Professional Information For Human Medicine

SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

REMIFENTANIL 1 MG B. BRAUN, Sterile powder for solution for injection or infusion

REMIFENTANIL 2 MG B. BRAUN , Sterile powder for solution for injection or infusion

REMIFENTANIL 5 MG B. BRAUN , Sterile powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial (4 mL) of **REMIFENTANIL 1 MG B. BRAUN** contains remifentanil hydrochloride (1,1 mg) equivalent to 1 mg remifentanil.

One vial (6 mL) of **REMIFENTANIL 2 MG B. BRAUN** contains remifentanil hydrochloride (2,2 mg) equivalent to 2 mg remifentanil.

One vial (10 mL) of **REMIFENTANIL 5 MG B. BRAUN** contains remifentanil hydrochloride (5,5 mg) equivalent to 5 mg remifentanil.

Each mL of **REMIFENTANIL 1 MG/ 2 MG/ 5MG B. BRAUN** contains 1 mg remifentanil when reconstituted as directed.

Sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Sterile powder for solution for injection or infusion.

White to off-white or yellowish, compact powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

REMIFENTANIL B. BRAUN is indicated as a narcotic analgesic or adjuvant for use during induction and/or maintenance of inhalation anaesthesia during surgical procedures, including cardiac surgery.

REMIFENTANIL B. BRAUN is indicated for the provision of analgesia as an aid to sedation (up to 72 hours sedation) in mechanically ventilated intensive care patients. Safety and efficacy beyond 72 hours has not been demonstrated.

4.2. Posology and method of administration

Posology

Continuous infusion of **REMIFENTANIL B. BRAUN** must be administered by a calibrated infusion device into a fast-flowing IV line or via a dedicated IV line. This infusion line should be connected at, or close to, the venous cannula and primed, to minimise the potential dead space.

Care should be taken to avoid obstruction or disconnection of infusion lines and to adequately clear the lines to remove residual **REMIFENTANIL B. BRAUN** after use (see section 4.4).

REMIFENTANIL B. BRAUN is for intravenous use only and must not be administered by epidural or intrathecal injection.

Reconstitution: See section 6.6.

GENERAL ANAESTHESIA:

The administration of **REMIFENTANIL B. BRAUN** must be individualized based on the patient's response.

Adults*:*

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

Dosing Guidelines for Adults			
Indications	**Bolus Infusion of REMIFENTANIL B. BRAUN (µg/kg)**	**Continuous Infusion of Remifentanil (µg/kg/min)**	
		Starting Rate	Range
With Induction of anaesthesia in ventilated patients	1 (given over not less than 30 seconds)	0,5 - 1,0	-
Maintenance of anaesthesia in ventilated patients - isoflurane (starting dose 0,5 MAC) - propofol (starting dose 100 µg/kg/min)	0,5 - 1,0 0,5 - 1,0	0,25 0,25	0,05 - 0,5 0,05 - 0,5

At the doses recommended, **REMIFENTANIL B. BRAUN** significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane should be administered as recommended above to avoid excessive depth of anaestheisa (see section 4.5).

Induction of anaesthesia: **REMIFENTANIL B. BRAUN** should be administered with a hypnotic agent, such as isoflurane, for the induction of anaesthesia. **REMIFENTANIL B. BRAUN** can be administered at an infusion rate of 0,5 - 1,0 µg/kg/min with or without an initial bolus infusion 1 µg/kg over not less than 30 seconds.

If endotracheal intubation is to occur more than 8 to 10 minutes after the start of the **REMIFENTANIL B. BRAUN** infusion, then a bolus infusion is not necessary.

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

The use of **REMIFENTANIL B. BRAUN** to treat pain during the post-operative period is not recommended in patients who are breathing spontaneously.

Guidelines for discontinuation: Due to the very rapid offset of action of **REMIFENTANIL B. BRAUN** , residual opioid activity will be reduced 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 **REMIFENTANIL B. BRAUN** . 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 leve of post-operative care.

Concomitant medication: **REMIFENTANIL B. BRAUN** decreases the amounts or doses of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see section 4.5).

Paediatric population

Paediatric patients (1 - 12 years of age):

Induction of anaesthesia: **REMIFENTANIL B. BRAUN** is not recommended for the induction of anaesthesia as insufficient dat are available.

Maintenance of anaesthesia:

Dosing Guidelines for Maintenance of Anaesthesia in Paediatric Patients (1 - 12 years of age)			
Concomitant Anaesthetic Agent	**Bolus Infusion of REMIFENTANIL B. BRAUN**	**Continuous Infusion of REMIFENTANIL B. BRAUN (µg/kg/min)**	
		Starting Rate	Typical Maintenance Rates
Halothane (starting dose 0,3 MAC)	1	0,25	0,05 to 1,3
Sevoflurane (starting dose 0,3 MAC)	1	0,25	0,05 to 0,9
Isoflurane (starting dose 0,5 MAC)	1	0,25	0,06 to 0,9

When given by bolus infusion, **REMIFENTANIL B. BRAUN** should be administered over not less than 30 seconds. Surgery should no commence until at least 5 minutes after the start of the **REMIFENTANIL B. BRAUN** 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, the **REMIFENTANIL B. BRAUN** 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 the **REMIFENTANIL B. BRAUN** .

Guidelines for discontinuation: Following discontinuation of infusion, the onset of analgestic effect of the **REMIFENTANIL B. BRAUN** is rapid and similar to that seen in adult patients.

Appropriate post-operative analgesic requirements should be anticipate and implemented (see **Adults - *Guidelines for discontinuation***).

Neonates/infants (aged less than 1 year):

The pharmacokinetic profile of remifentanil in neonates/infants (aged less than 1 year) is comparable to that seen in adults after correction of 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 B. BRAUN (µg/kg)**	**Continuous Infusion of REMIFENTANIL B. BRAUN (µg/kg/min)**	
		Starting Rate	Typical Infusion Rates
Intubation	Not recommended	1	-
Maintenance of anaesthesia:		1	0,003 to 4
• Isoflurane (starting dose 0,4 MAC)	0,5 to 1	1	0,01 to 4,3
• Propofol (starting dose 50 µg/kg/min)	0,5 to 1	1	0 to 1
Continuation of post-operative analgesia, prior to extubation.	Not recommended		

Induction period of anaesthesia: After administration of hypnotic to achieve loss of consciousness, **REMIFENTANIL B. BRAUN** should be administered at an infusion rate of 1 µg/kg/min.

The use of bolus infusions of **REMIFENTANIL B. BRAUN** 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 **REMIFENTANIL B. BRAUN** 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 µg/kg. These dosing recommendations also supply during hypothermic cardiopulmoanry bypass (see section 5.2).

Concomitant medication: At the doses recommend above, **REMIFENTANIL B. BRAUN** 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 anaethesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with **REMIFENTANIL B. BRAUN**

Continuation of post-operative analgesia prior to extubation: It is recommended that the infusion of **REMIFENTANIL B. BRAUN** 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 infusion should be maintained initially at a rate of 1 µg/kg/min until the patient is ready to be weaned from the ventilator.

Guidelines for discontinuation: Prior to discontinuation of **REMIFENTANIL B. BRAUN** , patients must be given alternative analgesic and sedative agent 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.

It is recommended that the **REMIFENTANIL B. BRAUN** infusion is discontinued by reducing the infusion rate in three or four steps of 50 % at 10 minute intervals. During weaning from the ventilator the **REMIFENTANIL B. BRAUN** 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 population:

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

USE IN INTENSIVE CARE:

REMIFENTANIL B. BRAUN can be used for the provision of analgesia or up to 72 hours and as an aid to short-term sedation in mechanically ventilated intensive care patients.

It is recommended that **REMIFENTANIL B. BRAUN** is initiated at an infusion rate of 0,1 µg/kg/min (6 µg/kg/h) to 0,15 µg/kg/min (9 µg/kg/h). The infusion rate should be titrated in increments of 0,025 µg/kg/min (1,5 µg/kg/h) to achieve the desired level of analgesia. A period of at least 5 minutes should be allowed between dose adjustments. The level of analgesia should be carefully monitored, regularly reassessed and the **REMIFENTANIL B. BRAUN** infusion rate adjusted accordingly. If an infusion rate of 0,2 µg/kg/min (12 µg/kg/h) is reached and the desired level of sedation is not achieved, it is recommended that dosing with an appropriate sedative agent is initiated (see below). The dose of sedative agent should be titrated to obtain the desired level of sedation. Further increases

to the **REMIFENTANIL B. BRAUN** infusion rate in increments of 0,025 µg/kg/min (1,5 µg/kg/h) 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 patients:

Dosing Guidelines for Use of REMIFENTANIL B. BRAUN within the Intensive Care Setting	
CONTINUOUS INFUSION µg/kg/min (µg/kg/h)	
Starting Rate	Range
0,1(6) to 0,15(9)	0,006(0,36) to 0,74(44,4)

Bolus doses of **REMIFENTANIL B. BRAUN** are not recommended in the intensive care setting.

The use of **REMIFENTANIL B. BRAUN** will reduce the dosage requirement of any concomicant sedative agents by approximately 50 %. 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 administered as an mixture.

Additional analgesia for ventilated patients undergoing stimulating procedures: An increase in the existing **REMIFENTANIL B. BRAUN** 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 a **REMIFENTANIL B. BRAUN** infusion rate of at least 0,1 µg/kg/min (6 µg/kg/h) 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 % - 50 % in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0,25 µg/kg/min (15 µg/kg/h), maximum 0,75 µg/kg/min (45 µg/kg/h), has been administered for provision of additional anaesthesia during stimulating procedures.

Establishment of alternative analgesia prior to discontinuation of REMIFENTANIL* B. BRAUN *: Due to the very rapid offset of action of **REMIFENTANIL B. BRAUN** , no residual opioid activity will be present within 5 to 10 minutes after discontinuation regardless of the duration of infusion. Prior to discontinuation of **REMIFENTANIL B. BRAUN**, patients must be given alternative analgesic and sedative agents at a sufficient time in advance, to allow the therapeutic effects of these agents to become established. It is therefore recommended that the choice of agent(s), the dose and the time of administration, are planned prior to discontinuation of **REMIFENTANIL B. BRAUN**.

***Guidelines for extubation and* discontinuation of REMIFENTANIL B. BRAUN**:
In order to ensure a smooth emergence from a **REMIFENTANIL B. BRAUN based** regimen, it is recommended that the infusion rate of **REMIFENTANIL B. BRAUN** is

titrated in stages to 0,1 µg/kg/min (6 µg/kg/h) 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-minute intervals until the infusion is discontinued. During weaning from the ventilator, the **REMIFENTANIL B. BRAUN** infusion should not be increased, and only down titration should occur, supplemented as required with alternative analgesics.

Upon discontinuation of **REMIFENTANIL B. BRAUN**, the IV cannula should be, cleared or removed to prevent subsequent inadvertent administration.
When other opioid agents are administered as part of the regimen for transition to alternative analgesia, the patient must be carefully monitored. The benefit of providing adequate analgesia must always be balanced against the potential risk of respiratory depression with these agents.

Paediatric intensive care patients:

There are no data available on use in paediatric patients.

Renally-impaired intensive care patients:

No adjustments to the doses recommended above are necessary in renally-impaired patients including those undergoing renal replacement therapy.

SPECIAL POPULATIONS:

Elderly population (over 65 years of age):

General anaesthesia: The initial starting dose of remifentanil should be half the recommended adult dose and then titrated to individual patient need, as an increased sensitivity to the pharmacological effects of remifentanil 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 **Cardiac Anaesthesia – Method of Administration**).

Intensive care: No initial dose reduction is required (see Use in Intensive care).

Renal impairment:

No dosage adjustment is necessary in patients with impaired renal function, including intensive care patients.

Hepatic impairment:

No dosage adjustment is necessary. However, patients with severe hepatic impairment may be more sensitive to the respiratory depressant effects of remifentanil. These patients should be closely monitored, and the dose of remifentanil titrated to individual patient need.

Obese patients:

For obese patients (greater than 30 % over their ideal body weight) the dosage of **REMIFENTANIL B. BRAUN** 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.

Neurosurgery:

Limited clinical experience in patients undergoing neurosurgery has shown that no special dosage recommendation is 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 **REMIFENTANIL B. BRAUN** in this population. Initial dosage reduction and subsequent titration to effect is therefore recommended.

Cardiac anaesthesia: No initial dose reduction is required (see **Cardiac Anaesthesia - Method of Administration**).

Long-term use in the ICU: No data are available on the long-term (longer than 72 hours) use of **REMIFENTANIL B. BRAUN** in ICU patients.

Method of administration

REMIFENTANIL B. BRAUN is for intravenous use only administered via calibrated infusion device.

4.3. Contraindications

As glycine is present in the formulation, **REMIFENTANIL B. BRAUN** is contra-indicated for epidural and intrathecal use (see section 5.3)

- Hypersensitivity to ~~the~~ remifentanil and other fentanyl analogues or to any of the excipients listed in section 6.1.
- Safety in pregnancy and lactation has not been established (see section 4.6).
- **REMIFENTANIL B. BRAUN** should not be used with nitrous oxide and oxygen alone at altitudes above sea level.
- **REMIFENTANIL B. BRAUN** should not be used unless artificial ventilation is planned.

4.4. Special warnings and precautions for use

Remifentanil, such as **REMIFENTANIL B. BRAUN** , 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 medicine 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 (see section 4.2). As mechanically ventilated, intensive care patients were not studied beyond three days, no evidence of safety and efficacy for longer treatment has been established. Therefore, a longer usage is not recommended in intensive care patients.

Rapid offset of action/transition to alternative anagesia: Due to the very rapid offset of action of remifentanil such as **REMIFENTANIL B. BRAUN** , patients merge rapidly from anaesthesia and no residual opioid activity will be present within 5 - 10 minutes after the discontinuation of **REMIFENTANIL B. BRAUN** . During administration of remifentanil such as **REMIFENTANIL B. BRAUN** as a μ-opioid agonist the potential for the development of tolerance and hyperalgesia should be paid attention to.

Therefore, prior to discontinuation of **REMIFENTANIL B. BRAUN** , patients must be given alternative analgesic and sedative agents at a sufficient time in advance to allow the therapeutic effects of these agents to become more established and to prevent hyperalgesia and concomitant haemodynamic changes.

For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to discontinuation of **REMIFENTANIL B. BRAUN** . 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. When other opioid

agents are administered as part of the regimen for transition to alternative analgesia, the benefit of providing adquate post-operative analgesia must always be balanced against the potential risk of respiratory depression with these agents.

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

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 remifentanil such as **REMIFENTANIL B. BRAUN** 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 anaeshesia should be treated by the administation of a neuromuscular blocking agent and/or additional hypnotic agents. Muscle rigidity seen during the use of **REMIFENTANIL B. BRAUN** as an analgesic may be treated by stopping or decreasing the rate of administration of **REMIFENTANIL B. BRAUN**. Resolution of muscle rigidity after discontinuing the infusion of remifentanil such as **REMIFENTANIL B. BRAUN** occurs within minutes. Alternatively, a μ-opioid antagonist may be adminstered; however this may reverse or attenuate the analgesic effect of **REMIFENTANIL B. BRAUN** .

Respiratory depression - preventive measures and treatment: As with all potent opioids, profound analgesia is accompanied by marked respiratory depression. Therefore, **REMIFENTANIL B. BRAUN** should only be used in areas where facilities for monitoring and dealing with respiratory depression are available. Special care should be taken in patients with impaired lung function and with severe hepatic impairment. These patients may be slightly more sensitive to the respiratory depressant effects of remifentanil such as **REMIFENTANIL B. BRAUN**. They should be closely monitored and the dose of **REMIFENTANIL B. BRAUN** titrated to individual patient need.

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, remifentanil such as **REMIFENTANIL B. BRAUN** has not been shown to cause recurrent respiratory depression even after prolonged administration. However in the presence of confounding factors (e.g. inadvertent administration of bolus doses and concomitant administration of longer acting opioids), respiratory depression occurring up to 50 minutes after discontinuation of infusion has been reported (see also section 4.5). As many factors may effect post-operative recovery, it is important to ensure that full consciousness and adequate sponatneous ventilation are achieved before the patient is discharged from the recovery area.

Cardiovascular effects: Hypotension and bradycardia, which can give rise to asystole and cardiac arrest (see section 4.5 and section 4.8), may be managed by reducing the rate of infusion of **REMIFENTANIL B. BRAUN** or the dose of concurrent anaesthetics or by using UV fluids, vasopressor or anticholinergic agents as appropriate.

Debilitated, hypovolaemic, hypotensive and elderly patients may be more susceptible to the cardiovascular effects of remifentanil such as **REMIFENTANIL B. BRAUN**.

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

Drug abuse: As with other opioids, remifentanil such as **REMIFENTANIL B. BRAUN** may produce dependence.

Paediatric populations

Neonates and infants: There is limited data available on use in neonates/infants under 1 year of age (see section 4.2 and section 5.1).

REMIFENTANIL B. BRAUN is not recommended for use as the sole agent in general anaesthesia.

4.5. Interaction with other medicines and other forms of interaction

Remifentanil such as **REMIFENTANIL B. BRAUN** is not metabolised by plasma cholinesterase, therefore, interactions with medicine metabolised by this enzyme are not anticipated.

- *CNS depressant medicine:* As with other opioids, remifentanil such as **REMIFENTANIL B. BRAUN** , whether given by manually controlled infusion or TCI, decreases the amounts or doses of inhaled and IV anaesthetics, and benzodiazepines required for anaesthesia (see section 4.2). If doses of concomitantly administered

CNS depressant medicine are not reduced patients may experience an increased incidence of adverse effects associated with these agents. The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

- *Other opioids:* Information of medicine interactions with other opioids in relation to anaesthesia is very limited.
- *Cardiac depressant medicine, such as beta-blockers and calcium channel blocking agents:* The cardiovascular effects of remifentanil such as **REMIFENTANIL B. BRAUN** (hypotension and bradycardia), may be exacerbated in patients receiving concomitant cardiac depressant medicine, such as beta-blockers and calcium channel blocking agents (see also sections 4.4).
- Serotonergic medicine

Co-administration of remifentanil such as **REMIFENTANIL B. BRAUN** with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) or Monoamine Oxidase Inhibitors (MAOIs) may increase the risk of serotonin syndrome, a potentially life-threatening condition. Caution should be exercised with concomitant use of MAOIs. Irreversible MAOIs should be discontinued at least 2 weeks prior to remifentanil use.

4.6. Fertility, pregnancy and lactation

Pregnancy:

There are no data from the use of remifentanil such as **REMIFENTANIL B. BRAUN** in pregnant women.

Labour and Delivery: There are insufficient data to recommend remifentanil such as **REMIFENTANIL B. BRAUN** for use during labour and caesarean section. It is known that remifentanil crosses the placental barrier and fentanyl analogues can cause respiratory

depression in the child. In case remifentanil is administered nevertheless, the patient and the neonate must be monitored for signs of excess sedation or respiratory depression (see section 4.4).

Breastfeeding:

It is not known whether remifentanil such as **REMIFENTANIL B. BRAUN** 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 breastfeeding for 24 hours following administration of **REMIFENTANIL B. BRAUN**.

Fertility:

No data available.

4.7. Effects on ability to drive and use machines

Remifentanil such as **REMIFENTANIL B. BRAUN** has major influence on the ability to drive and use machines. The physician has to decide when these activities may be resumed.

If an early discharge is envisaged after application of **REMIFENTANIL B. BRAUN**, following treatment using anaesthetic agents, patient should be advised not to drive or operate machinery. It is advisable that the patient is accompanied when returning home and that alcoholic drink is avoided.

4.8. Undesirable effects

Summary of the safety profile

The most common undesirable effects associated with remifentanil such as **REMIFENTANIL B. BRAUN** are direct extensions of μ-opioid agonist activities. These adverse events resolve within minutes of discontinuing or decreasing the rate of **REMIFENTANIL B. BRAUN** administration.

Tabulated summary of adverse reactions

Frequent	**Less frequent**	**Frequency not known**
Immune system disorders		
	Hypersensitivity reactions including anaphylaxis have been reported in patients receiving **REMIFENTANIL B. BRAUN** in conjuction with one or more anaesthetic agents	
Psychiatric disorders		
		Medicine dependence
Nervous system disorders		
Skeletal muscle rigidity	Sedation (during awakening after general anaesthesia).	Convulsions
Cardiac disorders		
Bradycardia	Asystole/cardiac arrest with preceding bradycardia in patients treated with **REMIFENTANIL B. BRAUN** in	Atrioventricular block Arrhythmia

	combination with other anaesthetics	
Vascular disorders		
Hypotension, post-operative hypertension		
Respiratory, thoracic and mediastinal disorders		
Acute respiratory depression, apnoea Cough	Hypoxia	
Gastrointestinal disorders		
Nausea, vomiting	Constipation	
Skin and subcutaneous tissue disorders		
Pruritis		
General disorders and administration site conditions		
Post-operative shivering	Post-operative pain	Medicine tolerance

Discontinuation of treatment:

Symptoms following withdrawal of **REMIFENTANIL B. BRAUN** including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days (see section 4.4).

Post-marketing information:

The following adverse events have been determined from post-marketing reporting;

Immune System Disorders: allergic reactions including anaphylaxis have been reported in patients receiving **REMIFENTANIL B. BRAUN** in conjunction with one or more anaesthetic agents.

Cardiac Disorders: cardiac arrest, asystole usually preceded by bradycardia, have been reported in patients receiving **REMIFENTANIL B. BRAUN** in conjunction with other anaesthetic agents.

Patients with severe hepatic impairment are more sensitive to the respiratory depressant effects.

Rapid offset of action:

Due to the very rapid offset of action of **REMIFENTANIL B. BRAUN** no residual opioid activity will be present within 5 to 10 minutes after discontinuation of **REMIFENTANIL B. BRAUN**. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesic should be administered prior to or immediately following discontinuation of **REMIFENTANIL B. BRAUN**. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reaction after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9. Overdose

Symptoms:

As with all potent opioid analgesics, overdose would be manifested by an extension of the pharmacologically predictable actions of remifentanil such as **REMIFENTANIL B. BRAUN** i.e. respiratory depression, bradycardia, hypotension and skeletal muscle rigidity. Due to the very short duration of action of remifentanil such as **REMIFENTANIL B. BRAUN** , the potential for deleterious effects due to overdose is limited to the immediate time period following medicine administration. Response to discontinuation of the medicine is rapid, with return baseline within ten minutes.

Treatment:

In the event of overdose, or suspected overdose, the following actions should be taken:

- discontinue administration of **REMIFENTANIL B. BRAUN**,
- maintain a patent airway,
- initiate assisted or controlled ventilation with oxygen,
- maintain adequate cardiovascular function.

If depressed respiration is associated with muscle rigidity, a neurouscular 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 and muscle rigidity. The duration of respiratory depression following overdose with **REMIFENTANIL B. BRAUN** is unliely to exceed the duration of action of opioid antagonist.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Class of Medicine: A 2.9 Other Analgesics.

Pharmacotherapeutic group: Opiod anaesthetics

ATC Code: N01AH06

Mechanism of action:

Remifentanil is a selective μ-opioid agonist with a rapid onset and very short duration of action. The μ-opioid activity of remifentanil, is antagonised by narcotic antagonists, such as naloxone.

Other pharmacological effects:

Assays of histamine in patients and healthy volunteers have shown no elevation in histamine levels after administration of remifentanil in bolus doses up to 30 μg/kg.

Paediatric population

Neonates/infants (aged less than 1 year):

In a randomised (ration of 2:1, remifentanil:halothane), open label, parallel group, multicentre study 60 young infants and neonates ≤ 8 weeks of age (mean 5,5 weeks) 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 infusiion rates 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 60 % nitrous oxide (N_2O) plus 40 % oxygen. Recovery tumes were superior in the remifentanil relative tot the halothane groups (not significant). Use for Total Intravenous Anaesthesia (TIVA) - children aged 6 months to 16 years TIVA with remifentanil in paediatric surgery was compared to

inhalatin anaesthesia in three randomised, open-label studies. The results are summarised in the table below.

Surgical Intervention	**Age (y), (N)**	**Study Condition (maintenance)**	**Extubation (min) (mean (SD))**
Lower abdominal/urological surgery	0,5 - 16 (120)	TIVA: propofol (5 - 10 mg/kg/h) + remifentanil (0,125 µg/kg/min) Inhalational anaesthesia: sevoflurane (1,0 - 1,5 MAC) + remifentanil (0,125 - 1,0 µg/kg/min)	11,8 (4,2) 15,0 (5,6) ($p < 0,05$)
ENT-surgery	4 - 11 (50)	TIVA: propofol (3 mg/kg/h) + remifentanil (0,5 µg/kg/min) Inhalational anaesthesia: desflurane (1,3 MAC) + N_2O mixture	11 (3,7) 9,4 (2,9) not significant
General or ENT surgery	2 - 12 (153)	TIVA: propofol (100 - 200 µg/kg/min) + remifentanil (0,2 - 0,5 µg/kg/min)	Comparable extubation times (based on

		Inhalational anaesthesia: sevoflurane (1,0 - 1,5 MAC) + N_2O mixture	limited data)

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

5.2. Pharmacokinetics properties

Absorption:

Since remifentanil is administered intravenously, its bioavailability is 100 %.

Blood concentrations of remifentanil are proportional tot the dose administered throughout the recommended dose range. For every 0,1 µg/kg/min incrase in i.v. infusion rate, the blood concentration of remifentanil will rise to 2,5 ng/mL.

Distribution:

Remifentanil is approximately 70 % bound to plasma proteins.

In a human clinical trial, the average maternal remifentanil concentrations were approximately twice those seen in the foetus. In some cases, however, foetal concentrations were similar to those in the mother. The umbilical arteriovenous ratio of remifentanil concentrations was approximately 30 % suggesting metabolism of

remifentanil in the neonate. Remifentanil related material is transferred to the milk of lactating rats.

Biotransformation:

Remifentanil is an esterse 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 crboxylic acid metabolite (1/4600th as potent as remifentanil).

Studies in man indicated that all pharmacological activity is assocuated witht eh parent compound. The activity of this metabolite is therefore not of any clinical consequence. The half life of the metabolite in healthy adults is 2 hours. Approximately 95 % of remifentanil as the carboxylic acid metabolite is recovered in the urine in patients with normal renal function. Remifentanil is not a substrate for plasma cholinesterase.

Elimination:

Approximately 95 % of remifentanil in the form of the carboxylic acid metabolite is recovered in the uring in patients with normal renal function. Following administration of the recommended doses of remifentanil, the effective biological half-life is 3 - 10 minutes. The average clearance of remifentanil in young healthy adults is 40 mLg/min/kg, the central volume of distribution is 100 mL/kg and the steady-state volume of distribution is 350 mL/kg.

Pharmacokinetics in special populations or special conditions

Cardiac anaesthesia:

The clearance of remifentanil is reduced by approximately 20 % during hypotermic (28 ˚C) cardiopulmonfary bypass. A decrease in body temperature lowers elimination clearance by 3 % per degree centigrade.

Renal impairment:

The rapid recovery from remifentanil-based sedation and analgesia is unaffected by renal status.

The pharmacokinetics of remifentanil 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 acitd metabolite is reduced in patients with renal impairment. In intensive care patients with moderate/severe renal impairment, the concentration of carboxylic acid metabolite is expected to reach approximately 100-fold the level of remifentanil at steady-state. Clinical data demonstrate that the accumulation of the metabolite does not result in clinically relevant μ-opioid effects even after administration of remifentanil infusions for up to 3 days in these patients.

Up to now, data on safety and pharmcokinetic activity of metabolites after infusion of remifentanil for more than 3 days are lacking.

Renal replacement therapy: There is no evidence that remifentanil is extracted during renal replacement therapy. The carboxylic acid metabolite is extracted during haemodialysis by 30 %. In patients with anuria the half-life of the carboxylic acid metabolite is increased to 30 hours.

Hepatic impairment:

The pharmacokinetics of remifentanil 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 susceptible to the respiratory depressant effects of remifentanil. These patients should be closely monitored and the dose of reifentanil should be titrated to the indiviual patient need.

Elderly:

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

Paediatric population:

In children aged 1 to 12 years, remifentanil clearance and volume of distribution decreases with increasing age; the values of these parameters in neonates are approximately twice those of healthy young adults.

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 elimination half-life of remifentanil in neonates is not significantly different from that of young healthy adults.

Changes in analgesic effect after changes in infusion rate of remifentanil should be rapid and similar to those seen in young healthy adults. The pharmacokinetics of the carboxylic

acid metabolite in paediatric patients between 2 and 17 years of age are similar to those seen in adults after correcting for diffences in body weight.

5.3. Preclinical safety data

Non-clinical safety data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Intrathecal administration to dogs of the glycine formulation alone (i.e. without remifentanil) evoked agitation, pain and hind limb dysfunction and incoordination. These effects are believed to be secondary to the glycine excipient. Because of the better buffering properties of blood, the more rapid dilution, and the low glycine concentration of **REMIFENTANIL B. BRAUN ,** this finding has no clinicaal relevance for intravenous administration of **REMIFENTANIL B. BRAUN.**

Remifentanil, like other opioid agonists, produced increases in action potential duration (APD) in dog isolated Purkinje fibres. There were no effects at a concentration of 0,1 micromolar (38 ng/mL). Effects were seen at a concentration of 1 micromolar (377 ng/mL), and were statistically significant at a concentration of 10 micromolar (3770 ng/mL). These concentrations are 12-fold and 119-fold respectively the highest likely free concentrations (or 3-fold and 36-fold respectively, the highest likely blood concentrations) following the maximum recommended therapeutic dose.

Expected signs of μ-opioid intoxication were observed in non-ventilated mice, rats and dogs after large single bolus intravenous doses of remifentanil. In these setudies, the most sensitive species, the male rat, survived following administration of 5 mg/kg.

Intracranial bleedings in dogs caused by hypixia declined within 14 days after stopping remifentanil application.

Mutagenic an tumorigenic potential:

Remifentanil did not yield positive in a series of in vitro and in vivo genotoxicity tests, except in the in vitro mouse lymphoma tk assay, which gave a possitive result with metabolic activation.

Since the mouse lymphoma results could not be considered in further in vitro and in vivo tests treatment with remifentanil is not considered to pose a genotoxic hazard to patients.

Long term animal carcinogencity studies have not been performed with remifentanil.

Reproductive toxicity:

Placental transfers studies in rats and rabbits showed that pups are exposed to remifentanil and/or its metabolites during growth and development. Remifentanil-related material is transferred to the milk of lactating rats.

Remifentanil has been shown to reduce fertility in male rats when administered daily by intravenous injection for at least 70 days at a dose of 0,5 mg/kg, or approximately 250 times the maximum recommended human bolus dose of 2 µg/kg. The fertility of female rats was not affected at dose up to 1 mg/kg when administered for at least 15 days prior to mating. No teratogenic effects have been observed with remifentanil at doses up to 5 mg/kg in rats and 0,8 mg/kg in rabbits. Administration of remifentanil to rats throughout late gestation and lactation at doses up to 5 mg/kg IV had no significant effecton the survival, development, or reproductive performance of the F1 generation.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Glycine

Hydrochloric Acid (for pH-adjustment)

6.2. Incompatibilities

REMIFENTANIL B. BRAUN must not be mixed with other medicinal products except those mentioned in section 6.6.

It should not be mixed Lactated Ringer's Injection or Lactated Ringer's and glucose 50 mg/mL (5 %) solution for injection. **REMIFENTANIL B. BRAUN** should not be mixed with propofol in the same intravenous admixture solution. For compatibility when given into a running i.v. catheter, please see section 6.6.

Administration of **REMIFENTANIL B. BRAUN** into the same intravenous line with blood/serum/plasma is not recommended as non-specific esterase in blood products may lead to the hydrolysis of remifentanil to its inactive metabolite.

6.3. Shelf life

Unopened:

REMIFENTANIL 1 MG B. BRAUN: 2 years

REMIFENTANIL 2 MG B. BRAUN: 2 years

REMIFENTANIL 5 MG B. BRAUN: 2 years

After reconstitution/dilution:

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 immedieately. 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 ºC to 8 ˚C, unless reconstituton has taken place in controlled and validated aseptic conditions,

6.4. Special precautions for storage

Keep in original container until required for use.

Store at or below 25 ˚C.

Do not refrigerate or freeze.

For storage conditions of the reconstituted/diluted medicine product, see section 6.3.

6.5. Nature and contents of container

REMIFENTANIL 1 MG B. BRAUN ; 4 mL vial of colourless type I glass with bromobutyl rubber stopper and cap.

REMIFENTANIL 2 MG B. BRAUN ; 6 mL vial of colourless type I glass with bromobutyl rubber stopper and cap.

REMIFENTANIL 5 MG B. BRAUN ; 10 mL vial of colourless type I glass with bromobutyl rubber stopper and cap.

Pack sizes: 5 vials per pack.

Not all pack sizes may be marketed

6.6. Special precautions for disposal and other handling

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

The containers are for single use only. After use discard container and any remaining contents.

Reconstitution:

REMIFENTANIL B. BRAUN should be prepared for intravenous use by adding the appropriate volume (as stated in the table below) of one of the below listed diluents to give a reconstituted solution with a concentration of approximately 1 mg/ mL.

Presentation	Volume of diluent to be added	Concentration of the reconstituted solution
REMIFENTANIL 1 MG B. BRAUN	1 mL	1 mg/ mL
REMIFENTANIL 2 MG B. BRAUN	2 mL	1 mg/ mL
REMIFENTANIL 5 MG B. BRAUN	5 mL	1 mg/ mL

Shake until completely dissolved. The reconstituted solution should be clear, colourless and free of visible particles.

Further dilution:

After reconstitution, **REMIFENTANIL 1 MG/ 2 MG/ 5 MG B. BRAUN** may be further diluted (see section 6.3 for storage conditions of the reconstituted/diluted product and below for the recommended diluents).

For manually-controlled infusion this medicinal product can be diluted to concentrations of 20 to 250 µg/ mL (50 µg/ mL is the recommended dilution for adults and 20 to 25 µg/ mL for paediatric patients aged 1 year and over).

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

One of the following solutions should be used for dilution:

- Water for Injections
- Glucose 50 mg/ mL (5 %) solution for injection
- Glucose 50 mg/ mL (5 %) solution for injection 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

The solution is to be inspected visually for particulate matter prior to administration. The solution should only be used if the solution is clear and free from particles.

The following intravenous fluids may also be used when administered into a running IV cateter:

- Lactated Ringer's Injection
- Lactated Ringer's and glucose 50 mg/ mL (5 %) solution for injection

REMIFENTANIL B. BRAUN is compatible with propofol when administered into a running IV catheter.

REMIFENTANIL B. BRAUN should not be mixed with propofol in the same intravenous admixture solution.

REMIFENTANIL B. BRAUN should not be administered into the same intravenous line with blood/serum/plasma, as non-specific esterases in blood products may lead to the hydrolysis of remifentanil to its inactive metabolite.

REMIFENTANIL B. BRAUN should not be mixed with other therapeutic agents prior to administration.

Intravenous infusions **REMIFENTANIL B. BRAUN** should be prepared at the time of administration (see section 6.3).

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

REMIFENTANIL 1 MG B. BRAUN - 50/2.9/0961

REMIFENTANIL 2 MG B. BRAUN - 50/2.9/0962

REMIFENTANIL 5 MG B. BRAUN - 50/2.9/0963

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 May 2022

10. DATE OF REVISION OF THE TEXT

27 October 2025