ULTIWELL INJECTION 1MG
ULTIWELL INJECTION 5MG
Remifentanil Hydrochloride for Injection

QUALITATIVE AND QUANTITATIVE COMPOSITION
Utliwell 1mg:
Each vial contains 1mg remifentanil (as hydrochloride)

Ultiwell 5mg:
Each vial contains 5mg remifentanil (as hydrochloride)

PRODUCT DESCRIPTION
A white or off-white loose block

After reconstitution: drug product become colorless transparent liquid.

PHARMACODYNAMICS
Pharmacotherapeutic group: Opioid anaesthetics, ATC code: N01AH06
Remifentanil is a selective mu-opioid agonist with a rapid onset and very short duration of action. The mu-opioid activity, of remifentanil, is antagonised by narcotic antagonists, such as naloxone.

Neonates/infants (aged less than 1 year):
In young infants and neonates ≤8 weeks of age with an ASA physical status of I-II who were undergoing pyloromyotomy, the efficacy and safety of remifentanil (given as a 0.4 μg/kg/min initial continuous infusion plus supplemental doses or infusion rate changes as needed) was compared with halothane (given at 0.4% with supplemental increases as needed). Maintenance of anaesthesia was achieved by the additional administration of 70% nitrous oxide (N20) plus 30% oxygen. Recovery times were superior in the remifentanil relative to the halothane groups (not significant).

In lower abdominal/urological surgery comparing remifentanil/propofol with remifentanil/sevoflurane, hypotension occurred significantly more often under remifentanil/sevoflurane, and bradycardia occurred significantly more often under remifentanil/propofol. In ENT surgery comparing remifentanil/propofol with desflurane/nitrous oxide, a significantly higher heart rate was seen in patients receiving desflurane/nitrous oxide compared with remifentanil/propofol and with baseline values.

Assays of histamine have shown no elevation in histamine levels after administration of remifentanil in bolus doses up to 30 micrograms/kg.

PHARMACOKINETICS
ABSORPTION
Blood concentrations of Utliwell are proportional to the dose administered throughout the recommended dose range. For every 0.1 micrograms/kg/min increase in infusion rate, the blood concentration of Utliwell will rise 2.5 nanograms/ml.

DISTRIBUTION
The central volume of distribution is 100 ml/kg, and the steady-state volume of distribution is 350 ml/kg.
Remifentanil is approximately 70% bound to plasma proteins.

METABOLISM
Remifentanil is an Esterase Metabolised Opioid that is susceptible to metabolism by non- specific blood and tissue esterases. The metabolism of remifentanil results in the formation of an essentially

inactive carboxylic acid metabolite (1/4600th as potent as remifentanil). The half-life of the metabolite in healthy adults is 2 hours. Approximately 95% of Utliwell is recovered in the urine as the carboxylic acid metabolite. Remifentanil is not a substrate for plasmacholinesterase.

ELIMINATION
Following administration of the recommended doses of Utliwell, the effective biological half-life is 3 to 10 minutes. The average clearance of remifentanil in young healthy adults is 40 ml/min/kg.

SPECIAL PATIENT POPULATIONS
• **Cardiac anaesthesia**
The clearance of remifentanil is reduced by up to 20% during hypothermic (28°C) cardiopulmonary bypass. A decrease in body temperature lowers elimination clearance by 3% per °C.

• **Renal impairment**
The rapid recovery from remifentanil-based sedation and analgesia is unaffected by renal status. The pharmacokinetics of Utliwell are not significantly changed in patients with varying degrees of renal impairment even after administration for up to 3 days in the intensive care setting.
The clearance of the carboxylic acid metabolite is reduced in patients with renal impairment. In intensive care patients with moderate/severe renal impairment, the concentration of the carboxylic acid metabolite may exceed 250-fold the level of remifentanil at steady-state in some patients. Accumulation of the metabolite does not result in clinically relevant mu-opioid effects even after administration of Utliwell infusions for up to 3 days in these patients.
There is no evidence that remifentanil is extracted during renal replacement therapy. The carboxylic acid metabolite is extracted during haemodialysis by at least 30%.

• **Hepatic impairment**
The pharmacokinetics of Utliwell are not changed in patients with severe hepatic impairment awaiting liver transplant, or during the anhepatic phase of liver transplant surgery. Patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of remifentanil. These patients should be closely monitored and the dose of Utliwell should be titrated to the individual patient need.

• **Paediatric patients**
In paediatric patients 5 days to 17 years of age, the average clearance and steady state volume of distribution of remifentanil are increased in younger children and decline to young healthy adult values by age 17. The half-life of remifentanil is not significantly different in neonates suggesting that changes in analgesic effect after changes in infusion rate of Utliwell should be rapid and similar to that seen in young healthy adults. The pharmacokinetics of the carboxylic acid metabolite in paediatric patients 2 to 17 years of age are similar to those seen in adults after correcting for differences in body weight.

• **Elderly**
The clearance of remifentanil is slightly reduced (approximately 25%) in elderly patients (greater than 65 years) compared to young patients. The pharmacodynamic activity of remifentanil increases with increasing age.
Elderly patients have a remifentanil EC50 for formation of delta waves on the electroencephalogram (EEG) that is 50% lower than young patients; therefore, the initial dose of Utliwell should be reduced by 50% in elderly patients and then carefully titrated to meet the individual patient need.

• **Placental and milk transfer**
The concentration of remifentanil in foetal blood was approximately 50% of that in maternal blood. The foetal arterio-venous ratio of remifentanil concentrations was approximately 30% suggesting metabolism of remifentanil in the neonate.

INDICATION

Utliwell is indicated as an analgesic agent for use during induction and/or maintenance of general anaesthesia during surgical procedures including cardiac surgery, and also for continuation of analgesia into the immediate post-operative period under close supervision, during transition to longer acting analgesia.

Utliwell is indicated for provision of analgesia and sedation in mechanically ventilated intensive care patients.

RECOMMENDED DOSAGE

Ultiwell should be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by persons specifically trained in the use of anaesthetic drugs and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation. Such training must include the establishment and maintenance of a patent airway and assisted ventilation.

Continuous infusions of Ultiwell must be administered by a calibrated infusion device into a fast-flowing i.v. line or via a dedicated i.v. line. This infusion line should be connected at, or close to, the venous cannula and primed, to minimise the potential dead space (*see Instructions for Use/ Handling* for additional information, including tables with examples of infusion rates by body weight to help titrate Ultiwell to the patient's anaesthetic needs).

Care should be taken to avoid obstruction or disconnection of infusion lines and to adequately clear the lines to remove residual Ultiwell after use. (*see Warnings and Precautions)*

Ultiwell is for intravenous use only and must not be administered by epidural or intrathecal injection (*see Contraindications*).

Ultiwell for injection is stable for 24 hours at room temperature (25oC) after reconstitution and further dilution to 20 to 250 micrograms/ml (50 micrograms/ml is the recommended dilution for adults and 20 to 25 micrograms/ml for paediatric patients aged 1 year and over) with one of the following i.v. fluids listed below:

− sterilised water for injections

− 5% dextrose injection

− 5% dextrose and 0.9% sodium chloride injection

− 0.9% sodium chloride injection

- 0.45% sodium chloride injection

(*see Instructions for Use/ Handling* for additional information, including tables to help titrate Ultiwell to the patient's anaesthetic needs).

The administration of Ultiwell during general anaesthesia must be individualised based on the patient's response. It is not recommended for use as the sole agent in general anaesthesia.

General Anaesthesia

Adults

The following table summarises the starting infusion rates and dose range:

DOSING GUIDELINES FOR ADULTS

INDICATION	BOLUS INFUSION (micrograms/kg)	CONTINUOUS INFUSION (micrograms/kg/min)	
		Starting Rate	Range
Induction of anaesthesia in ventilated patients	1(give over not less than 30 seconds)	0.5 to 1	–
Maintenance of anaesthesia in ventilated patients			
• Nitrous oxide (66%)	0.5 to 1	0.4	0.1 to 2
• Isoflurane (starting dose 0.5MAC)	0.5 to 1	0.25	0.05 to 2

• Propofol (Starting dose 100 micrograms/kg/min)	0.5 to 1	0.25	0.05 to 2
Spontaneous ventilation anaesthesia	Not recommended	0.04	0.025 to 0.1
Continuation of analgesia into the immediate post-operative period	Not recommended	0.1	0.025 to 0.2

When given by bolus injection at induction Ultiwell should be administered over not less than 30 seconds.

At the doses recommended above, Ultiwell significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid excessive depth of anaesthesia (*see Concomitant medication* in this section). No data are available for dosage recommendations for simultaneous use of other hypnotics with Ultiwell.

Induction of anaesthesia:

Ultiwell should be administered with a hypnotic agent, such as propofol, thiopentone, or isoflurane, for the induction of anaesthesia. Ultiwell can be administered at an infusion rate of 0.5 to 1 micrograms/kg/min with or without an initial bolus infusion of 1 microgram/kg over not less than 30 seconds. If endotracheal intubation is to occur more than 8 to 10 minutes after the start of the infusion of Ultiwell, then a bolus infusion is not necessary.

Maintenance of anaesthesia

After endotracheal intubation, the infusion rate of Ultiwell should be decreased, according to anaesthetic technique, as indicated in the above table. Due to the fast onset and short duration of action of remifentanil, the rate of administration during anaesthesia can be titrated upward in 25% to 100% increments or downward in 25% to 50% decrements, every 2 to 5 minutes to attain the desired level of mu-opioid response. In response to light anaesthesia, supplemental bolus infusions may be administered every 2 to 5 minutes.

Anaesthesia in spontaneously breathing anaesthetised patients with a secured airway (e.g. laryngeal mask anaesthesia)

In spontaneously breathing anaesthetised patients with a secured airway respiratory depression is likely to occur. Special care is needed to adjust the dose to the patient requirements and ventilatory support may be required. The recommended starting infusion rate for supplemental analgesia in spontaneously breathing anaesthetised patients is 0.04 micrograms/kg/min with titration to effect. A range of infusion rates from 0.025 to

0.1 micrograms/kg/min has been studied. Bolus injections are not recommended in spontaneously breathing anaesthetised patients.

Continuation into the immediate post-operative period

In the event that longer acting analgesia has not been established prior to the end of surgery, Ultiwell may need to be continued to maintain analgesia during the immediate post-operative period until longer acting analgesia has reached its maximum effect.

In ventilated patients, the infusion rate should continue to be titrated to effect.

In patients who are breathing spontaneously, the infusion rate of Ultiwell should initially be decreased to a rate of 0.1 micrograms/kg/min. The infusion rate may then be increased or decreased by not greater than 0.025 micrograms/kg/min every 5 minutes, to balance the patient's level of analgesia and respiratory rate. Ultiwell should only be used in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function, under the close supervision of persons specifically trained in the recognition and management of the respiratory effects of potent opioids.

The use of bolus injections of Ultiwell to treat pain during the post-operative period is not recommended in patients who are breathing spontaneously.

Concomitant medication:

Ultiwell decreases the amounts or doses of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia.

Doses of the following agents used in anaesthesia: isoflurane, thiopentone, propofol and temazepam have been reduced by up to 75% when used concurrently with Ultiwell.

Guidelines for discontinuation

Due to the very rapid offset of action of Ultiwell no residual opioid activity will be present within 5 to 10 minutes after discontinuation. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to or immediately following discontinuation of Ultiwell. Sufficient time must be allowed to reach the maximum effect of the longer acting analgesic. The choice of analgesic should be appropriate for the patient's surgical procedure and the level of post-operative care.

Paediatric patients (1 to 12 years of age)

Induction of anaesthesia

There are insufficient data to make a dosage recommendation.

Maintenance of anaesthesia:

DOSING GUIDELINES FOR MAINTENANCE OF ANAESTHESIA IN PAEDIATRIC PATIENTS (1 to 12 years of age)

CONCOMITANT ANAESTHETIC AGENT	BOLUS INFUSION OF REMIFENTANIL (micrograms/kg)	CONTINUOUS INFUSION OF REMIFENTANIL (micrograms/kg/min)	
		Starting Rate	Typical Maintenance Rates
Nitrous oxide (70%)	1	0.4	0.4 to 3
Halothane (starting dose 0.3MAC)	1	0.25	0.05 to 1.3
Sevoflurane (starting dose 0.3MAC)	1	0.25	0.05 to 0.9
Isoflurane (starting dose 0.5MAC)	1	0.25	0.06 to 0.9

When given by bolus infusion, Ultiwell should be administered over not less than 30 seconds. Surgery should not commence until at least 5 minutes after the start of the Ultiwell infusion, if a simultaneous bolus dose has not been given. Paediatric patients should be monitored and the dose titrated to the depth of analgesia appropriate for the surgical procedure.

Concomitant medication

At the doses recommended above, Ultiwell significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane, halothane and sevoflurane should be administered as recommended above to avoid excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with Ultiwell (*see Dosage and Administration- General Anaesthesia - Adults- Concomitant medication*).

Guidelines for discontinuation

Following discontinuation of the infusion, the offset of analgesic effect of Ultiwell is rapid and similar to that seen in adult patients. Appropriate post-operative analgesic requirements should be anticipated and implemented (*see Dosage and Administration- General Anaesthesia- Adults- Guidelines for discontinuation*).

Neonates/infants (aged less than 1 year)

The pharmacokinetic profile of Ultiwell in neonates/infants (aged less than 1 year) is comparable to that seen in adults after correction for body weight differences. However, there are insufficient clinical data to make dosage recommendations for this age group.

Cardiac anaesthesia

- **Adults**

DOSING GUIDELINES FOR CARDIAC ANAESTHESIA

INDICATION	BOLUS INFUSION OF REMIFENTANIL (micrograms/kg)	CONTINUOUS INFUSION OF REMIFENTANIL (micrograms/kg/min)	
		Starting Rate	Typical Infusion Rates
Intubation	Not recommended	1	_
Maintenance of anaesthesia			
• Isoflurane (starting dose 0.4MAC)	0.5 to 1	1	0.003 to 4
• Propofol (Starting dose 50 micrograms/kg/min)	0.5 to 1	1	0.01 to 4.3
Continuation of post-operative analgesia, prior to extubation	Not recommended	1	0 to 1

Induction period of anaesthesia:

After administration of hypnotic to achieve loss of consciousness, Ultiwell should be administered at an initial infusion rate of 1 microgram/kg/min. The use of bolus injections of Ultiwell during induction in cardiac surgical patients is not recommended. Endotracheal intubation should not occur until at least 5 minutes after the start of the infusion.

Maintenance period of anaesthesia:

After endotracheal intubation the infusion rate of Ultiwell should be titrated according to patient need. Supplemental bolus doses may also be given as required. High risk cardiac patients, such as those with poor ventricular function, should be administered a maximum bolus dose of 0.5 micrograms/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (*see Pharmacokinetics*).

Concomitant medication:

At the doses recommended above, Ultiwell significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with Ultiwell (*see Dosage and Administration- General Anaesthesia- Adults- Concomitant medication*)..

Continuation of post-operative analgesia prior to extubation

It is recommended that the infusion of Ultiwell should be maintained at the final intra- operative rate during transfer of patients to the post-operative care area. Upon arrival into this area the patient's level of analgesia and sedation should be closely monitored and the Ultiwell infusion rate adjusted to meet the individual patient's requirements.

Guidelines for discontinuation

Prior to discontinuation of Ultiwell, patients must be given alternative analgesic and sedative agents at a sufficient time in advance. The choice and dose of agent(s) should be appropriate for the patient's level of post-operative care (*see Dosage and Administration- General Anaesthesia- Adults- Guidelines for discontinuation*).

It is recommended that the Ultiwell infusion is discontinued by reducing the infusion rate by 25% decrements in at least 10 minutes intervals until the infusion is discontinued.

During weaning from the ventilator, the Ultiwell infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

It is recommended that haemodynamic changes such as hypertension and tachycardia should be treated with alternative agents as appropriate.

• Paediatric Patients

There are insufficient data to make a dosage recommendation for use during cardiac surgery.

Use in Intensive Care

Ultiwell can be initially used alone for the provision of analgesia and sedation in mechanically ventilated intensive care patients.

It is recommended that Ultiwell is initiated at an infusion rate of 0.1 micrograms/kg/min to 0.15 micrograms/kg/min. The infusion rate should be titrated in increments of 0.025 micrograms/kg/min to achieve the desired level of analgesia and sedation. A period of at least 5 minutes should be allowed between dose adjustments. The level of analgesia and sedation should be carefully monitored, regularly reassessed and the Ultiwell infusion rate adjusted accordingly. If an infusion rate of 0.2 micrograms/kg/min is reached and the desired level of sedation is not achieved, it is recommended that dosing with an appropriate sedative agent is initiated. The dose of sedative agent should be titrated to obtain the desired level of sedation. Further increases to the Ultiwell infusion rate in increments of 0.025 micrograms/kg/min may be made if additional analgesia is required.

The following table summarises the starting infusion rates and typical dose range for provision of analgesia and sedation in individual patient:

DOSING GUIDELINES FOR USE WITHIN THE INTENSIVE CARE SETTING

CONTINUOUS INFUSION micrograms/kg/min	
Starting Rate	Range
0.1 to 0.15	0.006 to 0.74

Bolus doses of Ultiwell are not recommended in the intensive care setting.

The use of Ultiwell will reduce the dosage requirement of any concomitant sedative agents. Typical starting doses for sedative agents, if required, are given below:

RECOMMENDED STARTING DOSE OF SEDATIVE AGENTS, IF REQUIRED

Sedative Agent	Bolus (mg/kg)	Infusion (mg/kg/h)
Propofol	Up to 0.5	0.5
Midazolam	Up to 0.03	0.03

To allow separate titration of the respective agents, sedative agents should not be prepared as one mixture in the same infusion bag.

Additional analgesia for ventilated patients undergoing stimulating procedures
An increase in the existing Ultiwell infusion rate may be required to provide additional analgesic cover for ventilated patients undergoing stimulating and/or painful procedures such as endotracheal suctioning, wound dressing and physiotherapy. It is recommended that an Ultiwell infusion rate of at least 0.1 micrograms/kg/min should be maintained for at least 5 minutes prior to the start of the stimulating procedure. Further dose adjustments may be made every 2 to 5 minutes in increments of 25% to 50% in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0.25 micrograms/kg/min, maximum 0.75 micrograms/kg/min, has been administered for provision of additional anaesthesia during stimulating procedures.

Guidelines for discontinuation
Prior to discontinuation of Ultiwell, patients must be given alternative analgesic and sedative agents at a sufficient time in advance. The appropriate choice and dose of agent(s) should be anticipated and implemented.
In order to ensure a smooth emergence from a remifentanil-based regimen it is recommended that the infusion rate of Ultiwell is titrated in stages to 0.1 micrograms/kg/min over a period up to 1 hour prior to extubation.

Following extubation, the infusion rate should be reduced by 25% decrements in at least 10 minutes intervals until the infusion is discontinued. During weaning from the ventilator the

Ultiwell infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

- **Paediatric intensive care patients**

There are no data available on use in paediatric patients.

OTHER POPULATIONS

- **Elderly (over 65 years of age)**

GENERAL ANAESTHESIA

The initial starting dose of Ultiwell administered to patients over 65 should be half the recommended adult dose and then titrated to individual patient need as an increased sensitivity to the pharmacological effects of Ultiwell has been seen in this patient population.

This dose adjustment applies to use in all phases of anaesthesia including induction, maintenance and immediate post-operative analgesia.

CARDIAC ANAESTHESIA:

No initial dose reduction is required. (see *Dosage and Administration- Cardiac Anaesthesia- Dosing guidelines*).

INTENSIVE CARE:

No initial dose reduction is required. (see *Dosage and Administration- Use in Intensive Care)*.

- **Obese patients**

It is recommended that for obese patients the dosage of Ultiwell should be reduced and based upon ideal body weight as the clearance and volume of distribution of remifentanil are better correlated with ideal body weight than actual body weight in this population.

- **Renal impairment**

No dosage adjustment relative to that used in healthy adults is necessary in renally impaired patients, including those undergoing renal replacement therapy, as the pharmacokinetic profile of Ultiwell is unchanged in this patient population.

- **Hepatic impairment**

No adjustment of the initial dose, relative to that used in healthy adults, is necessary as the pharmacokinetic profile of Ultiwell is unchanged in this patient population. However, patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of remifentanil. These patients should be closely monitored and the dose of Ultiwell titrated to individual patient need.

- **Neurosurgery**

Limited clinical experience in patients undergoing neurosurgery has shown that no special dosage recommendations are required.

- **ASA III/IV patients**

GENERAL ANAESTHESIA:

As the haemodynamic effects of potent opioids can be expected to be more pronounced in ASA III/IV patients, caution should be exercised in the administration of Ultiwell in this population. Initial dosage reduction and subsequent titration to effect is therefore recommended.

CARDIAC ANAESTHESIA:

No initial dose reduction is required. (see *Dosage and Administration- Cardiac Anaesthesia- Dosing guidelines*).

INSTRUCTION FOR USE/HANDLING

Ultiwell is stable for 24 hours at room temperature (25°C) after reconstitution and further dilution to 20 to 250 micrograms/ml (50 micrograms/ml is the recommended dilution for adults and 20 to 25 micrograms/ml in paediatric patients aged 1 year and over) with one of the following i.v. fluids listed below:

− sterile water for injections

− 5% dextrose injection

− 5% dextrose and 0.9% sodium chloride injection

− 0.9% sodium chloride injection

- 0.45% sodium chloride injection

Ultiwell has been shown to be compatible with the following i.v. fluids when administered into a running IV catheter:

− Lactated Ringer's and 5% dextrose injection

− Lactate Ringer's solution for injection

Ultiwell has been shown to be compatible with propofol when administered into a running IV catherter.

The following tables give guidelines for infusion rates of Ultiwell.

Table 1. Ultiwell for Injection Infusion Rates (ml/kg/h)

Drug Delivery Rate (micrograms/kg/min)	Infusion Delivery Rate (ml/kg/h) for Solution Concentrations of			
	20 micrograms/ml 1 mg/50 ml	25 micrograms/ml 1 mg/40 ml	50 micrograms/ml 1 mg/20 ml	250 micrograms/ml 10 mg/40 ml
0.0125	0.038	0.03	0.015	Not recommended
0.025	0.075	0.06	0.03	Not recommended
0.05	0.15	0.12	0.06	0.012
0.075	0.23	0.18	0.09	0.018
0.1	0.3	0.24	0.12	0.024
0.15	0.45	0.36	0.18	0.036
0.2	0.6	0.48	0.24	0.048
0.25	0.75	0.6	0.3	0.06
0.5	1.5	1.2	0.6	0.12
0.75	2.25	1.8	0.9	0.18
1.0	3.0	2.4	1.2	0.24
1.25	3.75	3.0	1.5	0.3
1.5	4.5	3.6	1.8	0.36
1.75	5.25	4.2	2.1	0.42
2.0	6.0	4.8	2.4	0.48

Table 2. Ultiwell for Injection Infusion Rates (ml/h) for a 20 micrograms/ml Solution

Infusion Rate (micrograms/kg/min)	Patient Weight (kg)						
	5	10	20	30	40	50	60
0.0125	0.188	0.375	0.75	1.125	1.5	1.875	2.25
0.025	0.375	0.75	1.5	2.25	3.0	3.75	4.5
0.05	0.75	1.5	3.0	4.5	6.0	7.5	9.0
0.075	1.125	2.25	4.5	6.75	9.0	11.25	13.5

0.1	1.5	3.0	6.0	9.0	12.0	15.0	18.0
0.15	2.25	4.5	9.0	13.5	18.0	22.5	27.0
0.2	3.0	6.0	12.0	18.0	24.0	30.0	36.0
0.25	3.75	7.5	15.0	22.5	30.0	37.5	45.0
0.3	4.5	9.0	18.0	27.0	36.0	45.0	54.0
0.35	5.25	10.5	21.0	31.5	42.0	52.5	63.0
0.4	6.0	12.0	24.0	36.0	48.0	60.0	72.0

Table 3. Ultiwell for Injection Infusion Rates (ml/h) for a 25 micrograms/ml Solution

Infusion Rate (micrograms /kg/min)	Patient Weight (kg)									
	10	**20**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**
0.0125	0.3	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3.0
0.025	0.6	1.2	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0
0.05	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
0.075	1.8	3.6	5.4	7.2	9.0	10.8	12.6	14.4	16.2	18.0
0.1	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0
0.15	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8	32.4	36.0
0.2	4.8	9.6	14.4	19.2	24.0	28.8	33.6	38.4	43.2	48.0

Table 4. Ultiwell for Injection Infusion Rates (ml/h) for a 50 micrograms/ml Solution

Infusion Rate (micrograms/kg/min)	Patient Weight (kg)							
	30	**40**	**50**	**60**	**70**	**80**	**90**	**100**
0.025	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3.0
0.05	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0
0.075	2.7	3.6	4.5	5.4	6.3	7.2	8.1	9.0
0.1	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
0.15	5.4	7.2	9.0	10.8	12.6	14.4	16.2	18.0
0.2	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0
0.25	9.0	12.0	15.0	18.0	21.0	24.0	27.0	30.0
0.5	18.0	24.0	30.0	36.0	42.0	48.0	54.0	60.0
0.75	27.0	36.0	45.0	54.0	63.0	72.0	81.0	90.0
1.0	36.0	48.0	60.0	72.0	84.0	96.0	108.0	120.0
1.25	45.0	60.0	75.0	90.0	105.0	120.0	135.0	150.0
1.5	54.0	72.0	90.0	108.0	126.0	144.0	162.0	180.0
1.75	63.0	84.0	105.0	126.0	147.0	168.0	189.0	210.0
2.0	72.0	96.0	120.0	144.0	168.0	192.0	216.0	240.0

Table 5. Ultiwell for Injection Infusion Rates (ml/h) for a 250 micrograms/ml Solution

Infusion Rate (micrograms/kg/min)	Patient Weight (kg)							
	30	**40**	**50**	**60**	**70**	**80**	**90**	**100**
0.1	0.72	0.96	1.20	1.44	1.68	1.92	2.16	2.40
0.15	1.08	1.44	1.80	2.16	2.52	2.88	3.24	3.60
0.2	1.44	1.92	2.40	2.88	3.36	3.84	4.32	4.80

0.25	1.80	2.40	3.00	3.60	4.20	4.80	5.40	6.00
0.5	3.60	4.80	6.00	7.20	8.40	9.60	10.80	12.00
0.75	5.40	7.20	9.00	10.80	12.60	14.40	16.20	18.00
1.0	7.20	9.60	12.00	14.40	16.80	19.20	21.60	24.00
1.25	9.00	12.00	15.00	18.00	21.00	24.00	27.00	30.00
1.5	10.80	14.40	18.00	21.60	25.20	28.80	32.40	36.00
1.75	12.60	16.80	21.00	25.20	29.40	33.60	37.80	42.00
2.0	14.40	19.20	24.00	28.80	33.60	38.40	43.20	48.00

ROUTE OF ADMINISTRATION
Lyophilized powder for reconstitution for intravenous (IV) administration

CONTRAINDICATIONS
As glycine is present in the formulation, Ultiwell is contraindicated for epidural and intrathecal use.

Hypersensitivity to the active substance, other fentanyl analogues, or to any of the excipients.

Ultiwell is contraindicated for use as the sole agent for induction of anaesthesia.

WARNING AND PRECAUTIONS

Ultiwell should be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function, and by persons specifically trained in the use of anaesthetic drugs and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation. Such training must include the establishment and maintenance of a patent airway and assisted ventilation. The use of Ultiwell in mechanically ventilated intensive care patients is not recommended for a duration of treatment greater than 3 days.

Patients with a known hypersensitivity to opioids of a different class may exhibit a hypersensitivity reaction following administration of Ultiwell. Caution should be exercised before using Ultiwell in these patients.

Rapid offset of action /Transition to alternative analgesia

Due to the very rapid offset of action of Ultiwell, no residual opioid activity will be present within 5 to 10 minutes after the discontinuation of Ultiwell. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to discontinuation of Ultiwell. The possibility of tolerance, hyperalgesia and associated haemodynamic changes should be considered when used in Intensive Care Unit. Prior to discontinuation of Ultiwell, patients must be given alternative analgesic and sedative agents. Sufficient time must be allowed to reach the therapeutic effect of the longer acting analgesic. The choice of agent(s), the dose and the time of administration should be planned in advance and individually tailored to be appropriate for the patient's surgical procedure and the level of post-operative care anticipated. When other opioid agents are administered as part of the regimen for transition to alternative analgesia, the benefit of providing adequate post-operative analgesia must always be balanced against the potential risk of respiratory depression with these agents.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Ultiwell with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. If the decision is made to newly prescribe a

benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.
If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response. If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Ultiwell is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (See Drug Interactions).

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs
Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of Ultiwell with serotonergic drugs (See Interactions with Other Medicaments). This may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (See Interactions with Other Medicaments). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Ultiwell if serotonin syndrome is suspected.

Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual Function/Reproduction
Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See Postmarketing Experience)

Discontinuation of Treatment
Symptoms following withdrawal of Ultiwell including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days. Where reported, re-introduction and tapering of the infusion has been beneficial. The use of Ultiwell in mechanically ventilated intensive care patients is not recommended for duration of treatment greater than 3 days.

Inadvertent administration
A sufficient amount of Ultiwell may be present in the dead space of the IV line and/or cannula to cause respiratory depression, apnoea and/or muscle rigidity if the line is flushed with IV fluids or other drugs. This may be avoided by administering Ultiwell into a fast flowing IV line or via a dedicated IV line which is removed when Ultiwell is discontinued.

Muscle rigidity - prevention and management

At the doses recommended muscle rigidity may occur. As with other opioids, the incidence of muscle rigidity is related to the dose and rate of administration. Therefore, bolus injections should be administered over not less than 30 seconds.
Muscle rigidity induced by Ultiwell must be treated in the context of the patient's clinical condition with appropriate supporting measures including ventilatory support.
Excessive muscle rigidity occurring during the induction of anaesthesia should be treated by the administration of a neuromuscular blocking agent and/or additional hypnotic agents. Muscle rigidity seen during the use of Ultiwell as an analgesic may be treated by stopping or decreasing the rate of administration of Ultiwell. Resolution of muscle rigidity after discontinuing the infusion of **Ultiwell** occurs within minutes.
Alternatively, an opioid antagonist may be administered, however this may reverse or attenuate the analgesic effect of Ultiwell.

Respiratory depression – prevention and management
As with all potent opioids, profound analgesia is accompanied by marked respiratory depression. Therefore, Ultiwell should only be used in areas where facilities for monitoring and dealing with respiratory depression are available. The appearance of respiratory depression should be managed appropriately, including decreasing the rate of infusion by 50%, or by a temporary discontinuation of the infusion. Unlike other fentanyl analogues, Ultiwell has not been shown to cause recurrent respiratory depression even after prolonged administration. However, as many factors may affect post-operative recovery it is important to ensure that full consciousness and adequate spontaneous ventilation are achieved before the patient is discharged from the recovery area.

Cardiovascular effects
The risk of cardiovascular effects such as hypotension and bradycardia (*see section 4.8*), which may rarely lead to asystole/cardiac arrest may be reduced by lowering the rate of infusion of Ultiwell or the dose of concurrent anaesthetics or by using IV fluids, vasopressor or anticholinergic agents as appropriate.
Debilitated, hypovolaemic, and elderly patients may be more sensitive to the cardiovascular effects of Ultiwell.

Neonates/infants
There is limited data available on use in neonates/infants under 1 year of age.

Drug abuse
As with other opioids Ultiwell may produce dependency.

INTERACTION WITH OTHER MEDICAMENTS
Ultiwell is not metabolised by plasmacholinesterase therefore interactions with drugs metabolised by this enzyme are not anticipated.
As with other opioids, Ultiwell decreases the amounts or doses of inhaled and i.v. anaesthetics, and benzodiazepines required for anaesthesia (see *Dosage and Administration*). If doses of concomitantly administered CNS depressant drugs are not reduced, patients may experience an increased incidence of adverse effects associated with these agents.
The cardiovascular effects of Ultiwell (hypotension and bradycardia), may be exacerbated in patients receiving concomitant cardiac depressant drugs, such as beta- blockers and calcium channel blocking agents.

<u>Benzodiazepines</u>
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at GABAA sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Ultiwell if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See Warnings and Precautions)

STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Ultiwell should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is not known whether remifentanil is excreted in human milk. However, because fentanyl analogues are excreted in human milk and remifentanil-related material was found in rat milk after dosing with remifentanil, nursing mothers should be advised to discontinue breast feeding for 24 hours following administration of remifentanil.

Labour and delivery

The safety profile of remifentanil during labour or delivery has not been demonstrated. There are insufficient data to recommend remifentanil for use during labour and Caesarean section. Remifentanil crosses the placental barrier and fentanyl analogues can cause respiratory depression in the child.

ADVERSE EFFECTS

Summary of the safety profile

The most common undesirable effects associated with remifentanil are direct extensions of mu-opioid agonist pharmacology. These adverse events resolve within minutes of discontinuing or decreasing the rate of remifentanil administration.

Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Adverse reactions**
Immune System Disorders	Rare	Allergic reactions including anaphylaxis have been reported in patients receiving remifentanil in conjunction with one or more anaesthetic agents
Psychiatric disorders	Not known	Drug dependence
Nervous System Disorders	Very common	Skeletal muscle rigidity
	Rare	Sedation (during recovery from general anaesthesia)
	Not known	Convulsions
Cardiac Disorders	Common	Bradycardia
	Rare	Asystole/cardiac arrest, usually preceded by bradycardia, has been reported in patients receiving remifentanil in conjunction with other anaesthetic agents
	Not known	Atrioventricular block
Vascular Disorders	Very common	Hypotension

	Common	Post-operative hypertension
Respiratory, Thoracic and Mediastinal Disorders	Common	Acute respiratory depression, apnoea
	Uncommon	Hypoxia
Gastrointestinal Disorders	Very common	Nausea, vomiting
	Uncommon	Constipation
Skin and Subcutaneous Tissue Disorders	Common	Pruritus
General Disorders and Administration Site Conditions	Common	Post-operative shivering
	Uncommon	Post-operative aches
	Not known	Drug tolerance

Discontinuation of treatment
Symptoms following withdrawal of remifentanil including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days.

Postmarketing Experience:
Serotonin syndrome (See Warnings and Precautions)

Adrenal insufficiency (See Warnings and Precautions)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

OVERDOSE AND TREATMENT
Symptoms
As with all potent opioid analgesics, overdose would be manifested by an extension of the pharmacologically predictable actions of remifentanil. Due to the very short duration of action of Ultiwell, the potential for deleterious effects due to overdose is limited to the immediate time period following drug administration. Response to discontinuation of the drug is rapid, with return to baseline within ten minutes.
Management
In the event of overdose, or suspected overdose, take the following actions: discontinue administration of Ultiwell, maintain a patent airway, initiate assisted or controlled ventilation with oxygen, and maintain adequate cardiovascular function. If depressed respiration is associated with muscle rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressor agents for the treatment of hypotension and other supportive measures may be employed.
Intravenous administration of an opioid antagonist such as naloxone may be given as a specific antidote in addition to ventilatory support to manage severe respiratory depression. The duration of respiratory depression following overdose with Ultiwell is unlikely to exceed the duration of action of the opioid antagonist.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

After anaesthesia with remifentanil the patient should not drive or operate machinery. The physician should decide when these activities may be resumed. It is advisable that the patient is accompanied when returning home and that alcoholic drink is avoided.

STORAGE CONDITIONS
Store below 25°C, well- sealed.

The reconstituted solution of Ultiwell is chemically and physically stable for 24 hours at room temperature(25°C). However, Ultiwell does not contain an antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions, reconstituted product should be used promptly, and any unused material discarded.

DOSAGE FORMS AND PACKAGING AVAILABLE

Container	Concentration	Quantity
2 mL Single-Dose Vial	1 mg lyophilized powder	Box of 5 vials per carton
10 mL Single-Dose Vial	5 mg lyophilized powder	Box of 5 vials per carton

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