

# **NEW ZEALAND DATA SHEET**

## **1. PRODUCT NAME**

NAROPIN 2 mg/mL WITH FENTANYL 2 microgram/mL (ropivacaine hydrochloride plus fentanyl citrate)

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each mL of solution for infusion contains ropivacaine hydrochloride 2 mg and fentanyl citrate 2 microgram.

For full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

NAROPIN WITH FENTANYL is a sterile, isotonic solution with nominal osmolality of 288 mOsmol/kg and pH of 4.0 – 6.0.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Acute Pain Management: Continuous epidural infusion e.g. postoperative or labour pain.

### **4.2 Dose and method of administration**

Tolerability varies between patients. The lowest dosage that results in effective analgesia should be used and should be based on the status of the patient and the analgesia required. Careful observation of the patient must be maintained during the infusion.

#### **Adults**

Recommended doses for NAROPIN WITH FENTANYL for injection in the average healthy 70 kg adult for up to 72 hours.

<b>Epidural administration Continuous infusion</b>	<b>Volume mL/hour</b>	<b>Dosage</b>	
		<b>Ropivacaine</b>	<b>Fentanyl</b>
Naropin 2 mg/mL + Fentanyl 2 microgram/mL	6-14	12-28 mg/hr	12-28 microgram/hr

#### **Children**

Until further experience has been gained, NAROPIN WITH FENTANYL cannot be recommended for use in children below the age of 12 years.

### **Elderly or debilitated patients**

Debilitated or elderly patients, including those with partial or complete heart conduction block, advanced liver disease or severe renal dysfunction should be given reduced dosage commensurate with their physical condition. Clinical studies with this group of patients have not been performed. (See section 4.4).

### **Test Dose**

For epidural analgesia, a 3-5 mL test dose of a local anaesthetic, preferably containing up to 5 microgram of adrenaline (e.g. Xylocaine 2% with Adrenaline 1:200,000), should be administered. Verbal contact and repeated monitoring of the heart rate and blood pressure should be maintained for 5 minutes following the test dose after which, in the absence of signs of intravascular or intrathecal injection, the main dose may be administered.

An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block. If toxic symptoms or signs occur, the infusion should be stopped immediately.

### **Analgesia**

When calculating the dosage for postoperative analgesia, the use of intraoperative local anaesthetics and opioids should be taken into account.

When prolonged blocks are used, either by continuous infusion or repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Cumulative doses of up to 800 mg ropivacaine for surgery and postoperative analgesia administered over 24 hours were well tolerated, as were postoperative continuous epidural infusions of ropivacaine with 2 microgram fentanyl at rates up to 14 mL/hour for 72 hours.

## **4.3 Contraindications**

### **1. Hypersensitivity**

NAROPIN WITH FENTANYL solutions are contraindicated in patients with known hypersensitivity to local anaesthetics of the amide type or a known intolerance to fentanyl.

### **2. Bronchial asthma.**

See also section 4.4.

### **3. Head injuries and increased intracranial pressure –**

As for any opioid analgesic, fentanyl should not be used in patients susceptible to respiratory depression, such as comatose patients who may have head injuries or a brain tumour. Fentanyl may obscure the clinical course of patients with head injury.

### **4. Concomitant MAO Inhibitors**

Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics and the use of fentanyl in patients who have received MAO inhibitors within 14 days is not recommended. (See section 4.5).

### **5. Myasthenia gravis**

Fentanyl may cause muscle rigidity upon IV administration. Therefore, the need for reversal and muscle relaxants contraindicates its use in patients with a history of myasthenia gravis.

## **4.4 Special warnings and precautions for use**

### **General**

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and medicines necessary for monitoring and emergency resuscitation should be immediately available. Patients receiving major blocks should have an IV line inserted before the blocking procedure. The clinician responsible should be appropriately trained and familiar with diagnosis and treatment of side effects, systemic toxicity and other complications. (See section 4.9).

### **Patients in poor general condition**

Patients in poor general condition due to ageing or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention although regional anaesthesia is frequently the optimal anaesthetic technique in these patients. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimise the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly.

### **Cardiovascular effects**

Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

There have been rare reports of cardiac arrest during the use of ropivacaine for epidural anaesthesia of peripheral nerve blockade, especially after unintentional accidental intravascular administration in elderly patients and in patients with concomitant heart disease. In some instances, resuscitation has been difficult. Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the possibility of a successful outcome.

### **Patients with renal and hepatic impairment**

Ropivacaine is metabolised in the liver and should therefore be used with caution in patients with severe liver disease and repeated doses may need to be reduced due to delayed elimination. Normally there is no need to modify the dose in patients with impaired renal function when used for single dose or short term treatment. Acidosis and reduced plasma protein concentration, frequently seen in patients with chronic renal failure may increase the risk of systemic toxicity (see section 4.2).

Fentanyl should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

### **Hypotension and bradycardia**

Epidural anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced, e.g. by injecting a vasopressor. Hypotension should be treated promptly with a sympathomimetic, repeated as necessary.

Fentanyl may produce bradycardia, which may be treated with atropine; however, it should be used with caution in patients with cardiac bradyarrhythmias.

### **Post-operative monitoring**

Adequate facilities should be available for post-operative monitoring and ventilation. Resuscitative equipment, oxygen and an opioid antagonist should be readily available to manage apnoea.

### **Acute porphyria**

Ropivacaine is possibly porphyrinogenic and should only be prescribed to patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken in the case of vulnerable patients.

**Horner's syndrome**

Following epidural administration, high sympathetic blockade or cranial spread of local anaesthetic especially in pregnant women may occasionally result in Horner's syndrome characterised by miosis, ptosis, and anhidrosis. Spontaneous resolution occurs upon discontinuation of treatment, but close supervision of patients undergoing epidural anaesthesia is recommended in order to address the potential risk of cardiorespiratory collapse due to a high sympathetic block.

**Respiratory depression**

Naropin with Fentanyl should be used with caution in patients with severe impairment of pulmonary function because of the possibility of respiratory depression (e.g. chronic obstructive pulmonary disease, patients with decreased respiratory reserve, or any patient with potentially compromised respiration). In such patients, opioids may further decrease respiratory drive and increase airway resistance. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists. Consult individual product information (nalorphine or naloxone) before employing opioid antagonists.

**Muscle rigidity**

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the dose and speed of injection and may be reduced by slow infusion. It is likely to arise following epidural injection. However, if this effect occurs, it may be managed by the use of assisted or controlled respiration and, if necessary, by administration of a neuromuscular blocking agent compatible with the patient's condition. Nonepileptic myoclonic movements can occur.

**Sphincter of Oddi spasm**

As has been observed with all opioid analgesics, episodes suggestive of Sphincter of Oddi Spasm may occur with fentanyl.

**Abuse and dependence**

Fentanyl has abuse potential. Psychological and physical dependence may occur with repeated or prolonged dosing.

**Concomitant use of Monoamine Oxidase Inhibitors (MAOIs)**

Fentanyl is not recommended for use in patients who require the concomitant administration of MAOIs due to the risk of serotonin toxicity (see section 4.5).

**Concomitant use of Benzodiazepines and other Central Nervous System (CNS) Depressants**

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of fentanyl with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see section 4.5).

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a

lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, 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 fentanyl is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant 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 additional CNS depressants including alcohol and illicit drugs (see section 4.5).

#### **4.5 Interaction with other medicines and other forms of interaction**

Ropivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics e.g. certain anti-arrhythmics, such as lignocaine and mexiletine, since the toxic effects are additive. Specific interactions studies with ropivacaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised (see section 4.4).

#### **CYTOCHROME P450**

In healthy volunteers ropivacaine clearance was reduced by 77% during co-administration of fluvoxamine, a potent competitive inhibitor of P4501A2. CYP1A2 is involved in the formation of 3-hydroxy-ropivacaine, a major metabolite. Thus strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin, given concomitantly with ropivacaine can cause a metabolic interaction leading to an increased ropivacaine plasma concentration. Prolonged administration of ropivacaine should therefore be avoided in patients treated with strong inhibitors of CYP1A2 such as fluvoxamine and enoxacin.

#### **BENZODIAZEPINES AND OTHER CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANTS**

Benzodiazepines and other CNS depressant drugs, e.g. barbiturates, neuroleptics, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxant general anaesthetics, drugs with antihistamines-sedating actions such as antipsychotics, other opioids and alcohol will have additive or potentiating effects with fentanyl. Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see Section 4.4).

#### **SEROTONERGIC MEDICINES INCLUDING MONOAMINE OXIDASE INHIBITORS (MAOIS)**

Caution is advised when fentanyl is coadministered with drugs that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]), antidepressants, migraine medicines and sibutramine. This may occur within the recommended dose.

Signs of serotonin syndrome include confusion, agitation, fever, sweating, ataxia, hyperreflexia, diarrhoea and clonus (spontaneous, induced and myoclonus). Immediate withdrawal of the serotonergic medicines usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

Severe and unpredictable potentiation of opiate effects and/or serotonergic effects by MAOIs has been reported with fentanyl. Fentanyl should not be used within 14 days after discontinuation of treatment with MAOIs. (See section 4.3).

#### **NITROUS OXIDE**

Nitrous oxide has been reported to produce cardiovascular depression when given with high doses of fentanyl.

#### **AMIODARONE**

Profound bradycardia, sinus arrest and hypotension have occurred when patients receiving amiodarone have been given fentanyl for anaesthesia.

### **4.6 Fertility, pregnancy and lactation**

#### **Pregnancy**

Apart from obstetric use, there are no adequate data on the use of ropivacaine in pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see PRECLINICAL SAFETY DATA).

Ropivacaine crosses the placenta and may lower the heart rate of the foetus causing foetal bradycardia. Therefore, careful monitoring of the foetal heart rate is recommended.

The safe use of fentanyl in pregnant women has not been established with respect to possible adverse effects upon foetal development. Opioid analgesics may cause respiratory depression in the newborn infant and should only be used during labour after weighing the needs of the mother against the risk to the foetus. Withdrawal symptoms in newborn infants have been reported with prolonged use of this class of drugs.

Therefore it should be used in women of childbearing potential only when in the judgement of the physician the potential benefits outweigh the possible hazards.

#### **Lactation**

Fentanyl may enter the maternal milk. Therefore, breastfeeding is not recommended for 24 hours following the administration of the medicine.

The excretion of ropivacaine or its metabolites in human milk has not been studied. Based on the milk/plasma concentration ratio in rats, the estimated daily dose to a pup will be about 4% of the dose given to the mother. Assuming that the milk/plasma concentration ratio in humans is of the same order, the total ropivacaine dose to which the baby is exposed by breast feeding is far lower than by exposure *in utero* in pregnant women at term.

### **4.7 Effects on ability to drive and use machines**

Depending on the dose, NAROPIN WITH FENTANYL may have a very mild effect on mental function and co-ordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

### **4.8 Undesirable effects**

Adverse reactions to ropivacaine are rare in the absence of overdosage or inadvertent intravascular injection. Adverse reactions to fentanyl are similar to those observed with other

opioid agonist analgesics. The adverse reactions to NAROPIN WITH FENTANYL are similar to those observed with the individual agents.

These adverse reactions are in general dose related and may result from high plasma levels caused by excessive dosage, rapid absorption or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. They should be distinguished from the physiological effects of the nerve block itself e.g. a decrease in blood pressure and bradycardia during epidural anaesthesia.

Pronounced acidosis, hyperkalaemia or hypoxia in the patient may increase the risk and severity of toxic reactions.

The following list of adverse events is based upon experience with the monotherapies in their usual dosage range. These events are considered to be of clinical importance, regardless of causal relationship.

### Table of Adverse Drug Reactions

(Pooled data from all types of blocks)

<b>Very common (&gt;1/10)</b>	<i>Vascular Disorders:</i> Hypotension
	<i>Gastrointestinal Disorders:</i> Nausea
<b>Common (&gt;1/100)</b>	<i>Nervous System Disorders:</i> Paraesthesia, Dizziness, Headache <sup>a</sup>
	<i>Cardiac Disorders:</i> Bradycardia <sup>a</sup> , Tachycardia
	<i>Vascular Disorders:</i> Hypertension
	<i>Gastrointestinal Disorders:</i> Vomiting <sup>a</sup>
	<i>Renal and Urinary Disorders:</i> Urinary retention <sup>a</sup> , Oliguria
	<i>General Disorders and Administration Site Conditions:</i> Temperature elevation, Rigor, Back pain, Chest Pain, Insomnia
<b>Uncommon (&gt;1/1,000)</b>	<i>Psychiatric Disorders:</i> Anxiety
	<i>Nervous System Disorders:</i> Symptoms of CNS toxicity (Convulsions, Grand mal convulsions, Seizures, Light headedness, Circumoral paraesthesia, Numbness of the tongue, Hyperacusis, Tinnitus, Visual disturbances, Dysarthria, Muscular twitching, Tremor) <sup>b</sup> , Hypoaesthesia <sup>a</sup>
	<i>Vascular Disorders:</i> Syncope*
	<i>Respiratory, Thoracic and Mediastinal Disorders:</i> Dyspnoea <sup>a</sup>
	<i>General Disorders and Administration Site Conditions:</i> Hypothermia <sup>a</sup>
<b>Rare (&gt;1/10,000)</b>	<i>Cardiac Disorders:</i> Cardiac arrest, Cardiac arrhythmias
	<i>Immune system disorder:</i> Allergic reactions (anaphylactic reactions, anaphylactic shock, angioneurotic oedema and urticaria)

**Unknown** Cough, Constipation

*Gastrointestinal Disorders: Dysphagia*

- a These reactions are more frequent after spinal anaesthesia.
- b These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption (see section 4.9).

### **CLASS RELATED ADVERSE DRUG REACTIONS**

This section includes complications related to anaesthetic technique regardless of the local anaesthetic used.

**Neurological complications:** Neuropathy and spinal cord dysfunctions (e.g. anterior spinal artery syndrome, arachnoiditis, cauda equina syndrome), have been associated with intrathecal and epidural anaesthesia.

**Total spinal block:** Total spinal block may occur if an epidural dose is inadvertently administered intrathecally, or if a too large an intrathecal dose is administered.

**Neurological:** Neuropathy and spinal cord dysfunction (e.g. anterior spinal artery syndrome, arachnoiditis, cauda equina syndrome) have been associated with regional anaesthesia, regardless of the local anaesthetic drug used. Convulsions have been observed following unintended intravascular injection of ropivacaine.

**Other:** Blurred vision, miosis, diaphoresis, post operative mental depression, paradoxical CNS excitation, delirium and spasm of the Sphincter of Oddi.

### **CLINICAL TRIALS USING NAROPIN 2 mg/mL WITH FENTANYL 2 microgram/mL**

Clinical trials in patients undergoing epidural infusion for postoperative pain show that the following events were more common in patients receiving NAROPIN WITH FENTANYL than in the group receiving NAROPIN alone: pruritis, ileus, hypomagnesaemia, hypoglycaemia, atelectasis, urine abnormalities, laboratory test abnormalities.

The following events were less common in the NAROPIN WITH FENTANYL group than the plain NAROPIN group: hypothermia, chest pain, vasospasm, coughing.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to <https://pophealth.my.site.com/carmreportnz/s/>.

### **4.9 Overdose**

The symptoms of NAROPIN WITH FENTANYL overdosage are expected to reflect those seen with overdosage of the individual drugs. Systemic toxic reactions may involve the central nervous system and the cardiovascular system.

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15-60 minutes after injection) due to the slower increase in local anaesthetic blood concentration.

## SYMPTOMS

### Acute Systemic Toxicity

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system (CVS). Such reactions are caused by high blood concentration of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas, (see section 4.4). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

**Central Nervous System Toxicity** is a graded response with symptoms and signs of escalating severity. The first symptoms are usually light-headedness, circumoral paraesthesia, numbness of the tongue, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour.

Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly during convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases apnoea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery follows the redistribution of the local anaesthetic agent from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the agent have been injected.

**Cardiovascular Toxicity** may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

Overdose due to fentanyl may result in narcosis (which may be preceded by marked skeletal muscle rigidity), cardiorespiratory depression accompanied by cyanosis, followed by a fall in body temperature, circulatory collapse, coma and possibly death.

## TREATMENT

If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately and CNS symptoms (convulsion, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant drugs.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor and or inotropic agents should be considered. Children should be given doses commensurate with their age and weight.

Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts.

If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration.

The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained.

If severe or persistent hypotension occurs, the possibility of hypovolaemia should be considered and managed with appropriate parenteral fluid therapy.

A specific opioid antagonist, such as nalorphine or naloxone, should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdose of fentanyl is usually longer than the duration of opioid antagonist action.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

#### Ropivacaine

Ropivacaine has both anaesthetic and analgesic effects. At high doses it produces surgical anaesthesia with motor block, while at lower doses it produces sensory block (analgesia) with limited and non-progressive motor block.

The duration and intensity of ropivacaine sensory block are not improved by the addition of adrenaline.

Ropivacaine, like other local anaesthetics, causes reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres.

Local anaesthetics may have similar effects on other excitable membranes, e.g. in the brain and myocardium. If excessive amounts of medicine reach the systemic circulation, symptoms and signs of toxicity may appear, emanating from the central nervous and cardiovascular systems.

Cardiac effects measured *in vivo* in animal studies showed that ropivacaine has a lower cardiac toxicity than bupivacaine.

Pregnant ewes showed no greater sensitivity to ropivacaine than non-pregnant ewes.

Healthy volunteers exposed to intravenous infusions tolerated ropivacaine well. The clinical experience with this medicine indicates a good margin of safety.

Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration, depending on the extent of the concomitant sympathetic block.

#### Fentanyl

Fentanyl is an opioid analgesic. A dose of 100 microgram is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of pethidine. The principal actions of

therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation associated with opioid analgesics may last longer than the analgesic effect. As the dose of opioid is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnoea. Fentanyl appears to have less emetic activity than either morphine or pethidine.

Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl. Recent assays in man show no clinically significant histamine release at doses up to 50 microgram/kg. Fentanyl preserves cardiac stability and blunts stress-related hormonal changes at higher doses.

Fentanyl produces minimal cortical depression and may act by filling receptor sites located in the thalamus, midbrain and spinal cord. A specific morphine antagonist (e.g. nalorphine or naloxone) produces reversal of respiratory, cardiovascular, miotic and motor incoordination effects and also produces reversal of analgesia, euphoria and sedation. Rigidity of the diaphragm and intercostal muscles can be eliminated by suxamethonium. Cholinergic effects such as bradycardia are reversed by atropine.

As with longer-acting opioid analgesics, the duration of the respiratory depressant effect of fentanyl may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO<sub>2</sub> stimulation following administration of fentanyl to man:

1. Diminished sensitivity to CO<sub>2</sub> stimulation may persist longer than depression of respiratory rate. Fentanyl frequently slows the respiratory rate.
2. Altered sensitivity to CO<sub>2</sub> stimulation has been demonstrated for up to four hours following a single intravenous dose of 600 microgram fentanyl to healthy volunteers.
3. Duration and degree of respiratory depression is dose related.
4. The peak respiratory effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection. (See also section 4.4 concerning respiratory depression).

## 5.2 Pharmacokinetic properties

### Ropivacaine

Ropivacaine has a chiral centre and is the pure S-(-)-enantiomer. Ropivacaine has a pK<sub>a</sub> of 8.1 and a distribution ratio of 141 (25°C n-octanol/phosphate buffer pH 7.4).

The plasma concentration of ropivacaine depends upon the dose, the route of administration and the vascularity of the injection site. Ropivacaine follows linear pharmacokinetics and the maximum plasma concentration is proportional to the dose.

Ropivacaine shows complete and biphasic absorption from the epidural space with half-lives of the two phases of the order of 14 minutes and 4 hours. The slow absorption is the rate-limiting factor in the elimination of ropivacaine, which explains why the apparent elimination half-life is longer after epidural than after intravenous administration.

The pharmacokinetic profile of ropivacaine following experimental IV administration is summarised below:

Plasma clearance	440 mL/min
Unbound plasma clearance	8 L/min
Renal clearance	1 mL/min

Volume of distribution at steady-state	47 L
Unbound volume of distribution at steady-state	819 L
Terminal half-life	1.8 h
Unbound fraction	0.06
Hepatic extraction ratio	0.4
Major metabolite	3-OH-ropivacaine

Ropivacaine is mainly bound to  $\alpha_1$ -acid glycoprotein in plasma with an unbound fraction of about 6%. An increase in total plasma concentrations during continuous epidural infusion has been observed, related to a postoperative increase of  $\alpha_1$ -acid glycoprotein.

Variations in unbound, i.e. pharmacologically active, concentration have been much less than in total plasma concentration.

Ropivacaine readily crosses the placenta and equilibrium in regard to unbound concentration will be rapidly reached. The degree of plasma protein binding in the foetus is less than in the mother, which results in lower total plasma concentrations in the foetus.

Ropivacaine is extensively metabolised, predominantly by aromatic hydroxylation. In total 86% of the dose is excreted in the urine after intravenous administration of which only about 1% relates to unchanged medicine. The major metabolite is 3-hydroxyropivacaine, about 37% of which is excreted in the urine, mainly conjugated. Urinary excretion of 4-hydroxyropivacaine, the N-dealkylated metabolite and the 4-hydroxy-dealkylated accounts for 1-3%. Conjugated and unconjugated 3-hydroxyropivacaine shows only detectable concentrations in plasma. 3-hydroxy- and 4-hydroxyropivacaine have a local anaesthetic activity although less than that of ropivacaine.

During epidural infusion, both PPX and 3-hydroxy-ropivacaine are the major metabolites excreted in the urine. Total PPX concentration in the plasma was about half of that of total ropivacaine, however, mean unbound concentrations of PPX was about 7 to 9 times higher than that of unbound ropivacaine following continuous epidural infusion up to 72 hours. The threshold for CNS-toxic unbound plasma concentrations of PPX in rats is about twelve times higher than that of unbound ropivacaine.

Impaired renal function has little or no influence on ropivacaine pharmacokinetics. The renal clearance of PPX is significantly correlated with creatinine clearance. A lack of correlation between total exposure, expressed as AUC, with creatinine clearance indicates that the total clearance of PPX includes a non-renal elimination in addition to renal excretion. Some patients with impaired renal function may show an increased exposure to PPX resulting from a low non-renal clearance. Due to the reduced CNS toxicity of PPX as compared to ropivacaine the clinical consequences are considered negligible in short-term treatment.

There is no evidence of *in vivo* racemisation of ropivacaine.

## Fentanyl

The pharmacokinetics of fentanyl can be described by a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half-life of 219 minutes. The volume of distribution for fentanyl is 4 L/kg.

Fentanyl plasma protein binding capacity increases with increasing ionisation of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. It accumulates in skeletal muscle and fat, and is released slowly into the blood.

Fentanyl is primarily transformed in the liver and demonstrates a high first pass clearance with approximately 75% of an intravenous dose excreted in urine, primarily as metabolites with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the faeces, primarily as metabolites.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride

Water for injections

Hydrochloric acid and sodium hydroxide for pH adjustment.

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

24 months.

For storage after opening, see section 6.6.

### 6.4 Special precautions for storage

Store below 30°C. Do not freeze.

### 6.5 Nature and contents of container

100 mL & 200 mL Polybag<sup>®</sup> infusion bags in Sterile AstraZeneca Theatre Pack<sup>™</sup> (5's)

### 6.6 Special precautions for disposal and other handling

NAROPIN WITH FENTANYL injection solutions do not contain a preservative. Each Polybag is intended for single use only, not exceeding 24 hours. Any solution remaining from an opened Polybag should be discarded.

The intact container must not be re-autoclaved. A blistered container should be chosen when a sterile outside is required.

## 7. MEDICINE SCHEDULE

Controlled Drug B3.

## 8. SPONSOR

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## 9. DATE OF FIRST APPROVAL

3 February 2000

## 10. DATE OF REVISION OF THE TEXT

8 November 2024

## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of “Fentanyl has abuse potential. Psychological and physical dependence may occur with repeated or prolonged dosing.” {Source: Australian PI.}
4.6	Addition and slight rearrangement of existing text for “..withdrawal symptoms in newborn infants have been reported with prolonged use of this class of drugs.” {Source: Australian PI.}
4.8	<ul style="list-style-type: none"> <li>• Addition of dysphagia as an undesirable effect with a frequency ‘not known’. {Source: Australian TGA request.}</li> <li>• Updated URL for reporting suspected adverse reactions.</li> </ul>
4.4	Addition of subheadings & minor reorganization of existing text to improve readability