	0.9067 - 1.0615
AUC	0.9814	14.85	0.9085 - 1.0600

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Gene mutation assays (bacteria and mammalian cells *in vitro*) and chromosomal aberration studies (human lymphocytes *in vitro* and mouse bone marrow erythrocytes *in vivo*) showed no evidence of genotoxic effects.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol, methionine, poloxamer, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dihydrate, sodium hydroxide and phosphoric acid (for pH adjustment) and water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

24 months

Information on the shelf life can be found on Medsafe Product Detail. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

OVIDREL should be stored at 2°C to 8°C (Refrigerate. Do not freeze) in its original container. Protect from light.

Prior to use and within its shelf life, OVIDREL pre-filled pen can also be stored below 25˚C for up to 28 days in its original container and protected from light. It must be discarded if not used after these 28 days.

6.5 NATURE AND CONTENTS OF CONTAINER

OVIDREL is supplied in boxes of 1 pre-filled pen.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

OVIDREL is supplied by:

Healthcare Logistics

58 Richard Pearse Drive

Airport Oaks

Auckland

New Zealand

E-mail: medinfo.australia@merckgroup.com

Phone: 0800 426 252

9 DATE OF FIRST APPROVAL

10 March 2011

10 DATE OF REVISION

29 July 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Updated the adverse reactions reporting webpage for New Zealand
4.9	Modification of risk assessment wording in the management of overdose