HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

11 June 2008

NAROPEINE 2 mg/ml, solution for injection in vial presentation
Box of 5 vials containing 10 ml (CIP : 559 917-7)
Box of 5 vials containing 20 ml (CIP : 559 922-0)

NAROPEINE 2 mg/ml, solution for injection in bag presentation
Box of 5 bags containing 100 ml (CIP : 559 943-8)
Box of 5 bags containing 200 ml (CIP : 560 009-3)

Applicant: ASTRAZENECA

Ropivacaine hydrochloride

ATC Code: N01BB09

List II
The 2 mg/ml vials are for hospital use only; the 2 mg/ml bags are for hospital prescription only.

Marketing Authorisation date (by mutual recognition): 20 August 1996

Reason for request: Inclusion on the list of medicines approved for use by hospitals in the following two extensions of indication:

- **In adults and children over 12 years old** for the 2 mg/ml solution in bag presentation: in the **"treatment of acute pain by continuous peripheral nerve block, either by continuous infusion or by intermittent bolus administration (post-operative pain)"** (extension of indication dated December 2003).

- In children aged under 12 **years old** for the 2 mg/ml solution in vial and bag presentations: in children aged 1 to 12 (extension of indication dated October 2001 for vials and May 2007 for bags) and in children aged under 1 (extension of indication dated May 2007 for both vials and bags): in the **"treatment of acute per- and post-operative pain in neonates, infants and children up to the age of 12, by caudal epidural block and by continuous epidural infusion"**.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Ropivacaine hydrochloride

1.2. Indications

"Adults and children over 12:

2 mg/ml, 7.5 mg/ml and 10 mg/ml solutions for injection (vial and bag):

- Surgical anaesthesia:
  - Epidural block for surgery, including Caesarean sections.
  - Parietal infiltration (peripheral nerves and infiltrations).
  - Peripheral block (plexus and trunk blocks)

- Treatment of acute pain:
  - Continuous epidural infusion or intermittent bolus administration (pain after surgery or vaginal labour).
  - Parietal infiltration (peripheral nerves and infiltration).

2 mg/ml solution for injection (bag):

- Treatment of acute pain:

- **Continuous peripheral nerve block either by continuous infusion or by intermittent bolus administration (post-operative pain).**

Children aged 0 to 12:

2 mg/ml solution for injection (vial and bag):

- Treatment of acute per- and post-operative pain in neonates, infants and children aged up to 12:

- **Caudal epidural block.**
- **Continuous epidural infusion.**

The 2 mg/ml concentration of ropivacaine is suitable for the treatment of acute pain".

1.3. Dosage

Ropivacaine must only be used by or under the supervision of doctors who are experienced in locoregional anaesthesia techniques.

1.3.1 In adults and children over 12

The experience of the doctor and information as to the patient's clinical condition are important in selecting the dose. The doses shown in this table are the doses needed to obtain a satisfactory block. They are guidelines to use in adults. Time to take effect and duration may vary from one individual to the next. The figures in the "dose" column are the average doses required. Practitioners are advised to consult standard reference works available for information on factors affecting specific blocking techniques and the individual needs of each patient.

Table 1: Doses needed to obtain a satisfactory block in adults and children over12 years of age

Indication	Concentration (mg/ml)	Volume (ml)	Dose (mg)
2 mg/ml solution, in bag presentation: peripheral nerve block (femoral or interscalene block): continuous infusion or intermittent bolus administration (post-operative pain)	2	5-10 ml/h 10 ml	10-20 mg/h

- In clinical studies, epidural infusion of NAROPEINE 2 mg/ml alone or in combination with fentanyl 1 to 4 µg/ml has been used to treat post-operative pain in the 72 hours following surgery. This combination improves analgesia but entails the adverse effects caused by opiates. This combination has been investigated only for NAROPEINE 2 mg/ml.
- It is important to take into account of the risks of reaching toxic plasma concentrations or inducing local nerve trauma when administering continuous epidural infusion or repeated injection in order to establish peripheral nerve blocks.
- In clinical studies, 300 mg of NAROPEINE 7.5 mg/ml has established the femoral nerve block and 225 mg of NAROPEINE 7.5 mg/ml has established the interscalene block (both prior to surgery). NAROPEINE 2 mg/ml maintained analgesia.
  Infusion or repeated injection of 10 to 20 mg per hour for 48 hours produced adequate and well-tolerated pain control.

1.3.2 <u>In children aged 0 to 12 (2 mg/ml solution for injection, vial and bag presentation)</u>.

- There are no records on the use of ropivacaine in premature infants.
- The doses stated in this table are guidelines for paediatric use. Individual variations may occur. It may be necessary to reduce the dose in children weighing over 25 kg; the dose must be based on the ideal weight.
- Practitioners are advised to consult the standard reference works available for information on factors dependent on the technique and those dependent on the patient.

Table 2: Dose guidelines for paediatric use

Treatment of acute per- and post-operative pain:			
	Concentration mg/ml	Volume ml/kg	Dose mg/kg
Caudal epidural block: single injection (blocks below D 12 in children weighing up to 25 kg)	2	1	2
Continuous epidural infusion (in children weighing up to 25 kg):			
From 0 to 6 months:			
- Bolus dose[(a)]	2	0.5-1	1-2
- Infusion lasting up to 72 hours	2	0.1 ml/kg/h	0.2 mg/kg/h
From 6 to 12 months:			
- Bolus dose[(a)]	2	0.5-1	1-2
- Infusion lasting up to 72 hours	2	0.2 ml/kg/h	0.4 mg/kg/h
From 1 to 12 years:			
- Bolus dose[(b)]	2	1	2
- Infusion lasting up to 72 hours	2	0.2 ml/kg/h	0.4 mg/kg/h

[(a)] The lower doses are recommended for thoracic epidural blocks, and the higher doses for lumbar and caudal epidural blocks.
[(b)] Recommended for lumbar epidural blocks. In practice, the bolus dose must be reduced for thoracic epidural analgesia.

A single injection of a 2 mg/ml concentration of ropivacaine produces adequate post-operative pain control for most patients below D 12 where the dose of 2 mg/kg is administered in a volume of 1 ml/kg.

Doses of up to 3 mg/kg of ropivacaine 3 mg/ml have been investigated in children aged over four. However, this concentration is associated with a higher incidence of motor block.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

N : NERVOUS SYSTEM
N01 : ANAESTHETICS
N01B : LOCAL ANAESTHETICS
N01BB : AMIDES
N01BB09 : ROPIVACAINE

2.2. Medicines in the same therapeutic category

Long-acting, injectable, amino-amide, local anaesthetics (bupivacaine, levobupivacaine, ropivacaine) for locoregional analgesia administered by any anaesthetic technique.

NB: The proprietary drugs listed below have an indication specifying that they are to be used in the treatment of acute per- and post-operative pain; the dosages stated are those given in the Posology section of the SPC.

Strictly comparable medicinal products (same indication, same administration route)

A- In adults and children over 12: treatment of acute pain: continuous peripheral nerve block, either by continuous infusion or by intermittent bolus administration (post-operative pain):

Bupivacaine:
- "Regional anaesthesia: peripheral blocks (trunk and plexus), for surgical anaesthesia or analgesia, including obstetric procedures": BUPIVACAINE AGUETTANT 0.25% solution for injection

- "Analgesia by various types of block":
  - BUPIVACAINE ADRENALINE AGUETTANT 0.25% solution for injection
  - BUPIVACAINE ADRENALINE MERCK 0.25% solution for injection
  - BUPIVACAINE B BRAUN 0.25% (2.5 mg/ml) solution for injection
  - BUPIVACAINE MERCK 0.25% solution for injection

B- Treatment of acute per- and post-operative pain in neonates, infants and children aged up to 12 in the indication "continuous epidural infusion":
- BUPIVACAINE AGUETTANT 0.25% solution for injection "in continuous lumbar epidural infusion for children aged four months and over."
- BUPIVACAINE B BRAUN 0.25% (2.5 mg/ml) solution for injection
- BUPIVACAINE MERCK 0.25% solution for injection
- BUPIVACAINE ADRENALINE AGUETTANT 0.25% solution for injection
- BUPIVACAINE ADRENALINE MERCK 0.25% solution for injection

Other medicines in the same therapeutic class (same indication, different anaesthetic techniques)

A- Treatment of acute pain (post-operative pain) in adults and children over 12:

Bupivacaine by the "central" route:
- "Regional anaesthesia: central blocks (epidural and spinal), for surgical anaesthesia or analgesia, including obstetric procedures": BUPIVACAINE AGUETTANT 0.25% solution for injection
- "Epidural analgesia in the treatment of various forms of pain: neoplastic, post-operative, post-traumatic, arteritic."
  - BUPIVACAINE ADRENALINE AGUETTANT 0.25% solution for injection
  - BUPIVACAINE ADRENALINE MERCK 0.25% solution for injection
  - BUPIVACAINE MERCK 0.25% solution for injection
  - BUPIVACAINE B BRAUN 0.25% (2.5 mg/ml) solution for injection.

Levobupivacaine by the "central" route:
"Continuous epidural infusion or administration by a single bolus or repeated administration for the treatment of pain (especially post-operative or childbirth pain)": - CHIROCAINE 2.5 mg/ml solution for injection.

Ropivacaine by the "central" route:
- "Continuous epidural ifusion or intermittent bolus administration (pain after surgery or vaginal labour).": NAROPEINE 2 mg/ml; 7.5 mg/ml and 10 mg/ml solution for injection.

B- Treatment of acute per- and post-operative pain in neonates, infants and children aged up to 12:

Levobupivacaine for "infiltration analgesia (ilioinguinal blocks/hypogastric block) in children under 12":
- CHIROCAINE 2.5 mg/ml and 5 mg/ml solution for injection.

Bupivacaine: "by various types of block"
- BUPIVACAINE AGUETTANT 0.25% solution for injection
- BUPIVACAINE B BRAUN 0.25% (2.5 mg/ml) solution for injection
- BUPIVACAINE MERCK 0.25% solution for injection
- BUPIVACAINE ADRENALINE AGUETTANT 0.25% solution for injection
- BUPIVACAINE ADRENALINE MERCK 0.25% solution for injection.

2.3. Medicines with a similar therapeutic aim

The other local anaesthetics (mepivacaine: CARBOCAINE; lidocaine: XYLOCAINE) used for locoregional analgesia, opiate analgesics (in particular morphine, fentanyl[1], sufentanyl[2]) indicated in the treatment of acute per- and post-operative pain in adults and/or children, via oral or parenteral administration, and the other analgesics that are used in combination with them.

[1] The indications for fentanyl for injection are "Post-operative analgesia exclusively in patients under close medical supervision (intensive care unit, recovery room)" and "by epidural administration either in isolation or in combination with local anaesthetics".
[2] The indication for sufentanyl is: "In epidural administration, single dose or repeated doses, or in infusion, alone or in combination with a local anaesthetic for surgical, obstetric or post-operative analgesia". SUFENTA and SUFENTANYL RENAUDIN 10 µg/2 ml; 50 µg/10 ml and 250 µg/5 ml solutions for injection.

3 ANALYSIS OF AVAILABLE DATA

The pharmaceutical firm submitted two studies (SP-ROA-0026 and SP-ROP-0005) investigating the treatment of acute pain in adults and children over 12 by continuous peripheral nerve block.

Five studies investigating the treatment of acute per- and post-operative pain in neonates, infants and children up to 12 involving caudal epidural block and continuous epidural infusion were submitted: 3 (SP-ROA-11, 12 and 13) investigating caudal epidural block and 2 (SP-ROA-15 and 16) looking at continuous epidural infusion.

3.1. Efficacy

In the treatment of acute pain by continuous peripheral nerve block in adults and children over 12:

- A pharmacokinetic and dose-finding study (SP-ROA-0026, 27 adults) was conducted to assess the plasma concentration of ropivacaine and its principal metabolite during continuous post-operative interscalene infusion after an interscalene brachial plexus block performed for major shoulder surgery.
- A study (SP-ROP-0005, 138 adults) was conducted to compare the analgesic efficacy and tolerance of a femoral block using ropivacaine 2 mg/ml administered by three different routes (femoral block controlled by the patient by intermittent administration, continuous infusion in isolation, and continuous infusion combined with intermittent administration) in patients who had undergone major knee surgery (total knee prosthesis, crossed ligaments).

These two studies do not provide enough information to determine the therapeutic use of ropivacaine. Furthermore, these two studies were only carried out on patients aged over 18.

In the treatment of acute per- and post-operative pain in neonates, infants and children aged up to 12:
By caudal epidural block:

In neonates and infants:
- a non-comparative study (SP-ROA-12, 37 children) was conducted to determine the pharmacokinetic characteristics of ropivacaine after epidural injection for a single caudal block.

In children aged over one year:
- a non-comparative study (SP-ROA-11, 20 children) was conducted to assess the pharmacokinetic parameters of ropivacaine 2 mg/ml in children aged one to eight years after caudal injection of a single dose of ropivacaine to treat post-operative pain after surgery under general anaesthetic or sedation.
- The purpose of the second dose-finding study (SP-ROA-13, 110 children) was to assess the efficacy and tolerance of three dosages of ropivacaine (1, 2 and 3 mg/kg) administered at 1, 2 and 3 mg/ml to children aged between four and twelve years to treat pain after surgery for an inguinal hernia.

These three (non-comparative) studies do not provide enough information to determine the role of ropivacaine in therapeutic use.

By continuous epidural infusion
- A study (SP-ROA-16, 46 children) was conducted to determine the pharmacokinetic parameters of ropivacaine in neonates and infants after continuous epidural infusion for 36 to 72 hours.
- A study (SP-ROA-15, 34 children) was conducted to determine the pharmacokinetic parameters of ropivacaine in children aged one to twelve years after continuous epidural (lumbar) infusion for 24 to 72 hours.

These two (non-comparative) pharmacokinetic studies do not provide enough information to determine the role of ropivacaine in therapeutic use.

Other clinical data:
A bibliographic search (Medline database) of studies comparing the efficacy of long-acting amino-amide local anaesthetics (ropivacaine, bupivacaine and levobupivacaine) in per- and post-operative pain control was conducted. The results of several studies (ref.[3,4,5,6,7]) show comparable analgesic efficacy in both adults and children.

3.2. Adverse effects

The SPC for ropivacaine indicates that it has a similar adverse effect profile to other long-acting amide bond local anaesthetics. The percentage of patients likely to present adverse effects varies depending on the mode of administration.
Systemic or local adverse effects brought about by NAROPEINE usually occur following an overdose, rapid absorption or accidental intravascular injection. The adverse effects most often reported are nausea and arterial hypotension. It is difficult to distinguish between those attributable to the patient's clinical condition, those due to the expected effects of the block, and reactions to the drug.
Neuropathy and medullary abnormalities (such as anterior spinal artery syndrome, arachnoiditis, cauda equina syndrome) have been associated with locoregional anaesthesia, irrespective of the local anaesthetic used; these can in rare instances have permanent effects.

Data in the context of paediatric use of the 2 mg/ml solution for injection:
- A pooled population analysis was carried out on data collected from 192 children (see the SPC) to investigate the pharmacokinetics of ropivacaine in children from birth to twelve years.
- Particular attention is recommended in neonates in view of the immaturity of the metabolic pathways. The greater variability of ropivacaine plasma concentrations observed in neonates taking part in clinical trials seems to indicate that there may be an increase in the risk of systemic toxicity in this age group, especially during continuous epidural infusion. Severe cardiac disorders are rare.

[3] Simpson D, Curran MP, Oldfield V et al. Ropivacaine: a review of its use in regional anaesthesia and acute pain management. Drugs. 2005;65:2675-717.
[4] Ivani G, DeNegri P, Conio A et al. Comparison of racemic bupivacaine, ropivacaine, and levo-bupivacaine for pediatric caudal anesthesia: effects on postoperative analgesia and motor block. Reg Anesth Pain Med. 2002;27:157-61.
[5] Ingelmo PM, Locatelli BG, Sonzogni V et al. Caudal 0.2% ropivacaine is less effective during surgery than 0.2% levobupivacaine and 0.2% bupivacaine: a double-blind, randomized, controlled trial. Paediatr Anaesth. 2006 ;16(9):955-61 and Br J Anaesth 2005;94:366-71.
[6] Astuto M, Disma N, Arena C. Levobupivacaine 0.25% compared with ropivacaine 0.25% by the caudal route in children. Eur J Anaesthesiol. 2003 ;20:826-30.
[7] Breschan C, Jost R, Krumpholz R et al. A prospective study comparing the analgesic efficacy of levobupivacaine, ropivacaine and bupivacaine in pediatric patients undergoing caudal blockade. Paediatr Anaesth. 2005 ;15:301-6.

- The recommended doses for neonates are based on limited clinical data. Regular monitoring for systemic toxicity and local neurotoxicity is essential when administering ropivacaine to this age group. Monitoring must be continued after the infusion has been completed, as neonates eliminate ropivacaine more slowly.

The available clinical experience with ropivacaine shows a good safety margin when it is used at the recommended doses.

3.3. Conclusion

According to the information presented by the pharmaceutical company, the clinical assessment of ropivacaine (NAROPEINE) in the extensions of indication (treatment of acute post-operative pain by continuous peripheral nerve block, either by continuous infusion or by intermittent bolus administration in adults and children over 12 and treatment of acute per- and post-operative pain in neonates, infants and children aged up to 12 by caudal epidural block or continuous epidural infusion) is based on the results of pharmacokinetic and/or dose-finding studies. This non-comparative data does not provide enough information to determine the role of ropivacaine in therapeutic use.

Furthermore, the efficacy of locoregional analgesia also depends on the technique used (central or peripheral route); the technique selected depends on the type of surgery, the patient's age and his or her clinical condition.

Several published comparative studies show that the efficacy of ropivacaine in these indications is comparable to that of other long-acting amino-amide local anaesthetics (bupivacaine and levobupivacaine) used for per- and post-operative analgesia.

Clinical experience indicates a good safety margin at the recommended doses. Severe cardiac disorders and neurological complications are rare. On the basis of the clinical studies that are available, the safety profiles of the long-acting injectable local amino-amide anaesthetics (bupivacaine, levobupivacaine and ropivacaine) appear to be comparable.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit in the extensions of the indication

Management of post-operative pain is essential after surgery. Locoregional analgesia is justified in the treatment of severe pain, or pain that is expected to be severe after surgery. Effective control of pain is associated with fewer post-operative complications and more rapid functional recovery after orthopaedic surgery. Acute pain is very damaging to quality of life.

NAROPEINE is a symptomatic treatment of acute per- and post-operative pain in the context of locoregional analgesia.

Public health benefit

The public health burden represented by acute (post-operative) pain which could be treated by locoregional analgesia in adults and children can be regarded as moderate.

Improving the treatment of post-operative pain is part of the public health need for improvements in pain treatment (in particular GTNDO*: pain management). This need is only partially met by the other local anaesthetics that are currently available, especially among children.

For patients requiring post-operative analgesia, NAROPEINE offers only a potential advantage in terms of safety compared to bupivacaine (less likelihood of cardiac toxicity and less pronounced motor block). In view of the lack of (comparative) efficacy studies, NAROPEINE is not expected to have any additional impact in terms of morbidity and quality of life compared to levobupivacaine in particular.

NAROPEINE is therefore unlikely to be able to provide a supplementary response to the identified public health requirement.

Consequently, given the current state of knowledge and in view of the existence of other currently available local anaesthetics, NAROPEINE is not expected to benefit public health in these indications.

*Groupe Technique National de Définition des Objectifs [National Technical Objective Definition Group] (DGS-2003)

The efficacy/safety ratio of ropivacaine is high in these indications. Alternatives are available. NAROPEINE is a medication intended for first-line therapy.

The actual benefit of NAROPEINE is substantial in both extensions of indication.

4.2. Improvement in actual benefit

- "In the treatment of acute per- and post-operative pain in neonates, infants and children aged up to 12: - by caudal epidural block; - by continuous epidural infusion", the Committee is of the opinion that NAROPEINE 2 mg/ml solution for injection (vial and bag presentations) provides a minor improvement in actual benefit (IAB level IV) only in infants aged under four months.
- "In adults and children aged over 12 in the treatment of acute pain: continuous peripheral nerve block, either by continuous infusion or by intermittent bolus administration (post-operative pain)", NAROPEINE 2 mg/ml (bag presentations) solution for injection does not provide any improvement in actual benefit (IAB V).

4.3. Therapeutic use

The choice of anaesthetic technique and anaesthetic agent depends in particular on the surgical indication, the patient's clinical condition and the practitioner's experience. Several anaesthetic methods can be used: central or peripheral administration route, choice of peripheral nerve block, methods of administration (three administration routes are possible via the epidural route: bolus injection, continuous infusion and patient-controlled analgesia (PCA)).

In adults and children, locoregional anaesthesia is reserved for patients who have undergone surgery and are experiencing (or are expected to experience) severe pain.
Ropivacaine (NAROPEINE) can be prescribed as an alternative to levobupivacaine or bupivacaine.

The treatment of acute per- and post-operative pain by the locoregional route has been the subject of several publications produced by the SFAR [French Society for Anaesthesia and Intensive Care] in 1997[8], [9] and 1999 [10],[11].

4.3.1 In the treatment of acute per- and post-operative pain in paediatric medicine by caudal epidural block or continuous epidural infusion.

"The use of locoregional anaesthesia (LRA) in paediatric medicine reduces the need for per-operative anaesthetics and post-operative analgesics. LRA and general anaesthesia (GA) complement each other in ensuring optimum per- and post-operative management". (SFAR experts conference, 1997).
"Perimedullary anaesthesia involves invasive analgesic methods which must be reserved for patients undergoing surgery who are experiencing or are expected to experience severe pain. The analgesia is often greater than that obtained by the general route. The epidural route allows practitioners to administer morphine, local anaesthetics (LA) or a multi-drug combination in the context of multimodal analgesia. The combination of LAs and opiates by the epidural route is recommended". (SFAR/ANAES consensus conference, 1997).

"Epidural analgesia can be administered via the lumbar-thoracic route. It should ideally be reserved to children aged over four to six months, and the lumbar route is preferable (better risk/benefit ratio). This is because post-operative analgesia administered by epidural infusion exposes infants aged under four to six months to severe risks of accumulation for pharmacokinetic reasons. For this reason, the technique must be used only in specialised centres and for periods not exceeding 48 hours". (SFAR experts conference, 1999).

Choice of a local anaesthetic for use in locoregional analgesia [12]
- Most clinical studies have assessed LAs in the context of epidural analgesia involving a caudal block. This technique should preferably be used in children under eight and for sub-umbilical surgery (to resolve an inguinal hernia, perform orchidopexy, treat hypospadias, etc.).

[8] Prise en charge de la douleur postopératoire chez l'adulte et chez l'enfant [Management of post-operative pain in adults and children]. SFAR/ANAES consensus conference, 12 December 1997.
[9] Anesthésie loco-régionale chez l'enfant [Locoregional anaesthesia in children]. Experts conference 1997, SFAR. In Ann Fr Anesth Réanim 1997 ;16 : 2-7.
[10] Attitude pratique pour la prise en charge de la douleur post-opératoire [Practical approach to the management of post-operative pain]. Expert groups. SFAR 1999.
[11] Les blocs périphériques des membres de l'adulte [Peripheral limb blocks in adults]. Clinical practice guidelines. SFAR December 2003.
[12] Ref. : Mazoit J.-X. Anesthésiques locaux en pédiatrie. Critères de choix [Local anaesthetics in paediatric medicine. Selection criteria]. 12th session of the French Society for Paediatric Anaesthesia and Resuscitation (ADARPEF) - 27 September 2006.

- A peripheral block (such as an ilioinguinal block) may be more appropriate for children over eight.
- Continuous epidural block techniques, especially those involving the thorax, should be carried out only by trained practitioners and at centres with considerable experience.

Role of ropivacaine

Ropivacaine has been found to be comparable to levobupivacaine and bupivacaine in terms of analgesic efficacy (at equipotent doses).

Some experts believe that ropivacaine could, like levobupivacaine, be less cardiotoxic than bupivacaine. However, there is little clinical evidence that could confirm this for adults and children. The thinking is that the motor block induced by levobupivacaine and ropivacaine administered by the caudal or epidural route is shorter and less intense than that induced by bupivacaine.

Other forms of anaesthesia

"Continuous peripheral nerve block (CPNB) plays a major role in the management of post-operative pain in paediatric medicine. It is indicated after major surgery of the limbs, after surgery for which post-operative physiotherapy is immediate and essential, and for the treatment of algoneurodystrophy.

Ropivacaine, and perhaps levobupivacaine, seem to be the benchmark local anaesthetic used at low concentrations and a slow rate of administration[13].

4.3.2 Treatment of acute pain by continuous peripheral nerve block in adults and children over 12.

"Peripheral nerve blocks are indicated after orthopaedic surgery on the limbs. The use of a catheter, allowing for continuous or discontinuous administration of analgesics, prolongs analgesia and facilitates the post-operative rehabilitation of patients. Peripheral analgesic blocks are often associated with general analgesics, in particular non-steroidal anti-inflammatories (NSAIDs) and/or paracetamol (multimodal analgesia). Locoregional analgesia is better than that obtained with morphines administered via the general route or by PCA in the case of dynamic pain associated with active or passive mobilisation". (SFAR expert consensus, 1999: "practical approach to the management of post-operative pain").

Role of ropivacaine

According to the SFAR clinical guidelines (2003) on peripheral blocks of the limbs in adults:

- The pharmacological agents which can be used to produce plexus and trunk blocks of the limbs include short- to intermediate-acting LAs (lidocaine, mepivacaine) and long-acting LAs (ropivacaine, bupivacaine). Long-acting LAs must be used for all procedures likely to last one and a half hours or more.

  N.B.: levobupivacaine had not yet been granted a Marketing Authorisation, which is why its role was not discussed.

- The time until the block is in place is shorter with ropivacaine 0.75% than with bupivacaine 0.5%.
- The time that the block remains active after perinervous administration is similar for ropivacaine 0.75% and bupivacaine 0.5%.

Systemic adverse effects

- At equal doses, the systemic, cardiac and neurological toxicity of ropivacaine is less pronounced than the bupivacaine ones.

[13] Réf. : Lacroix F. Analgésie locorégionale périphérique continue chez l'enfant [Continuous peripheral locoregional analgesia in children]. Ann Fr Anesth Reanim 2007 ;26(6) : 554-559.

- All agents are liable to trigger convulsive events (1 in 800 to 1 in 1,500 blocks). The neurological toxicity ratio of bupivacaine, ropivacaine and lidocaine is 4:3:1 respectively.
- Bupivacaine, etidocaine and, at a lesser extent, ropivacaine, can trigger serious cardiac events which may lead to death. These events are rare.
- Allergy to amide LAs is very rare, but the adrenalin-based solutions contain preservatives which can trigger allergic reactions.

Some experts are of the opinion that "after having induced an initial block, long-acting local anaesthetics (ropivacaine, levobupivacaine and bupivacaine at low concentrations) are recommended for continuous analgesia. Compared to ropivacaine, bupivacaine exposes patients to a more powerful motor block and to cardiotoxicity and myotoxicity.
The clinical efficacy of levobupivacaine is comparable to bupivacaine one; its cardiotoxicity lies between the bupivacaine and that of ropivacaine ones"[14].
However, these observations are not validated by clinical data.

Other techniques
Perimedullary blocks[15] make use of rachianaesthesia (sub-arachnoid or intrathecal anaesthesia) or epidural techniques. Post-operative analgesia agents administered via the perimedullary route include local anaesthetics (in particular, ropivacaine, bupivacaine and levobupivacaine), opiates (morphine, alfentanyl, fentanyl and sufentanyl) which exert a synergic analgesic effect by the intrathecal and epidural routes when administered with adjuvant local anaesthetics (adrenaline, clonidine).

According to the SFAR expert consensus dated to 1999: ("practical approach to the management of post-operative pain"):
- Unless contraindicated, perimedullary analgesia (mainly via the epidural route) is reserved specifically for patients who may have a respiratory or cardiovascular handicap and/or who have undergone surgery that is known to be or likely to be painful. Lumbar or thoracic epidural analgesia is indicated particularly following surgery of the chest and abdomen, and for orthopaedic surgery.
- For orthopaedic surgery of the lower limbs, epidural analgesia follows on from the anaesthesia technique. However, comparable analgesia can be obtained by trunk nerve blocks.

4.4. Target population for the two extensions of indication

4.4.1 Extension of indication in adults and children over 12: treatment of acute pain by means of a continuous peripheral nerve block by continuous infusion or intermittent bolus infusion (post-operative pain).

The SFAR guidelines[16] indicate that procedures where patients are likely to benefit from continuous peripheral nerve block are surgery of the shoulder, knee, hip and foot. Data from the PMSI (2005) shows a total of approximately 170,000 procedures: 33,048 for shoulder surgery, 50,035 for knee surgery, 23,552 for hip surgery and 63,352 for foot surgery. The target population can be estimated at over 170,000 patients.

14 Fuzier R., Fourcade O. Cathéter nerveux périphérique [Peripheral nerve catheter]. Ann Fr Anesth Reanim. 2006;25(1):84-8.
15 Les blocs périmédullaires chez l'adulte. Recommandations pour la pratique clinique [Perimedullary blocks in adults. Clinical guidelines]. SFAR. 2006.
16 Les blocs périphériques des membres de l'adulte [Peripheral limb blocks in adults]. Clinical guidelines. SFAR. December 2003.

4.4.2 Extension of indication in children up to the age of 12 in the treatment of acute per- and post-operative pain by means of a caudal epidural block or continuous epidural infusion.

The caudal block is the most commonly practised locoregional anaesthesia technique in paediatric medicine. It is suitable for sub-umbilical surgery - resolving an inguinal hernia, orchidopexy, treating hypospadias. A survey[17] of 1,526 anaesthetists/resuscitation specialists into the practice of paediatric anaesthesia in France was conducted between 1993 and 1994. It was updated in 2006[18]. The preliminary work (47 participating centres) over the first three months is summarised below:

Table 3: Practice of anaesthesia in paediatric medicine

Procedures	Number over three months	Extrapolation to 12 months
Central GA + LRA	2,701	10,804
Peripheral GA + LRA	4,873	19,492
All GA	32,124	128,496
Single-injection LRA		
Upper limb	473	1,892
Lower limb	707	2,828
Trunk	3,136	12,544
Total	4,316	17,264
Catheter LRA		
Central LRA	341	1,364
Peripheral LRA	216	864
Total	557	2,228

The target population for NAROPEINE in paediatric medicine comprises:
- children undergoing surgery under general anaesthetic (GA) combined with locoregional anaesthetic: 30,296 children (2,701 + 4,873, or 7,574 per quarter extrapolated to 12 months).
- 2,228 of these children (557 per quarter extrapolated to 12 months) are operated under LRA administered via a catheter.

The target population for NAROPEINE would therefore be around 30,000 children, of whom slightly over 2,000 might benefit from continuous administration.

4.5 Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the two extensions of indication.

[17] Giaufré E. et al. Epidemiology and morbidity of regional anesthesia in children: a one-year prospective survey of the French-language society of pediatric anesthesiologists. Anesth Analg 1996; 83: 904-12.

[18] Lacroix F. et al. Enquête prospective Adarpef sur la morbidité de l'anesthésie locorégionale en pédiatrie : résultats préliminaires [Adarpef prospective survey on morbidity of locoregional anaesthesia in paediatric medicine: preliminary findings]. Annales Françaises d'Anesthésie et de Réanimation 2007; 26 : S187 (R424).