PACKAGE LEAFLET: INFORMATION FOR THE USER

Remifentanil 1 mg powder for concentrate for solution for injection or infusion
Remifentanil 2 mg powder for concentrate for solution for injection or infusion
Remifentanil 5 mg powder for concentrate for solution for injection or infusion

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Remifentanil is and what it is used for
2. What you need to know before you are given Remifentanil
3. How Remifentanil is given
4. Possible side effects
5. How to store Remifentanil
6. Contents of the pack and any other information

1. WHAT REMIFENTANIL IS AND WHAT IT IS USED FOR
Remifentanil belongs to a group of medicines known as opioids. These medicines are used widely to cause anaesthesia and or/ to relieve pain during an operation.

Remifentanil is used:
- as an analgesic, which helps to relieve pain, for use at the onset or during anaesthesia in conjunction with anaesthetic agents
- as an analgesic for patients 18 years of age or older who are mechanically ventilated in the intensive care unit.

2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN REMIFENTANIL
Remifentanil must not be given
- if you are allergic to Remifentanil or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to any medicine used in operations or if you had a side effect during an operation.
- Remifentanil must not be administered by epidural or intrathecal injection, because this medicine contains glycine.
- as sole medicine to initiate anaesthesia.

Warnings and precautions
Tell your doctor before you are given Remifentanil:
- If you are allergic to any other opioid medicines, such as morphine or codeine
- If you are over 65 years of age
- If you are dehydrated or have lost a lot of blood
- If you are feeling weak or unwell
- If you are overweight
- If you or anyone in your family have ever abused or been dependant on alcohol, prescription medicines or illegal drugs ("addiction")
- If you are a smoker
- If you have ever had problems with your mood (depression, anxiety or a personality disorder) or have been treated by a psychiatrist for other mental illnesses

This medicine contains remifentanil which is an opioid medicine. Repeated use of opioid painkillers may result in the drug being less effective (you become accustomed to it). It may also lead to dependence and abuse which may result in life-threatening overdose. If you have concern that you may become dependent on Remifentanil, it is important that you consult your doctor.

Withdrawal reactions including rapid heartbeat, high blood pressure and restlessness have occasionally been reported when treatment with this medicine is stopped suddenly, particularly when treatment has lasted more than 3 days (see also section 4. Possible side effects). If you experience these symptoms, your doctor may re-introduce the medicine and gradually reduce the dose.

If you are not sure if any of the above apply to you, talk to your doctor, pharmacist or nurse before you are given Remifentanil.

Other medicines and Remifentanil
Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. This includes herbal medicines. This is because Remifentanil can work with other medicines to cause side effects.
In particular tell your doctor or pharmacist if you are taking:
- medicines for your heart or blood pressure, such as beta-blockers (these include atenolol, metoprolol, carvedilol, propranolol and bisoprolol) or calcium channel blockers (these include amlodipine, diltiazem and nifedipine)
- medicines for the treatment of depression such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and Monoamine Oxidase Inhibitors (MAOIs). It is not recommended to use these medicines at the same time as Remifentanil as they may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Concomitant use of Remifentanil and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. The concomitant use of opioids and drugs used to treat epilepsy, nerve pain or anxiety (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and may be life-threatening.

However if your doctor does prescribe Remifentanil together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.

Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Your doctor will assess if having this medicine is necessary during pregnancy or breastfeeding.

The safety of this medicine has not fully been established in pregnant women. This medicine should only be given to pregnant women if the doctor considers that the benefit for the mother exceeds any possible risk to the foetus.

If you are given this medicine during labour or close to childbirth, it can affect your baby's breathing. You and your baby will be monitored for signs of excessive sleepiness and difficulty breathing.

In case of having this medicine, breast-feeding must be stopped during the following 24 hours.

Driving and using machines
After anaesthesia with Remifentanil you should not drive or operate machinery. The physician should decide when these activities may be resumed. It is advisable that you are accompanied when returning home and that alcoholic drink is avoided.

This medicine can affect your ability to drive.

Do not drive whilst taking this medicine until you know how this medicine affects you.

It may be an offence to drive if your ability to drive safely is affected.
There is further information for patients who are intending to drive in Great Britain - go to http://www.gov.uk/drug-driving-law

3. HOW REMIFENTANIL IS GIVEN
This medicine will always be given to you by a person who is qualified to do so. You will never be expected to give yourself this medicine.

Remifentanil can be given:
- as a single injection into your vein
- as a continuous infusion into your vein. This is where the drug is slowly given to you over a longer period of time.

The way you are given the drug and the dose you receive will depend on:
- your weight
- the operation you have
- how much pain you will be in
- how sleepy the medical staff want you to be in the Intensive Care Unit

The dose varies from one patient to another

For the Medical Profession

Refer to the Summary of Product Characteristics for the complete prescribing information.

The information provided in this section are the instructions for the preparation of Remifentanil powder for concentrate for solution for injection or infusion prior to administration and the guidelines for infusion rates for manually-controlled infusion.

Preparation guide for:
Remifentanil 1 mg powder for concentrate for solution for injection or infusion
Remifentanil 2 mg powder for concentrate for solution for injection or infusion
Remifentanil 5 mg powder for concentrate for solution for injection or infusion

Remifentanil Injection is a white to off-white powder, to be reconstituted before use. Remifentanil Injection is available in glass vials containing 1mg, 2mg or 5mg of remifentanil base.

Do not store above 25°C.

When reconstituted as directed, solutions of Remifentanil Injection are clear, colourless and practically free from particulate material and contain 1mg/ml of remifentanil base as remifentanil hydrochloride. Remifentanil Injection should not be administered without further dilution after reconstitution of the lyophilised powder.

It is important that you read this guide prior to the preparation of Remifentanil Injection. This information can also be found under sections 6.4 and 6.6 of the Summary of Product Characteristics.

Reconstitution of the lyophilised powder

Remifentanil Injection should be prepared for intravenous use by adding, as appropriate 1, 2 or 5ml of diluent (see list of diluents under 'Further Dilution') to give a reconstituted solution with a concentration of approximately 1 mg/ml remifentanil. The reconstituted solution is clear, colourless and practically free from particulate material. After reconstitution the solution should be visually inspected on contaminations, colour or a defective container. The solution should be discarded, if any of these modifications should appear. The reconstituted solution should be used immediately and is for single use only.

Further Dilution

After reconstitution, Remifentanil Injection should not be administered by manually-controlled infusion without further dilution to concentrations of 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 when used in maintenance of anaesthesia).

After reconstitution, Remifentanil Injection should not be administered by target-controlled infusion (TCI) without further dilution (20 to 50 micrograms/ml is the recommended dilution for TCI).

The dilution is dependent upon the technical capability of the infusion device and the anticipated requirements of the patient.

One of the following intravenous fluids listed below should be used for dilution

Water for Injections
Glucose 50 mg/ml (5%) solution for injection
Glucose 50 mg/ml (5%) and Sodium Chloride 9 mg/ml (0.9%) solution for injection
Sodium Chloride 9 mg/ml (0.9%) solution for injection
Sodium Chloride 4.5 mg/ml (0.45%) solution for injection

After dilution, the solution should be inspected visually to ensure it is clear, colourless, practically free from particulate matter and the container is undamaged. Any solution where such defects are observed must be discarded.

The reconstituted and further diluted solution of Remifentanil Injection should be used immediately.

Remifentanil Injection has been shown to be compatible with the following intravenous fluids *when administered into a running IV catheter:*

Lactated Ringer's solution for injection

Lactated Ringer's and Glucose 50 mg/ml (5%) solution for injection

Remifentanil Injection has been shown to be compatible with propofol *when administered into a running IV catheter.*

Guidelines for Infusion Rates

The tables below give guidelines for infusion rates of Remifentanil Injection for manually-controlled infusion:

Table 1: Remifentanil Injection Infusion Rates (ml/kg/h)

	Infusion Rate (ml/kg/h) for Solution Concentrations of			
Drug Delivery Rate (µg/kg/min)	**20µg/ml 1mg/50ml**	**25µg/ml 1mg/40ml**	**50µg/ml 1mg/20m**	**250µg/ml 10 mg/40ml**
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: Remifentanil Injection Infusion Rates (ml/h) for a 20ug/ml Solution

Infusion Rate (µg/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: Remifentanil Injection Infusion Rates (ml/h) for a 25 µg/ml Solution

Infusion Rate (µg/kg/min)	Patient Weight (kg)									
	10	**20**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**
0.125	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: Remifentanil Injection Infusion Rates (ml/h) for a 50 µg/ml Solution

Infusion Rate (µg/kg/min)	Patient Weight (kg)							
	30	**40**	**50**	**60**	**70**	**80**	**90**	**100**
0.25	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: Remifentanil Injection Infusion Rates (ml/h) for a 250 µg/ml Solution

Infusion Rate (µg/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	14.4	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

The following table provides the equivalent blood remifentanil concentration using a TCI approach for various manually-controlled infusion rates at steady state:

Table 6: Remifentanil Blood Concentrations (nanograms/ml) estimated using the Minto (1997) Pharmacokinetic Model in a 70 kg, 170 cm, 40 Year Old Male Patient for Various Manually-Controlled Infusion rates (micrograms/kg/min) at Steady State.

Remifentanil Infusion Rate (micrograms/kg/min)	Remifentanil Blood Concentration (nanograms/ml)
0.05	1.3
0.10	2.6
0.25	6.3
0.40	10.4
0.50	12.6
1.0	25.2
2.0	50.5

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If you are given too much
The effects of Remifentanil are carefully monitored throughout your operation and in intensive care, and appropriate action will be taken promptly if you receive too much.

After your operation
Tell your doctor or nurse if you are in pain. If you are in pain after your procedure, they will be able to give you other painkillers.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects although not everybody gets them.
These effects are normally mild to moderate.

Some people can be allergic to medicines. **You must tell your doctor or nurse immediately if you have:**
Rare: may affect up to 1 in 1,000 people
- sudden wheeze and chest pain or chest tightness
- swelling of your eyelids, face, lips, mouth or tongue
- a lumpy skin rash or 'hives' anywhere on the body
- collapse.

Tell your doctor immediately if you notice some of the following symptoms:
Very common: may affect more than 1 in 10 people
- Muscle stiffness
- Nausea
- Vomiting
- Decreased blood pressure

Common: may affect up to 1 in 10 people
- Slow heart rate
- Problems breathing
- Itching
- Cough

Uncommon: may affect up to 1 in 100 people
- Constipation
- Problems breathing (hypoxia)

Rare: may affect up to 1 in 1,000 people
- Allergic reaction, including anaphylaxis (allergic general reaction)
- Heart function disorders (cardiac arrest)

Not known: frequency cannot be estimated from the available data
- Drug dependence (physical need for Remifentanil)
- Convulsions (fits)
- Atrioventricular block (heart block)
- Drug tolerance (the need for increasing doses over time to get the same effect (drug tolerance)
- Irregular heartbeat (arrhythmia)
- Withdrawal syndrome (may manifest by the occurrence of the following side effects: increased heart rate, high blood pressure, feeling restless or agitated, nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating)

Other side effects that can happen when you wake up after having an anaesthetic include:
Common: may affect up to 1 in 10 people
- shivering
- increases in blood pressure

Uncommon: may affect up to 1 in 100 people
- aches

Rare: may affect up to 1 in 1,000 people
- feeling very calm or drowsy (sedation)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

5. HOW TO STORE REMIFENTANIL

Keep out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the vial and on the carton. The expiry date refers to the last day of the month.
Do not store above 25°C.

Shelf life after reconstitution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Shelf life after dilution:
All mixtures with infusion fluids should be used immediately.
After reconstitution the solution must not be used, if it is not clear, colourless and free of visible particles.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Remifentanil contains
The active substance is Remifentanil. Each vial contains 1 mg, 2 mg or 5 mg of Remifentanil (as hydrochloride).
After reconstitution the solution contains 1 mg/ml if prepared as recommended.
The other ingredients are: glycine and hydrochloric acid 37% (for pH-adjustment).

What Remifentanil looks like and contents of the pack
Remifentanil is a white to off-white powder for concentration for solution for injection or infusion.
Each carton of Remifentanil 1 mg contains 5 vials of 3 ml.
Each carton of Remifentanil 2 mg contains 5 vials of 3 ml.
Each carton of Remifentanil 5 mg contains 5 vials of 6 ml.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK.
Manufacturer: Laboratorio Reig Jofre, S.A., Gran Capitán, 10, 08970 Sant Joan Despí, Barcelona, Spain.

Other formats:
To listen or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 198 5000
Please be ready to give the following information:

Product Name	Reference Number
Remifentanil 1 mg powder for concentrate for solution for injection or infusion	**PL29831/0482**
Remifentanil 2 mg powder for concentrate for solution for injection or infusion	**PL29831/0483**
Remifentanil 5 mg powder for concentrate for solution for injection or infusion	**PL29831/0484**

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