Reclassification of a Medicine

for consideration by the

Medicine Classification Committee

Part A

1. **International Non-proprietary Name of the medicine**. Ropivacaine Hydrochloride

2. **Proprietary name(s).** Naropin

3. **Name and contact details of the company / organisation / individual requesting a reclassification**.

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Note: Contact details will be removed from the form prior to publication on the Medsafe website.

4. **Dose form(s) and strength(s) for which a change is sought**.

Ropivacaine (0.2%) 2 mg/mL, solution for injection
Ropivacaine (0.75%) 7.5 mg/mL, solution for injection

5. **Pack size and other qualifications**.

Ropivacaine 2 mg/mL, 10 mL and 20 mL vials
Ropivacaine 7.5 mg/mL, 10 mL and 20 mL vials

6. **Indications for which change is sought**. Ropivacaine to be exempt from prescription status when used by Podiatrists with the Scope of Practice (SoP) of Podiatric Surgeons for surgical anaesthesia when performing bone surgery and local infiltration.

7. **Present classification of the medicine**. Ropivacaine has prescription status.

8. **Classification sought**. Ropivacaine be exempt from prescription status for Podiatrists with the extended SoP of Podiatric Surgeons.

9. **Classification status in other countries (especially Australia, UK, USA, Canada).** Podiatric Surgeons in Australia, UK and Canada have exemption to use Ropivacaine, USA Podiatrists/Podiatric Physicians and Surgeons prescribe Ropivacaine.

10. **Extent of usage in New Zealand and elsewhere (eg, sales volumes) and dates of original consent to distribute.** Not applicable.

11. **Local data or special considerations relating to New Zealand (if applicable).** Ropivacaine to be exempt from prescription status by Podiatric Surgeons when performing surgical anaesthesia for bone surgery and local infiltration.

12**. Labelling or draft labelling for the proposed new presentation(s).** Not applicable

13. **Proposed warning statements (if applicable)**. None.

14. **Other products containing the same active ingredient(s) and which would be affected by the proposed change**. Not applicable.

Part B

1. Indications and dose

What is the medicine indicated for, and for which indication(s) is the reclassification application for?

Ropivacaine is indicated for surgical anaesthesia (field block- minor nerve and infiltration, major nerve), analgesia (field block) and peri-op and post-operative pain management. Under the Scopes of Practice (SoP) of the Podiatrists Board of New Zealand, Podiatric Surgeons perform bone procedures and therefore the use of Ropivacaine will assist in the increased duration of surgical anaesthesia and analgesia when compared to Lignocaine.

Podiatrist registered with the Podiatry Board are permitted to use Lignocaine for minor surgical procedures. Podiatrists have demonstrated competence to safely and effectively administer Lignocaine (a restricted medicine classification).

Lignocaine has a faster onset, low lipid solubility, and shorter duration than Ropivacaine. Ropivacaine's indication advantages in relation to prolonged post-op analgesia and anaesthesia with surgical procedures.

Podiatrists have been using other local anaesthetics as indicated by the comments made by Mr Street Orthopaedic Surgeon in a submission made in 2009. "At present, Podiatry prescribing is limited to the use of local anaesthetic agents, with this right being gained under the Medicines Regulations by the Profession in 1975. Lignocaine was approved but the use of Pravacaine, Rapivacaine and Bupivacaine have been used commonly" Street (2009).

What is the evidence that the proposed indication is an OTC indication ie, that the diagnosis and treatment can be understood by the consumer; that the risks of inappropriate treatment can be minimised?

The proposed indication for use of Ropivacaine is surgical anaesthesia (field block, major nerve) and analgesia (field block) and this does not fall under an OTC indication. Diagnosis and treatment are performed by registered healthcare practitioners, Podiatrists with the SoP as Podiatric Surgeons perform surgical several procedures to the foot under local anaesthesia. Consumers are advised of the risks and benefits of the treatment including the use of local anaesthesia. This currently applies to Lignocaine that is exempt from prescription status when used by Podiatrists when performing minor surgery (digital) and local infiltration.

Podiatrists have demonstrated competence to safely and effectively administer Lignocaine (a restricted medicine classification) to patients undergoing minor surgical procedures. This also applies to podiatric surgeons using other local anaesthetics since to 2009.

What is the treatment population for the indication (age; gender etc.)? – What is the dose and dose frequency of the medicine for this indication?
The general population that would require bone surgery to the foot and/or infiltration of local anaesthesia.

Adults and children over 12 years of age: Recommended dosages for Ropivacaine for surgical anaesthesia is based on the average healthy 70 Kg adult patient and is calculated based on 2mg/kg equating to 140mg in 24hours. (Medsafe data sheet for Ropivacaine).

Paediatrics: Children aged between 0 and up to and including 12 years. A single injection of Ropivacaine hydrochloride 0.5% (5 mg/mL) at a dose of 2 mg/kg produces safe and effective analgesia when used for peripheral nerve block in children. (Medsafe data sheet for Ropivacaine).

Older Adult Use: 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. (Medsafe data sheet for Ropivacaine).

2. Presentation

What is the proposed dose form and strength of the medicine to be reclassified?
Ropivacaine 2 mg/mL, solution for injection.
Ropivacaine 7.5 mg/mL, solution for injection. (Medsafe data sheet for Ropivacaine).

Is this the same for all indications? No
Surgical anaesthesia
Field Block: 0.75% (7.5mg/kg), 1-25 mL dose: 7.5- 188mg for minor nerves and infiltration. Major Nerve block: 0.75% (7.5mg/kg), 10-40 mL, dose: 75-300mg. (Medsafe data sheet for Ropivacaine).

Analgesia requirements for adults and children over 12 years of age is based on the average healthy 70 Kg adult patient and is calculated based on 2mg/kg. Field block: 0.2% (2mg/kg), 1-100 mL, dose: 2-200mg. (Medsafe data sheet for Ropivacaine).

What is the proposed pack size for reclassification?
Ropivacaine 2 mg/mL, 10 mL and 20 mL vials
Ropivacaine 7.5 mg/mL, 10 mL and 20 mL vials. (Medsafe data sheet for Ropivacaine).

What is the proposed packaging for the reclassified medicine? Does it include child resistant containers for liquids; a dosing device etc? Not applicable.

What disposal considerations need to be made for the medicine?

The vials are intended for single use only. Opened container for immediate use only. Any solution remaining from an opened container should be discarded. Ampoules - The polypropylene ampoules are specially designed to fit Luer lock and Luer fit syringes. The intact container must not be re-autoclaved. Blistered ampoules enclosed for use in sterile environments. (Medsafe data sheet for Ropivacaine).

What storage considerations need to be made for the medicine?
Store below 25ºC. Protect from light. Do not refrigerate. Do not freeze. (Medsafe data sheet for Ropivacaine).

How practical and easy to use is the proposed presentation? Very easy to use.

3. Efficacy/benefits

What is the evidence for efficacy and the degree of efficacy for the proposed indication(s)?
Keramidas and Rodopoulou (2007), compared the effects of between Ropivacaine and lidocaine in digital nerve blocks. They compared onset time of anaesthetic action, duration and time until first postoperative requirement for pain medication. Their investigation concluded that when performing digital blocks Ropivacaine can be used effectively as a local anaesthetic and procedures longer than 1.5 hours with longer post-operative analgesia than lidocaine. Therefore, Ropivacaine is indicated for surgical anaesthetic by Podiatric Surgeons.

To what extent is this medicine used for the proposed indication(s) ie, duration of use; frequency of use?
The extent depends on the number of patients requiring surgical anaesthesia, when used will be used once with MSD determined in a 24hour period.

What is the history of this medicine's use for the proposed indication(s) ie, number of users; number of countries used in?
Endorsed podiatric prescribers in Australia, Canada and USA have access to use Ropivacaine for surgical anaesthesia and analgesia. At 30 September 2018 there were 5,168 registered Podiatrists in Australia, 99 of whom were endorsed prescribers. In Australia, Podiatrists with prescribing endorsement have had access to Ropivacaine since 2011.

What is the evidence that improved access is beneficial?
Access to Ropivacaine use would increase the public access to minor foot procedures. Currently Podiatric Surgeons must use Ropivacaine under the guidance of a registered Medical Practitioner, increasing the cost to the patient. The necessity for use under guidance potentially increases waiting times for minor foot procedures that a routinely performed by Podiatric Surgeons.

What is the evidence of improved consumer involvement in their health?

Ethical reasons:

The addition of Ropivacaine would create choice for the patient. In consultation with the podiatric surgeon they would be able to make an informed decision as to what is the most suitable form of anaesthesia and analgesia for the procedure. This would facilitate the decision-making process and supports an active role for the patients in managing their own health.

What are the benefits from a consumer viewpoint?
No extra cost to patient care as Ropivacaine is being used part of the treatment, it would assist with increasing duration of anaesthesia and post- operative analgesia.

Health reasons:
The risks associated with general anaesthesia is greater than local anaesthesia. Patients have a choice, rather than general anaesthesia they can now have a choice of a long acting local anaesthetic. Keramidas and Rodopoulou (2007), compared the effects of between Ropivacaine and lidocaine in digital nerve blocks. They noted the onset time of anaesthetic action, duration and time until first postoperative requirement for pain medication. Their investigation concluded that when performing digital blocks Ropivacaine can be used effectively as a local anaesthetic and procedures longer than 1.5 hours with longer post-operative analgesia than lidocaine.

4. Contraindications and precautions

What are the contraindications for the medicine and how easy are they to identify and prevent?

Contraindications:

- Allergy or hypersensitivity to amide type local anaesthetics. Detection of suspected.
- Hypersensitivity by skin testing is of limited value. Skin changes, itchy, hives, wheal and erythema to anaphylaxis. Treatment of anaphylaxis protocol.
- Patients identified, and allergy/hypersensitivity maybe prevented as the patient undergoes an extensive questioning into their history which includes a known history of allergic reaction to any known medications and specifically asked about allergies or prior reactions to local anaesthesia.
- Intravenous administration- identification by aspiration of syringe whilst injecting and seeing a flash of blood in the syringe. This indicates the needle is within the vascular system.

- Local anaesthetics are contraindicated for epidural and spinal anaesthesia in patients with uncorrected hypotension. Podiatric Surgeons do not perform epidural and spinal anaesthesia as part of their SoP.
- Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection and/or in the presence of septicaemia.
- Intravenous regional anaesthesia (Bier's block) as unintentional passage of local anaesthetic into the systemic circulation, despite the use of a tourniquet, may cause systemic toxic reactions. Podiatric Surgeons do not perform (Bier's block) as part of their SoP.
- The use of Ropivacaine hydrochloride is not recommended for obstetric paracervical block. This is not performed by Podiatric Surgeons as part of their SoP.
- General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used, should be taken into account. This is not performed by Podiatric Surgeons as part of their SoP.

What are the precautions for this medicine and how easy are these to understand?

- The lowest dosage that results in effective anaesthesia should be used.
- The safe and effective use of local anaesthetics depends on correct dosage and technique, adequate precautions and readiness for emergencies.
- Debilitated, elderly patients and acutely ill patients including those with complete heart conduction block, advanced liver disease or severe renal impairment should be given reduced doses commensurate with their age and physical condition.
- Careful and constant monitoring of cardiovascular and respiratory vital signs. Awareness of early signs and symptoms of CNS toxicity.
- Ropivacaine should be used cautiously in patients with severe hepatic disease. Repeated doses may need to be reduced due to the increased elimination half-life.
- When used as a single dose or for short term treatment, dosage modification is not normally required for patients with impaired renal function.
- Ropivacaine should be used with caution in patients with known drug sensitivities.
- Local anaesthetics should be used with caution in patients with impaired cardiovascular function.
- Local anaesthetics should be given with great caution (if at all) to patients with pre-existing abnormal neurological pathology. Medsafe data sheet for Ropivicaine

Does the medicine have a low therapeutic index? Yes

What class effects need to be considered and what are the risks?
Reactions to Ropivacaine are characteristic of those associated with other amide-type local anaesthetics. A major cause of adverse reactions to this group of drugs may be associated with excessive plasma levels, which may be due to overdosage, rapid absorption, unintentional intravascular injection or slow metabolic degradation. (Medsafe data sheet for Ropivacaine).

What are the risks of the medicine being used in an OTC environment?
None as Ropivacaine is prescription only.

What other drug interactions need to be considered?
Should be used with caution when using other local anaesthetic agents or those similar in structure to amides as the toxic effects are additive. Alkaline solutions may use precipitation if added to Ropivacaine. Ropivacaine is metabolised by the enzymes CYP1A2 and CYP3A4 and drugs that inhibit these enzymes will affect the metabolism of Ropivacaine. Oral fluvoxamine, Ketoconazole, Cimetidine (theoretical), Paracetamol has been used in combination with Ropivacaine hydrochloride in the clinical programme, without clinical evidence of metabolic interactions. (Medsafe data sheet for Ropivacaine).

What food and/or drink interactions need to be considered?
Not applicable

Are there any other restrictions when taking the medicine ie, driving restrictions or operating machinery?
Local anaesthetics may have a very mild effect on mental function and co-ordination even in the absence of overt central nervous system toxicity and may temporarily impair locomotion and alertness. Patients and carers should be advised to not undertake skilled tasks (including driving) if the anaesthetised region impairs individual's ability to operate this task safely. Patients are advised at the time of scheduling surgery of the restrictions and are encouraged to bring a relative or family member to drive them home, not make a major decision or use of machinery until the next day. (Medsafe data sheet for Ropivacaine).

Are there any special populations where exposure to the medicine needs to be restricted? Yes

Pregnancy: Use in pregnancy-Category B1 - Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. **(**Medsafe data sheet for Ropivicaine).

Lactation: Excretion of Ropivacaine has not been investigated in human milk.

Debilitated and elderly patients: Debilitated and elderly patients and those with partial or complete heart block, advanced liver disease or severe renal dysfunction should be given reduced dose. (Medsafe data sheet for Ropivacaine).

5. Undesirable effects

What are the known undesirable effects and the frequencies of these?

Very common events (>10%) Cardiovascular: Hypotension. Gastrointestinal: Nausea

Common events (>1%) A large number of adverse events have been reported during clinical development, the majority related to the expected effects of the block and to the clinical situation rather than reactions to the drug. Hypotension and nausea have been registered in 39% and 25%, respectively, of the patients treated in clinical studies. Clinical importance: Cardiovascular: Bradycardia, hypertension and tachycardia. Nervous system: Paraesthesia, temperature elevation, rigors (chills), headache and dizziness. Gastrointestinal: Vomiting Other: Urinary retention, back pain, insomnia, chest pain, pain and oliguria .

Uncommon events (≤1%) ***Acute systemic toxicity: More serious but less common reactions that reflect acute systemic toxicity***, include dysarthria, muscular rigidity, muscle twitching, unconsciousness, convulsions, hypoxia, hypercapnia, apnoea, severe hypotension, bradycardia, arrhythmias and cardiac arrest. Convulsions, grand mal convulsions and seizures have been observed following unintended intravascular injection of Ropivacaine hydrochloride.

Rare (≤0.1%) Cardiac disorders: Cardiac arrest, cardiac arrhythmias General disorders and administration site conditions: Allergic reactions (anaphylactoid reactions, angioneurotic oedema and urticaria).

Do these vary for special populations? Yes

A Hypotension is less frequent in children (>1%)

B Vomiting is more frequent in children (>10%)

C These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption**.** (Medsafe data sheet for Ropivacaine).

What are the risks and consequences of known undesirable effects?

Local anaesthesia toxicity results in central nervous system excitation and then depression as well as cardiovascular effects of bradycardia and death. (Medsafe data sheet for Ropivacaine).

Are there any significant safety concerns for the medicine under review?
No

Have there ever been any withdrawals of the medicine or other regulatory actions taken for safety reasons (during a time period or in a specific jurisdiction)?
No

Are there any withdrawal effects following cessation of use of the medicine?
No

6. Overdose

Is there a potential for overdose of the medicine?
Yes, if maximum safe dose is not correctly calculated and administers too much. or clinician, inadvertent intravascular injection. Acute emergencies from local anaesthetics are generally related to high plasma levels or to unintended subarachnoid or intravascular injection of the local anaesthetic solution. If overdose occurs. Peak plasma levels may not be reached for 1-2 hours depending upon the injection site thus signs of toxicity may be delayed. Systemic toxicity would be low due to low dose administration. (Medsafe data sheet for Ropivacaine).

What are the consequences of overdose of the medicine?
Systemic toxicity will affect the Central nervous system and cardiovascular system and result in death. (Medsafe data sheet for Ropivacaine).

Are there any reports of overdose of the medicine?
There have been reports of cardiac arrest when Ropivacaine has been used for epidural anaesthesia or peripheral nerve blockade, especially after inadvertent intravascular administration, in the elderly and patients with concomitant heart disease. Resuscitation has been difficult in some cases. Prolonged resuscitation may be required if cardiac arrest occurs. (Medsafe data sheet for Ropivacaine).

7. Medication errors and abuse/misuse potential

Would reclassification affect the risk of unnecessary use?
No reclassification would not affect the risk of unnecessary use as only podiatrists with to SoP of Podiatric surgeons would have the use of Ropivacaine which currently number four in New Zealand.

Is the medicine be provided with necessary tools to allow correct dosing eg, liquids supplied with a measuring device?
The tool to ensure correct dosing is the calculation of maximum safe dose for and adult and child as discussed in section B part I.

What are the reported medication errors post-market?
There have been reports of cardiac arrest when Ropivacaine has been used for epidural anaesthesia or peripheral nerve blockade, especially after inadvertent intravascular administration, in the elderly and patients with concomitant heart disease**.** (Medsafe data sheet for Ropivacaine).

What are the reported cases of abuse/misuse/accidental overdose?
There have been reports of cardiac arrest when Ropivacaine has been used for epidural anaesthesia or peripheral nerve blockade, especially after inadvertent intravascular administration, in the elderly and patients with concomitant heart disease. (Medsafe data sheet for Ropivacaine).

How would reclassification affect import considerations?
Not applicable

What is the addiction potential of the medicine?
None

8. Communal harm and / or benefit

What are the possibilities of community harm resulting from wider use of the medicine in question (eg, the development of antibiotic resistance in bacteria or increased immunisation rates)?
Not applicable

What are the possibilities of community benefit resulting from wider use of the medicine in question (eg, greater herd immunity as a result of improved access to a communicable disease vaccine)?
Not applicable

9. Integrated benefit-risk statement

A summary of the reclassification benefits.
Podiatric Surgeons will have access to Ropivacaine when performing foot surgery. This will assist in patient having longer surgical anaesthetic and analgesia and reducing post-operative pain medication.

A summary of the reclassification risk of harm.

The risk of overdose by inadvertent intravascular injection or incorrect calculation of maximum safe dose could result in systemic toxicity resulting in respiratory depression and cardiac collapse which would result in death.

A summary of the need for the medicine at the classification proposed.
Podiatric Surgeons have been using long acting anaesthetics as noted by Orthopaedic Surgeon Richard Street since 2009, most likely under- standing orders. Reclassification for use only by Podiatrists with the added scope of practice that being Podiatric Surgeons would ensure restricted authorisation.

Precedent – how are other medicines in the same class classified?
Podiatrist registered with the Podiatry Board are permitted to use Lignocaine for minor surgical procedures. Podiatrists have demonstrated competence to safely and effectively administer Lignocaine (a restricted medicine classification).

10. Risk mitigating strategies

Are there any risk mitigation strategies required? If so, what risk mitigation strategies are required eg, healthcare professional education; integration of care; consumer information to be provided etc?
Podiatric surgeons will attend an education course on the indications of Ropivacaine, contraindications, precautions, review calculation of MSD and advanced anaesthetic foot blocks, and the further Annual Practicing Certificate requirements in submitting documentation with the use of Ropivacaine.

What is the evidence that these proposed risk mitigation strategies would be effective?
To date podiatrists have used Lidocaine safely since 2002, without any ADRs, this has been due to the rigorous undergraduate training in the safe use of Lidocaine. The strict adherence to preoperative history and physicals (vascular etc) and justification for the type of surgical procedure. The identification of patients that are at risk, checking for drug interactions with Lidocaine based on medication history the calculation of maximum safe dose of Lidocaine (3mg/kg). The safety whilst injecting with patients' vitals being monitored, aspirating during the injection to avoid intravascular injection and therefore systemic toxicity. To date these procedures have effectively mitigated the risk.

What post-market surveillance activities would be carried out?

Post-market surveillance (PMS) will be carried out systematically and proactively by the Podiatrists Board of New Zealand to collect and review experience gained from the use of Ropivacaine in clinical practice. The purpose is to identify any need for corrective action. A PMS plan will be developed and gathering non-serious and serious clinical incidents including Adverse Drug Reactions (ADRs).

The podiatric surgeon will be required to detail the use of Ropivacaine that is the procedure, calculated maximum safe dose (mg), volume of drug administered (mL), type of block performed and any documented ADRs.

The podiatric surgeon is required to report suspected adverse reactions after authorisation/administration of a medicine. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions. New Zealand Pharmacovigilance Centre.

The Podiatric Surgeon will be required to submit an anaesthetic log book each year when lodging their Annual Practicing Certificate, to the Podiatrists Board New Zealand. This is achievable as the information of the type of local anaesthesia used concentration, total dose (mg) and/or volume is recorded in the surgical report. The Podiatrists Board will also collect information regarding any feedback and complaints from patients that relate to the practitioners use of Ropivacaine.

Is the proposed reclassification supported by professional bodies? Yes,

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References

Street R. Submission: Designated Prescribing Rights for Podiatrists 2009.

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Keranidas EG, & Rodopoulou SG. Ropivacaine versus lidocaine in digital nerve blocks: a prospective study. *Plast Reconstr Surg.* 2007;119(7):2148-52

New Zealand Pharmacovigilance Centre. https://nzphvc.otago.ac.nz/reporting

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