

**Rapporteur's
Public Paediatric Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

Ropivacaine hydrochloride

**NaropinTM, NaropTM, NaropeineTM, NaropinaTM,
AnapeineTM**

DE/W/027/pdWS/001

Rapporteur:	Germany (DE)
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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	Ropivacaine hydrochloride
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	N01BB09
Pharmaceutical form(s) and strength(s):	2 mg/ml solution for infusion 2 mg/ml solution for injection 5 mg/ml solution for injection 7,5 mg/ml solution for injection 10 mg/ml solution for injection

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.1, 4.2., 4.4, 4.8, 5.2.

SmPC and PL should be specified for each strength.

Summary of outcome

- ☐ No change
- ☒ Change
 - ☐ New study data
 - ☐ New safety information
 - ☒ Paediatric information clarified: sections 4.1, 4.2, 4.4, 4.8, 5.2
 - ☒ New indication: sections 4.1, 4.2, 4.4

II. RECOMMENDATION¹

Overall conclusion

The paediatric information for the different strengths of ropivacaine has to be clarified. For the 2 mg/ml strength a new paediatric indication can be derived from the data submitted by the MAH.

Recommendation

Type IB variation to be requested from the MAH by 16th January 2012 to introduce the recommended wording (please refer to Section VIII) for the paediatric population in the SmPCs of the different strengths:

III. INTRODUCTION

Ropivacaine is a long acting local anaesthetic of the amide type, similar to bupivacaine, but with a lesser extent of CNS and cardiac toxicity and a lesser extent of motor block with equal sensory block.

Ropivacaine (NaropinTM, NaropTM, NaropeineTM, NaropinaTM) was initially approved in Sweden in 1995 and has so far been approved in more than sixty countries including the EU and the US.

Ropivacaine is approved for epidural administration, local infiltration and peripheral nerve blocks. The 5 mg/ml solution for injection is indicated for intrathecal administration for surgical anaesthesia only. At present, for the paediatric population (0 – 12 years with a body weight up to 25 kg) dosing recommendations are given for the 2 mg/ml solution for single and continuous caudal epidural block. In some countries (RMS excluded) approval has also been granted for peripheral nerve block in children aged 1 to 12 years.

AstraZeneca is not aware of any unsubmitted sponsored studies or data that relate to the paediatric use of ropivacaine. Nevertheless, Astra Zeneca submitted 6 completed paediatric studies for ropivacaine which have already been assessed during the variation procedure NL/H/104/01/II/43. These paediatric studies as well as the re-submitted Clinical Expert Statement have been the basis for the extension of the indication for ropivacaine 2 mg/ml for single caudal block (0-12 months) as well as extended duration of administration (continuous epidural administration) up to 72 hours. Approval of this variation has been granted in December 2007 by Austria, Belgium, Czech Rep. Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and UK.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Ropivacaine and that there is no consequential regulatory action in accordance with Article 45 of the Regulation (EC) No 1901/2006

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

For ropivacaine, several formulations are marketed:

2 mg/ml solution for infusion
2 mg/ml solution for injection
5 mg/ml solution for injection
7,5 mg/ml solution for injection
10 mg/ml solution for injection

IV.2 < Non-clinical aspects>

not applicable

IV.3 <Clinical aspects>

The MAH submitted reports for:

- **SP-ROA-0013:** Efficacy and tolerability of 1,2 and 3 mg/kg ropivacaine administered as a single caudal block for pain management after inguinal surgery in children aged 4-12 years with a body weight of up to 25 kg: a comparative, randomized and double-blind study.
- **SP-ROA-0011:** A pharmacokinetic evaluation of ropivacaine 2 mg/kg in 1-8-year-old children following single caudal block for per-and postoperative pain management.
- **SP-ROA-0014:** Documentation of efficacy and safety of ropivacaine in 1-12-year old children following ilioinguinal nerve block (3 mg/kg) for pain management
- **SP-ROA-0012:** A population pharmacokinetic evaluation of ropivacaine 2 mg/ml in children aged 0-12 months following single caudal block for per- and postoperative pain management
- **SP-ROA-0015:** A pharmacokinetic and clinical evaluation of continuous lumbar epidural infusion of ropivacaine for 24-72 hours in 1-12 year old children for postoperative pain management after major surgery
- **SP-ROA-0016:** A pharmacokinetic and clinical evaluation in an open study with continuous epidural infusion of ropivacaine for 36-72 hours in 0-12 month old patients for postoperative pain management after major abdominal surgery.
- Retrospective population pharmacokinetic analysis of ropivacaine (Naropin) in neonates, infants and children

The 6 completed paediatric studies for ropivacaine including the population pharmacokinetic analysis have already been assessed during the variation procedure NL/H/104/01/II/43. Together with the re-submitted Clinical Expert Statement they have been the basis for the extension of the indication for ropivacaine 2 mg/ml for single caudal block (0-12 months) as well as extended duration of administration (continuous epidural administration) up to 72 hours. Approval of this variation has been granted in December 2007 by Austria, Belgium, Czech Rep. Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and UK.

A 3-year PSUR work sharing procedure is underway for the period 15 September 2008 to 14 September 2009 with NL as the PSUR-RMS. The PSUR (Periodic Safety Update Report) for Ropivacaine hydrochloride (Narop, Naropin, Naropeine, Naropina, Anapeine) (2, 5, 7.5, and 10 mg/ml solution for injection and 2 mg/ml solution for infusion) has been submitted during this

Paediatric Worksharing Procedure as well. So far, no issues concerning either safety profile or benefit/risk ratio for the paediatric population could be detected. However, the Final Assessment Report of the PSUR Worksharing Procedure is not yet available.

The MAH presented literature references up to year 2003 with the Expert Report prepared for the above mentioned variation procedure. However, a statement about the impact of recent published data is missing as well as a review about available data concerning the use of ropivacaine for peripheral nerve block in children. As stated by the MAH this indication is approved only in some countries, which implies that there might be considerable off-label use in countries without approval.

The actual wording of the SmPC (August 2008) of Naropin™ is not in agreement with the Guideline on Summary of Product Characteristics Vol 2C NTA Rev 2, September 2009 (see also <http://eudrasmpc.eudra.org/>) and thus, is mistakable concerning the paediatric indication. This concern has already been raised during several European (DC/MR) Procedures for generic ropivacaine products. Hence, the actual requirements have been adopted in SmPC and PL (e.g. NL/H/1575/001-005/DC which was finalised in March 2010 with the following Member States: BE/BG/CY/DE/DK/EL/ES/FI/FR/IE/IT/LU/NO/PT/RO/SE/SI/UK involved).

*The MAH is asked to present a review of the recent published literature concerning the paediatric use of ropivacaine (all indications) as well as the Final Assessment Report of the PSUR Worksharing Procedure if already available.
The MAH should provide a proposal for the SmPC wording regarding the paediatric population in accordance with the actual SmPC –Guideline.*

The recommendations given below were endorsed by UK. No further comments have been given by other Member States.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

AstraZeneca is not aware of any unsubmitted sponsored studies or data that relate to the paediatric use of ropivacaine. The data submitted has already been assessed during the variation procedure NL/H/104/01/II/43. However, a review of recent published literature is missing.

➤ Recommendation

Based on the data submitted, the MAH should provide additional information and a proposal for SmPC and PL wording as part of this worksharing procedure. (see section VI "Request for supplementary information").

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

List of questions:

1. The MAH is asked to present a review of the recent published literature concerning the paediatric use of ropivacaine with a short statement about the relevance for consequential regulatory actions in accordance with Article 45 of the Regulation (EC) No 1901/2006.

2. The MAH is asked to review the paediatric indication peripheral nerve block taking into account also published data as this indication.
3. The Final Assessment Report of the PSUR Worksharing Procedure if already available.
4. The MAH should provide a proposal for the SmPC wording regarding the paediatric population in accordance with the actual SmPC –Guideline (NTA Rev 2, Vol. 2c, September 2009).

VII. ASSESSMENT OF RESPONSE TO QUESTIONS

Question 1

The MAH is asked to present a review of the recent published literature concerning the paediatric use of ropivacaine with a short statement about the relevance for consequential regulatory actions in accordance with Article 45 of the Regulation (EC) No 1901/2006.

Summary of the MAH's response

AstraZeneca has made a review on articles in peer reviewed journals from 2003 until 2010 in order to summarise the key information regarding efficacy and safety aspects when ropivacaine has been administered to paediatric patients. From this review it was concluded that Naropin can be safely and effectively used for the currently approved paediatric indications (caudal epidural block and continuous epidural infusion). It was further suggested that single infiltration with Naropin offer a less complicated technique and therefore is a valid option.

Assessment of the Applicant's response

In the majority of the publications (for details please refer to Appendix I), caudal epidural block is used which, since 2007, is an approved indication for ropivacaine in paediatric patients. No new regulatory relevant information regarding safety or dosing of ropivacaine for caudal epidural block could be drawn from these publications.

7 publications concerning the use of ropivacaine for local anaesthesia (infiltration, instillation, topical analgesia) in children have been discussed by the MAH as possibly indicating that ropivacaine is a frequently used drug for this application in children:

Sakellaris G et al.: Effects of ropivacaine infiltration on cortisol and prolactin responses to postoperative pain after inguinal hernioraphy in children. J Pediatr Surg 2004; 39(9): 1400-3

45 ASA I children aged 6-10 years undergoing hernia repair were randomised into 3 groups: infiltration with ropivacaine 0,5% (0,25 ml/kg) 2 min before incision, infiltration after hernia repair or no infiltration. Addition of local infiltration to general anaesthesia significantly decreased hormonal response to surgical stress and reduced postoperative pain intensity.

Biral E et al.: Multiple BM harvests in paediatric donors for thalassaemic siblings: safety, efficacy and ethical issues. Bone Marrow Transpl 2008; 42(6): 379-84

The study aimed to determine safety and efficacy involved in multiple bone marrow harvests in 7 paediatric donors aged 7-16 years for their thalassaemic siblings. BM harvests were performed under general anaesthesia. Patients received 0,75% ropivacaine 4 mg/kg as infiltration immediately after surgery with uneventful follow ups.

Gemma M et al.: Ropivacaine peritonsillar infiltration for analgesia after adenotonsillectomy in children: A randomised, double-blind, placebo-controlled Study. Ann Otolaryngol Rhinol Laryngol 2009; 118(3): 227-231

Intraoperative peritonsillar infiltration with 0,75% (0,2ml/kg) in 30 ASA I-II children aged 3-7 years did not show significant more postoperative pain relief compared to the control group (infiltration with normal saline).

Unal Y et al: Comparison of bupivacaine and ropivacaine on postoperative pain after tonsillectomy in paediatric patients. Intl J Pediatr Otorhinolaryngol 2007; 71(1): 83-7

In this prospective study 60 ASA I-II patients aged 4-17 years undergoing tonsillectomy were randomly allocated to bilateral peritonsillar infiltration with either 3-5 ml ropivacaine 0,2%, bupivacaine 0,25% or normal saline. Pain scores were significantly lower in the ropivacaine and bupivacaine groups.

Di Pace MR et al.: Efficacy of periportal infiltration and intraperitoneal instillation of ropivacaine after laparoscopic surgery in children. J Laparoendosc Adv Surg Techn Part A 2009; 19(6): 821-5

30 children mean age 11-12 (> 6 years) undergoing laparoscopic surgery received either local infiltration of port sites with 10 ml ropivacaine (0,75% in children > 10 years, 0,2% in children < 10 years), infiltration of port sites and an intraperitoneal instillation of 10 ml ropivacaine each or no treatment. At 6 and 12 hrs postoperative, pain relief was significantly better in the ropivacaine groups.

Ouaki J et al.: Continuous infusion of ropivacaine: an optimal postoperative analgesia regimen for iliac crest bone graft in children. Pediatr Anesth 2009; 19(9): 887-91

In 16 ASA I-III children aged 4-16 years undergoing maxillary alveolar graft with iliac crest bone, a continuous infusion of 0,2% ropivacaine (0,125 ml/kg/h) was performed with an initial bolus dose of 0,2-0,4 ml/kg at the iliac crest donor site. The median graft pain scores were 0 during the whole studied period. No AEs related to local anesthetic were observed.

Oghan F et al.: Does topical ropivacaine reduce the post-tonsillectomy morbidity in paediatric patients? Intl J Pediatr Otorhinolaryngol 2008; 72(3): 361-5

41 ASA I children aged 4-16 years were prospectively randomized to receive double-blind postoperatively a swab soaked with 2 ml of ropivacaine 1% or with saline in the tonsillar fossae. Ropivacaine significantly relieved postoperative pain and the authors judged this method as safe and effective.

The RMS agrees that possibly these publications are indicating that ropivacaine is a frequently used drug for local application in children, however they cover various methods of applications in small paediatric populations. Furthermore, different strengths of ropivacaine were used. In conclusion, the database is too small to derive safety and efficacy for an additional paediatric indication.

Frawley G et al.: Ropivacaine spinal anesthesia in neonates: a dose range finding study. Paediatr Anesth 2007; 17(2): 126-32

In this prospective study 50 premature children with a mean age of 43 weeks postmenstrual age and a mean weight of 3.7 kg were included. Ropivacaine in concentrations of 0.5, 0.75, 1.0, 1.25 and 1.5 mg/kg was administered intrathecally in order to determine the minimum local anaesthetic dose (MLAD) defined as the median effective local aesthetic dose for spinal anaesthesia in neonates. The dose-response curve for spinal anaesthesia including the clinically relevant ED₉₅ dose and to describe the duration of motor block following ropivacaine spinal anaesthesia was also determined. The motor block MLAD determined by the Dixon-Massey

method was 0.51 (0.38-0.64) mg/kg. The ED₅₀ (95% CI) was 0.50 (0.39- 0.63) mg/kg with an estimated ED₉₅ was 1.08 (0.70-1.67) mg/kg. Overall the mean duration of lower limb motor blockade was 1 h (51.5-68.5 min). The duration of anaesthesia far exceeded surgical duration in all successful cases. Ropivacaine was found to be an effective agent for spinal anaesthesia in neonates at a recommended dose of 1.08 mg/kg. The motor block duration, however, was significantly shorter than equivalent agents and highly variable in duration.

Frawley G et al.: Relative potencies of bupivacaine, levobupivacaine and ropivacaine for neonatal spinal anaesthesia. Br J Anaesth 2009; 103(5): 731-8

In this two-stage study the effective dose in 50% of the subjects (ED₅₀), the effective dose in 95% of the subjects (ED₉₅), and the relative analgesic potency of isobaric spinal bupivacaine, levobupivacaine and ropivacaine were determined in 151 expremature children, mean age 42.3 – 44.4 weeks postmenstrual age. Firstly, 81 infants were randomised in a Dixon-Massey study to describe the minimum local analgesic dose. Thereafter, a further 70 patients were randomly allocated to receive spinal anaesthesia with doses in the upper dose-response range to define the ED₉₅. The ED₅₀ doses for bupivacaine 0,5%, levobupivacaine 0,5%, and ropivacaine 0,5% were estimated by isotonic regression to be 0.30 mg/kg, 0.55 mg/kg and 0.50 mg/kg, respectively. The ED₉₅ of bupivacaine, levobupivacaine and ropivacaine were 0.96 mg/kg (95 CI 0.83-0.98), 1.18 mg/kg (1.05-1.22) and 0.99 mg/kg (0.73- 1.50) respectively. No blocks reached an excessive dermatomal height. No AEs related to the local anaesthetics occurred. From this study it is reported that appropriate doses for infant spinal anaesthesia are 1 mg/kg of isobaric 0.5% bupivacaine and ropivacaine and 1.2 mg/kg of isobaric 0.5% levobupivacaine.

Unfortunately, apart from these interesting two studies in expremature infants of whom nearly 100 patients were treated with ropivacaine, no further data is presented about the use of ropivacaine for spinal anaesthesia in children. From these two studies it can be derived that 1 mg/kg of ropivacaine 0,5% seems to be an appropriate dose for spinal anaesthesia in infants. Further studies have to confirm this.

Gouda N: Comparison of ropivacaine 0,1% and lidocaine 0,3% for intravenous regional anaesthesia in infants undergoing club foot release. Egypt J Anaesth 2003; 19(3): 255-60

36 infants aged 10-24 months undergoing elective release of congenital clubfoot were randomised to receive either 1 ml/kg lidocaine 0,3% or ropivacaine 0,1% for IVRA or no IVRA. All received general anaesthesia. Intraoperatively, IVRA patients maintained haemodynamic stability and consumed less anaesthetics. Postoperatively control patients showed higher pain scores. Ropivacaine provided a longer duration of postoperative analgesia compared to lidocaine.

With this single publication the database regarding intravenous regional anaesthesia in children is very scarce. No regulatory action is required.

Overall Summary and Conclusion

No changes regarding the caudal epidural block indication result from the presented literature. Although there might be a considerable off label use, the database for paediatric local infiltration and topical analgesia is rather small. This accounts also for the use of ropivacaine in spinal anaesthesia and intravenous anaesthesia in children. Thus, at present, no regulatory changes are required.

Question 2

The MAH is asked to review the paediatric indication peripheral nerve block taking into account also published data as this indication.

Summary of the MAH's response

AstraZeneca has made a review of the currently available documentation in the indication peripheral nerve block in paediatric patients, including

- one AstraZeneca sponsored study (SP-ROA-0014)
- a comprehensive population pharmacokinetic (popPK) analysis of 192 children
- a popPK modelling and predictions of plasma concentrations of ropivacaine and the metabolite PPX
- 25 published clinical studies including 693 children

From this review it was concluded that the currently available documentation provides support for inclusion of single and continuous peripheral nerve block in paediatrics. The following indication and posology for Acute Pain Management is therefore proposed to be included in the prescribing information:

Section 4.1 Therapeutic indications

Single and continuous peripheral nerve block in infants from 1 year and children up to and including 12 years.

Section 4.2 Posology and method of administration

TableX Dosage recommendations for paediatric patients			
	Concentration (mg/ml)	Volume (ml/kg)	Dose (mg/kg)
ACUTE PAIN MANAGEMENT			
(per- and postoperative)			
Peripheral Nerve Block in children 1 to 12 years*			
Single Injection (eg, ilioinguinal nerve block, brachial plexus block)	5.0	0.5-0.6	2.5-3.0
Continuous Infusion up to 72 hours	2.0	0.1-0.3 ml/kg/h	0.2-0.6 mg/kg/h

*Up to and including 12 years

Assessment of the Applicant's response

Pharmacokinetics in PNB

In regional anaesthesia, local anaesthetics are injected at the desired site of action, therefore plasma concentration is not directly related to efficacy. Ropivacaine is highly bound to plasma proteins, mainly α 1-acid glycoprotein (AAG) with an unbound fraction of 4-5%. The unbound fraction is responsible for the pharmacological and toxicological effects. PPX is a major metabolite during continuous infusion, its CNS toxicity is one-twelfth of unbound ropivacaine.

In patients aged 1 to 12 Years, the unbound fraction of ropivacaine is similar to that in older children and adults, in infants below the age of 6 months it is higher.

Unbound plasma concentrations of ropivacaine and PPX are reduced by a postoperative increase in AAG induced by surgery.

In adult volunteers (Knudsen et al 1997) a threshold for CNS toxicity was determined at a mean C_u of 0.6 mg/l in an intravenous tolerability study. The minimum unbound concentration of 0.34 mg/l is used as reference limit.

It is assumed that the concentration response in systemic toxicity is the same in children.

PNB has an important place as an alternative to general or epidural anesthesia. Continuous peripheral nerve block (CPNB) can offer prolonged (postoperative) pain relief. Side effects are less than with epidural analgesia. Regarding the use of ropivacaine for PNB in paediatric patients, the following data has been assessed:

SP-ROA-0014

Study design: open, non-comparative, multicenter study

Objectives:

Primary: Evaluation of the efficacy of ropivacaine in 1-12 year old children, following ilioinguinal nerve block for postoperative pain management

Secondary: Evaluation of safety and tolerability and systemic absorption of ropivacaine by estimation of the peak plasma concentration (C_{max} and half-life t_{1/2})

Diagnosis and main criteria for inclusion: 1-12 year old ASA I-II patients scheduled for elective unilateral surgery under general anesthesia/sedation in the inguinal region performed under peripheral nerve block.

Test Product: Ropivacaine 5 mg/ml, Batch No. 471-38-6

Method: single dose of 3 mg/kg as peripheral nerve block (ilioinguinal block), sampling of 7 peripheral venous blood samples up to 6 hours

Efficacy variables:

- postoperative pain (5 point objective pain scale)
- postoperative pain (investigator assessment)
- Time to administration of supplementary analgesics
- Proportion of patients receiving supplementary analgesics in the first six hours

Safety variables:

- Blood pressure and heart rate
- Adverse events
- Blood loss

Pharmacokinetic variables:

- C_{max}
- T_{max}
- Free plasma concentration (C_u)
- Free fraction (f_u)
- AAG
- T_{1/2}

Statistical methods:

Descriptive statistics and graphs, Hodges-Lehmann point estimates and 95% one-sample, two-sided Wilcoxon confidence intervals for continuous data

Results:

Number planned: 20, number enrolled and treated: 22

Males/females: 18/4

Mean age: 4.1 (1.0 – 11.2) years

Mean weight: 16.3 (10-35) kg

Efficacy: satisfactory postoperative pain relief in the majority of patients

13/22 patients without any supplementary analgesics during the observation period of 6 h

Safety: no safety problems related to the PNB were observed

Pharmacokinetic:

Absorption of ropivacaine was rapid with peak plasma concentrations 15-64 min after the start of injection. C_{max} of total ropivacaine was 1.5 ± 0.9 mg/l with the highest value of 4.8 mg/l. C_u after 30 min was 0.05 ± 0.03 mg/l and f_u was 4.1 ± 2.4%. Calculated peak C_u range was 0.02 – 0.136 mg/l. T_{1/2} was 2.0 ± 1.7 h.

Plasma levels of free ropivacaine were well below threshold levels for toxicity in adults

Paut 2004:

High plasma ropivacaine concentrations after fascia iliaca compartment block in children

In this prospective double-blind study a fascia iliaca compartment block was performed as part of anaesthetic management during elective orthopaedic surgery with Ropivacaine 0.7 ml/kg (randomized either 0.375 or 0.5% solution) in 6 children (5 – 15 years, 35.6 ± 10 kg). Venous blood samples were taken up to 6 h after injection. Satisfactory preoperative pain relief was achieved. No toxic effects were observed, but high maximal plasma concentrations (4.33-5.6 µg/ml) were measured in 3 of 4 patients of the Ropivacaine 0.5% group (3.5 mg/kg), which led to discontinuation of the study. Plasma concentrations in the 0.375% group (2.6 mg/kg) showed values within the safe range (0.66 and 0.98 µg/ml)

High Cmax values (4.33-5.6 µg/ml) after fascia iliaca compartment block with 3.5 mg/kg ropivacaine (7 ml/kg of 0.5%) were observed in 3 children without toxic effects.

Weintraud 2009:

Ultrasound Versus Landmark-Based Technique for Ilioinguinal-Iliohypogastric Nerve Blockade in children: The implications on plasma levels of ropivacaine

66 children (8-84 months) scheduled for inguinal hernia repair received INB with 0.35 ml/kg ropivacaine 0.5% (1.25 mg/kg) either by landmark-based (n=31) or by ultrasound-guided technique (n= 35). Blood samples were taken up to 30 min after injection. The ultrasound guided technique resulted in higher Cmax (1.78 ± 0.62 vs 1.23 ± 0.70 µg/ml) and shorter tmax (20.4 ± 8.6 vs 25.3 ± 7.6 min) values. Thus, reduction in the volume of the local anaesthetic should be considered using the ultrasound guided technique.

Plasma levels of ropivacaine were well below threshold levels for toxicity in adults with both techniques.

Population pharmacokinetic analysis

(AstraZeneca, Clinical Pharmacology Summary 2005)

A comprehensive population pharmacokinetic (PopPK) analysis was performed in 192 neonates, infants and children aged 0-12 years administered ropivacaine for ilioinguinal nerve block, single caudal block, or single caudal bolus plus continuous epidural infusion of ropivacaine. The objectives of this analysis, which included the ilioinguinal PNB study (SP-ROA-0014) mentioned above, were to build a popPK model, including an AAG binding isotherm, that simultaneously describes total and unbound ropivacaine and PPX pharmacokinetics in neonates, infants and children aged 0 to 12 years following a single caudal block/ilioinguinal nerve block or a single caudal bolus plus a continuous epidural infusion of ropivacaine. The analysis has already been assessed by the authorities during the course of a variation procedure.

No significant associations were found between gender, the physical status classification system of the American Society of Anesthesiologists' (ASA I to III) and total dose for any of the PK parameters. The absorption constant (k_a) was not found to be different for the ilioinguinal study vs. other studies. The fraction of dose metabolised (f_m) into PPX was 15%, with an inter-individual variability of 45% as estimated in the popPK analysis. The absence of a dose effect on unbound ropivacaine and PPX clearance supports a dose proportional increase in exposure to unbound ropivacaine and PPX.

For continuous peripheral block (0.6 mg ropivacaine/kg for 72 h) preceded by a single bolus (3

mg/kg), the simulations indicate that the median unbound peak concentration is 0.053 mgEq/L, which is well below the toxicity threshold (0.34 mg/L). The upper 90% confidence interval for the maximum unbound plasma concentration is 0.088 mgEq/L, one quarter of the toxicity threshold.

Based on these results and observed data from peripheral nerve block in infants and children 1 to 12 years old, where unbound plasma concentrations of ropivacaine after a single dose of 3 mg/kg single dose did not exceed 0.14 mg/L ([Study SP-ROA-0014](#)), systemic safety margins are considered to be adequate after single and continuous peripheral block, and similar to those after single caudal/continuous epidural routes of administration in this age group.

Unbound plasma concentrations of ropivacaine after a single dose of 3 mg/kg for PNB did not exceed 0.14 mg/L in infants and children 1 to 12 years old. Systemic safety margins are considered to be similar to those after single caudal/continuous epidural administration in this age group

Efficacy in PNB

Reviews:

Ivani et al. 2005

Continuous peripheral nerve blocks

In this Editorial the authors conclude that all studies published so far underline the efficacy and safety of analgesia via a peripheral catheter. Continuous peripheral nerve blocks are easy to perform and are reliable and safe both in infants and children. From the literature bolus doses of 0.4-0.6 ml/kg of ropivacaine 0.2% are recommended for postoperative analgesia (higher concentrations e.g. 0.5% are used intraoperatively). A continuous infusion is recommended at doses of 0.1-0.3 ml/kg/h of ropivacaine 0.2% (equivalent to 0.2-0.4 mg/kg/h). For infants < 6 months a 25-30% reduction is recommended.

Lacroix 2007

Continuous peripheral regional analgesia in children

In this review the author states that, although not authorized for children in this indication (PNB), the concentration used is ropivacaine 0.2% for greater and 0.1% for smaller children. Doses vary between 0.2 and 0.4 mg/kg/h

Retrospective studies

Dadure et al. 2009

Continuous peripheral nerve blocks for postoperative analgesia in children: feasibility and side effects in a cohort study of 339 catheters

The authors evaluated a total of 339 catheters in 292 children (ASA I-II) aged 0.6 – 17 years (7 – 116 kg). The most common location was popliteal nerve block (50.5%), followed by psoas compartment block (24%), femoral nerve block (14.5%), axillary block (5%), infraclavicular block (5%) and interscalene block (1%). Since 2005 only ropivacaine 0.1 or 0.2% was used as local anaesthetic (bupivacaine before). Mean bolus dose was 0.49-0.98 mg/kg, mean infusion dose was 0.11-0.22 mg/kg/h, median duration of CPNB was 61.6 h (0-264 h). Efficacy: 88% of children/parents were very satisfied, 11% satisfied, 60% of patients needed at least one rescue dose of analgesia.

Ganesh et al. 2007

Continuous Peripheral Nerve Blockade for Inpatient and Outpatient Postoperative Analgesia in Children

The authors evaluated a total of 226 peripheral nerve catheters in 217 patients aged 4 to 18 years. Local anaesthetic solution (0.125% bupivacaine, n = 164, 0.1% ropivacaine n= 12, 0.15% ropivacaine n = 27) was infused at 2-12 ml/h for a mean duration of 48.4 h (0 – 160 h). 2.8% had side effects: (prolonged numbness, superficial cellulitis, difficulty removing catheter, tinnitus), the overall failure rate was 15%. The authors conclude that as there is no comparison group their data has significant limitations in the assessment of outcome. Furthermore, pain scores at rest and at movement are lacking as well as a quantification of opioid use.

Brachial plexus block

Fleischmann E et al.: Brachial plexus anaesthesia in children: lateral infraclavicular vs axillary approach; Paediatric Anaesthesia 2003; 13:103-108

40 trauma paediatric ASA I-II patients aged 1 -10 years scheduled for forearm or hand surgery were randomly assigned to receive either axillary brachial plexus (ABP) or lateral vertical infraclavicular brachial plexus (LVIBP) using 0.5 ml/kg ropivacaine 0.5%. Mean sensory block duration was 352 ± 48 min / 343 ± 60 min respectively. Vester-Andersen's criteria were met by 80 / 100% of children after 30 min. Sensory and motor blockade was significantly more effective in the LVIBP group. No major complications were observed in either group.

Marhofer P et al.: Ultrasound guidance for infraclavicular brachial plexus anaesthesia in children. Anaesthesia, 2004; 59: 642-646

In this prospective, randomised study 40 children (1-10 y, ASA I-II) scheduled for arm and forearm surgery received infraclavicular brachial plexus anaesthesia with ropivacaine 0.5% 0.5 ml/kg by either nerve stimulation or ultrasound visualisation. All children met Vester-Andersen's criteria after 30 min. All anaesthetic procedures were uneventful. Direct ultrasound visualisation offered significant advantages compared to the nerve stimulation technique: lower VAS during puncture, shorter sensory onset times (5-15 vs 5-25 min), longer sensory block durations (280-480 vs 210-420 min) and better sensory and motor block scores after 10 min.

Maria B et al.: Vertical infraclavicular brachial plexus block in children: a preliminary study. Pediatric Anesthesia 2004; 14: 931-5

In this preliminary study 55 ASA I-II patients aged 5-17 y were scheduled for upper limb trauma surgery and receive a vertical infraclavicular brachial plexus (VIP) block with 0.5 ml/kg ropivacaine 0.5%. 54 of 55 of the blockades were effective for surgery, VAS scores at the end of the procedure were <3 in all of the patients. Mean sensory block duration was 8.45 ± 1.71 h, mean motor block duration was 6.52 ± 2.5 h. Two patients developed Horner's syndrome and one mild superficial hematoma at the puncture site occurred.

Maria B et al.: Ultrasound-guided supraclavicular vs infraclavicular brachial plexus blocks in children. Pediatric Anesthesia 2008; 18: 838-44

80 ASA I-II children aged 5-15 y scheduled for upper limb elective surgery were prospectively randomized to receive either ultrasound guided supra- or infraclavicular brachial plexus blockade with 0.5 ml/kg ropivacaine 0.5%. 95% (S) and 88% (I) of blocks achieved surgical anaesthesia, failures were because of arterial puncture and insufficient ulnar or radial block. No complications were reported in either group.

Thornton KL et al.: Comparison of 0.2% ropivacaine and 0.25% bupivacaine for axillary brachial plexus blocks in paediatric hand surgery. Paediatric Anaesthesia 2008; 13: 409-12

In a double-blind randomized study, 35 children undergoing hand surgery received axillary brachial plexus blocks with 0.5 ml/kg of either 0.2% ropivacaine or 0.25% bupivacaine. No significant differences between groups could be detected as regards pain scores, time to first dose of analgesic medication and analgesic requirements in the first 24 h.

In four published articles, single use of ropivacaine 0.5 % (0.5 ml/kg) in brachial plexus blockade was shown to be effective in 215 children aged 1-17 years.
In further 17 patients ropivacaine 0.2% (0.5 ml/kg) was shown to be effective in patients aged 1-11 y.
No safety concerns have been identified.

Fascia iliaca block

Duflo F et al. 2006: Efficacy and plasma levels of ropivacaine for children: controlled regional analgesia following lower limb surgery. Br J Anaesth 97(2): 250-4

30 children aged 7 – 15 years undergoing lower limb orthopaedic surgery were randomized to receive patient controlled regional analgesia (PCRA) or continuous regional analgesia (CRA) with ropivacaine 0.2% during the 48 h postoperative period. Patients of the PCRA group received bolus doses of 0.1 ml/kg with a lockout interval of 30 min, a background infusion rate of 0.02 ml/kg/h and a maximal dose of 1 ml/kg over 4 hrs. Patients of the CRA group received a continuous infusion of 0.1 ml/kg/h. The trigger button in the latter group was connected of PCRA, device but was unable to deliver any bolus. VAS, rescue analgesia, overall satisfaction, motor blockade and plasma ropivacaine concentrations were recorded. Both techniques were efficacious and satisfactory. No safety concerns have been reported. With the PCRA technique, smaller ropivacaine doses were necessary.

Lako SJ et al. 2009: Incisional continuous Fascia Iliaca Block Provides More Effective Pain Relief and Fewer Side Effects than Opioids After Pelvic Osteotomy in Children. Anesth Analg 109: 1799-803

The objective of this prospective, double blind randomized study was to compare efficacy and safety of a continuous incisional fascia iliaca compartment (FIC) block to standard postoperative opioid therapy. 30 ASA I-II children aged 3 mo to 6 yr undergoing pelvic osteotomy were included. At the end of surgery, group M received a bolus dose of morphine iv, group R a bolus ropivacaine 0.75% via FIC catheter. Postoperatively, group M received morphine iv 20 µg/kg/h and group R ropivacaine 0.2% 0.1 ml/kg/h via FIC catheter. In both groups, normal saline was administered along the other route. Assessment of pain, sedation, first oral intake and adverse events was performed for 48 h. 28 children completed the study. Patients in group M had significantly higher pain scores and were significantly more sedated. Conclusion: continuous incisional FIC block provides excellent postoperative pain relief, less sedation and better return of appetite than morphine iv after pelvic osteotomy in children.

Paut O et al. 2004: High plasma ropivacaine concentrations after fascia iliaca compartment block in children. Br J Anaesth 92: 416-8

In this prospective double-blind study a fascia iliaca compartment block was performed as part of anaesthetic management during elective orthopaedic surgery with Ropivacaine 0.7 ml/kg (randomized either 0.375 or 0.5% solution) in 6 children (5 – 15 years, 35.6 ± 10 kg). Venous blood samples were taken up to 6 h after injection. Satisfactory preoperative pain relief was achieved. No toxic effects were observed, but high maximal plasma concentrations (4.33-5.6 µg/ml) were measured in 3 of 4 patients of the Ropivacaine 0.5% group (3.5 mg/kg), which led to discontinuation of the study. Plasma concentrations in the 0.375% group (2.6 mg/kg) showed values within the safe range (0.66 and 0.98 µg/ml).

Wathen JE. Et al. 2007: A randomized controlled trial comparing a fascia iliaca compartment nerve block to a traditional systemic analgesic for femur fractures in a pediatric emergency department. Ann Em Med 50 No 2; 162-171

In this prospective randomized unblinded controlled trial 55 paediatric patients aged 16 months to 15 years with acute isolated femur fractures were randomized to receive either intravenous morphine sulphate (0,1 mg/kg) or a fascia iliaca compartment nerve block using ropivacaine 0,5% at a dose of 0,75 ml/kg for children less than 20 kg and 0,5 ml/kg for children greater than 20 kg with a maximum of 30 ml. Baseline pain scores were comparable in both groups. Pain management was superior in the PNB group at 30 min from baseline throughout the initial 6 hrs.

In two studies 30 patients (range 3 months – 15 years) received ropivacaine 0,2% for FIC as a continuous infusion at a rate of 0,1 ml/kg/h. Bolus doses of ropivacaine 0,5% (0,5-0,75 ml/kg) were given in two other studies in 30 patients to receive FIC. Analgesia was sufficient. No toxic effects have been observed.

Ilioinguinal-iliohypogastric nerve block (INB)

Tsuchiya N et al.: Comparison of ropivacaine with bupivacaine and lidocaine for ilioinguinal block after ambulatory inguinal hernia repair in children. Pediatric Anesthesia 2004; 14: 468-70

30 ASA I-II children aged 1-8 y undergoing inguinal hernia repair under sevoflurane/N₂O anaesthesia were randomized single-blind to receive 0,5 ml/kg of 0.2% ropivacaine (R, n= 10), 0,25% bupivacaine (B, n = 10) or 1% lidocaine (L, n= 10) for ilioinguinal block. Postoperative pain was assessed at 2h and 6 h by parents using the Wong-Baker FACES Pain Rating Scale. No differences could be found between R and B, but R and B were significantly more effective than L. No complications or clinical evidence of local anaesthetic toxicity were observed.

Weintraud 2009:

Ultrasound Versus Landmark-Based Technique for Ilioinguinal-Ilioypogastric Nerve Blockade in children: The implications on plasma levels of ropivacaine

66 children (8-84 months) scheduled for inguinal hernia repair received INB with 0,25 ml/kg ropivacaine 0.5% (1.25 mg/kg) either by landmark-based (n=31) or by ultrasound-guided technique (n= 35). Blood samples were taken up to 30 min after injection. The ultrasound guided technique resulted in higher C_{max} (1.78±0.62 vs 1.23±0.70 µg/ml) and shorter t_{max} (20.4 ± 8.6 vs 25.3 ± 7.6 min) values. Thus, reduction in the volume of the local anaesthetic should be considered using the ultrasound guided technique.

In total 76 children between 8 months and 8 years underwent INB with ropivacaine, of whom 10 patients received 0,5 ml/kg of 0.2% ropivacaine and 66 patients 0,25 ml/kg of 0.5% ropivacaine. Analgesia was sufficient. No safety concerns have been observed.

Popliteal fossa block (PFB)

Tobias JD, Mencia GA. Popliteal fossa block for postoperative analgesia after foot surgery in infants and children. Journal of Pediatric Orthopaedics 1999;19:511-514.

The efficacy of a popliteal fossa block (PFB) was evaluated after foot and ankle surgery in children. With the child still anesthetized, a PFB was performed with 0.75 ml/kg of 0.2% ropivacaine. Postoperative analgesia was assessed by using an objective pain score, assigned at 2-h intervals. Patients with scores of ≥ 3 received intravenous nalbuphine. PFBs were

performed in 20 children ranging in age from 0.5 to 12 years and in weight from 6 to 41 kg. In five patients, the PFB block was supplemented with a saphenous nerve block at the ankle. Results: The PFB was unsuccessful in one patient. The remaining 19 patients required no analgesic agents during the first 8 postoperative hours. Eight patients required no analgesic agents during the first 12 postoperative hours. The duration of the analgesia varied from 8 to 12 hours. PFB provides effective analgesia after foot and ankle surgery in children.

Berniere J, Schraye S, Piana F, Vialle R, Murat I. A new formula of age-related anatomical landmarks for blockade of the sciatic nerve in the popliteal fossa in children using the posterior approach. *Pediatric Anesthesia* 2008;18:602-5.

A prospective continuous study proposed the age-related landmarks of needle insertion in the popliteal fossa by posterior approach for sciatic nerve blockade in 21 children (aged 1-16 years) undergoing major orthopedic surgery under general anesthesia. Results: Postop analgesia was provided successfully with sciatic nerve block using the calculated theoretical landmarks with 1% lido 0.5 mL/kg after surgery followed by continuous infusion of 0.2% of ropi at the rate of 0.1-0.2 mL/kg/h. No complication was observed in this series of children. Conclusion: The suggested anatomical landmarks followed in children may help clinicians to perform nerve blocks in adults in popliteal fossa.

Dadure C, Bringuier S, Nicolas F, Bromilow L, Raux O, Rochette A, Capdevila X. Continuous epidural block versus continuous popliteal nerve block for postoperative pain relief after major pediatric surgery in children: A prospective, comparative randomized study. *Anesth Analg* 2006;102:744-9.

A prospective, randomized study evaluated the effectiveness and AEs of CPNB (continuous popliteal nerve blocks) or CEB (continuous epidural block) in children following pediatric surgery. After general anesthesia, 0.5 to 1 mL/kg of an equal-volume mixture of 0.25% bupivacaine and 1% lido with adrenaline was injected via epidural or popliteal catheters. Postop, 0.1 mL/kg/h (group CPNB, n = 25) or 0.2 mL/kg/h (group CEB, n = 27) of 0.2% ropi was administered for 48 h. Results: Postop analgesia was excellent for the two techniques and in the two age groups. Motor block intensity was equal between techniques. AEs (postop nausea or vomiting, urinary retention, and premature discontinuation of local anesthetic infusion in the 1-6-year old group) were significantly more frequent in the CEB group. 86 % of the parents in the CEB groups and 100% in the CPNB groups were satisfied. Conclusion: Both CEB and CPNB resulted in excellent postop analgesia. CPNB was associated with less urinary retention and nausea and vomiting. The authors recommend CPNB as the ideal form of postop analgesia after major pediatric surgery in 1 - 12-year old children.

PFB has been performed with ropivacaine 0,2% in a total of 66 paediatric patients (0,5 – 16 years). 20 patients received bolus doses of 0,75 ml/kg and 46 patients received continuous infusions of 0,1-0,2 ml/kg/h (48 h)
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Other peripheral nerve blocks

Single injection

Eccofey C, Becel C. Bloc pénien et ropivacaine/Penile block with ropivacaine. *Annales Francaises d'Anesthésie et de Réanimation* 2009;28:100-106.

This study aimed to assess the action of locoregional anesthetics including ropi when used to realize penile blocks before performing circumcision in 88 pediatric patients for phimosis. It is

mentioned that ropi 0.75% had been previously reported to cause transient ischemia in an adult man who had to have a penile block before circumcision ([Burke 2000](#)). It was observed that ropi (n = 73; age range 6 months- 15 years) did not cause transient ischemia in any of the cases. Conclusion: Penile blocks can be safely realized with ropi using the double puncture method.

Kachko L, Katz J, Axer-Siegel R, Friling R, Goldenberg-Cohen N, Simhi E et al. Sub Tenon's Ropivacaine Block for Pain Relief After primary Strabismus Surgery. Current Eye Research 2010 35:529-535

A prospective trial was conducted in 79 patients (age 1.0–65 years) scheduled for outpatient primary strabismus surgery. Half the patients were randomly allocated to receive sub-Tenon's block with ropivacaine 0.2% at conclusion of the operation. Primary outcome measures were VAS scores up to 24 hr post-operatively. Supplemental analgesia requirements and patient satisfaction were recorded as well. Results: There were no between-group differences in median VAS scores at arrival to the PACU and at discharge, with a borderline difference at 24 hr post-operatively ($p = 0.06$). At 12–16 hr postoperatively, the median score was 0.0 (range 0–5) in the study group and 4.0 (range 0–6) in the controls ($p < 0.001$). The lower VAS score in the study group was associated with a lower rate of supplemental analgesia use (21.9% versus 57.9%, $p = 0.001$), fewer doses of supplemental analgesia (10 doses versus 35, $p = 0.03$), and higher patient satisfaction ($p < 0.001$). Conclusions: Sub-Tenon's block with ropivacaine 0.2% at the completion of outpatient primary strabismus surgery with fixed sutures under GA reduces pain 12–16 hr post-operatively and analgesia requirements 4–23 hr postoperatively.

Mesnil M, Dadure C, Captier G, Raux O, Rochette A, Canaud N et al. A new approach for perioperative analgesia of cleft palate repair in infants: the bilateral suprazygomatic maxillary nerve block. Pediatric Anesthesia 2010;20:343–349

The primary aim of this prospective and descriptive study was to observe the effectiveness of BMB (bilateral maxillary nerve block) using a suprazygomatic approach on pain relief and consumption of rescue analgesics following CCP (congenital cleft palate) repair in infants. BMB was performed with 0.15 ml/kg ropivacaine 0.2%.

Complications related to this new technique in infants were reviewed. Postop analgesia, administration of rescue analgesics, AEs, and time to feed were recorded in the 48-h period following surgery and compared to retrospective data.

Results: 55% of the included 33 children, (3-12 months) did not require additional opioids intra-operatively. None needed morphine postop, and iv. nalbuphine was required in only 18%. Compared to retrospective data, BMB using a suprazygomatic approach seems to improve pain relief and to decrease peri operative consumption of opioid after CCP repair in infants.

Splinter W, Thomson M. Somatic paravertebral block decreases opioid requirements in children undergoing appendectomy. Canadian Journal of Anesthesia/Journal canadien d'anesthésie 2010 57:206-210

This prospective randomized controlled study compared SPVB (somatic paravertebral block) with no block in children undergoing appendectomy. SPVB subjects received a rightsided SPVB at T11, T12, and L1 using 0.2% ropi 0.25 mL/kg with adrenaline 1:200,000 preoperatively. The controls had only band-aids applied to skin. Results: SPVB subjects required significantly less morphine than control patients and time to their first dose was significantly longer. Incidence of vomiting was 11% with SPVB and 27% within the control patients. No other AEs were observed in either group. Conclusions: In children undergoing appendectomy, SPVB provides better pain relief than no block and reduces opioid requirements. AEs were not statistically different between groups.

Continuous infusion

Dadure C, Pirat P, Raux O, Troncin R, Rochette A, Ricard C, Capdevila X. Perioperative continuous peripheral nerve blocks with disposable infusion pumps in children: A prospective descriptive study. *Anesth Analg* 2003;97:687-90.

This prospective, descriptive study evaluated the effectiveness of disposable elastomeric pumps for perioperative continuous PNB (peripheral nerve blocks) analgesia after major orthopedic surgery. 25 Patients (1-15 y) received a 0.5 mL/kg bolus injection of a mixture of lidocaine 1% with adrenaline and bupivacaine 0.25% in axillary, femoral, or popliteal catheters. Postoperative a continuous infusion of ropivacaine 0.2% was administered at 0.1 mL/kg/h. Results: The median dose of ropivacaine was 10.1 mg/kg (range, 6.2- 12.6 mg/kg). The median pain scores were 0 for each period studied and the use of rescue analgesia was very small. A sensory block was noted after 1 h in 18/25 children but decreased from 6 h onwards. Motor block decreased totally from 6 h onwards. 2 children had nausea and 2 had pruritus.

Dadure C, Raux O, Gaudarc P, Sagintaah M, Troncin R, Rochette A, Capdevila X. Continuous psoas compartment blocks after major orthopaedic surgery in children: A prospective computed tomographic scan and clinical studies. *Anesth Analg* 2004;98:623-8. 39 (61)

This prospective study determined the feasibility and efficacy of CPCB (continuous psoas compartment block) after major femoral shaft or hip surgery, using landmarks defined by a preliminary CT (computed tomographic) scan study in different age groups of children. After a general anaesthesia for surgery and insertion of the CPCB catheter, patients were given 0.5 mL/kg of an equal-volume mixture of 0.5% ropivacaine and 1% lidocaine with adrenaline. After the surgery, patients received a continuous infusion of 0.2% ropivacaine (0.1 mg/kg/h). All patients were administered propacetamol and niflumic acid. Results: Postoperative analgesia was excellent. Sensory block was good and pain scores were very low. Motor blockade was mild. Parent satisfaction was achieved for 93% of the children. No report of hematoma, catheter infection, dyesthesia or local anesthetic toxicity, neurologic symptom or accidental removal of the catheter. AEs: Nausea/vomiting (n = 4) and pruritus (n = 3). Conclusion: CPCB with 0.2% ropiv provides effective analgesia with few AEs after major femoral shaft or hip surgery in children lidocaine, 1%, with adrenaline and 0.5% ropivacaine injected in the peripheral nerve block catheter. Then, a 20-min Bier block was performed using a tourniquet and 0.2 mL/kg lidocaine, 1%; 3 mL/kg hydroxyethyl starch 130/06; and 5 mg/kg buflomedil injected iv. A solution of 0.1 mL/kg/h continuous ropivacaine, 0.2%, was infused using an elastomeric pump for 96 h. Need for rescue analgesia, occurrence of side effects, and status of motor and sensory block were recorded at hours 1, 6, 12, 24, 48, 72, and 96. Children and parents completed a satisfaction assessment. All of the children had follow-up visits after 2 months. Results: Postoperative analgesia was excellent. The median pain score was 0 for each period studied. Motor blockade was minimal before 12 h (median, 1) and absent thereafter. One child needed rescue analgesia. All children were able to walk easily after the initial 24- h period (walking score, > 4). Children and parents were all satisfied. Children returned home under parental surveillance beginning in the 24th hour. Neither peripheral nerve block nor Bier block caused side effects. After 2 months, none of the children exhibited any clinical symptom of recurrent complex regional pain syndrome. Conclusion: Ambulatory continuous peripheral nerve block associated with an initial Bier block seems to be a significant and novel contribution to treat recurrent paediatric complex regional pain syndrome I. It allows complete pain relief, early mobilization, and rapid return home, representing a psychological advantage for these children.

Across all 25 studies, ropivacaine has been used safely and effectively in more than 693 paediatric patients for various peripheral nerve blocks. Patients aged 3 months and older have been treated. Most studies included children aged 1 year and older.

Depending on the site of injection and on age, bolus doses of 0,15-1 ml/kg of ropivacaine 0,2 – 0,5 % have been given. Approximately one third of the studied paediatric patients received ropivacaine 0,5%.

0,1 up to 0,4 ml/kg/h of ropivacaine 0,2% has been administered continuously for PNB up to 48 h.

No serious safety signals could be derived from the data presented. Across studies, there were reports of nausea/vomiting, urinary retention, paresthesiae, pruritus, persistent motor blockade, local reactions and Horner's syndrome (brachial plexus block). All AEs but pruritus are either listed in the current SPC or are in line with the blockade technique.

Safety of PNB

The MAH reported (search on 1 February 2011 in AstraZeneca's global patient safety database) 11 case reports in children up to and including the age of 13 describing use of ropivacaine as a peripheral nerve block were identified.

1. Spontaneous report of a 5 y old female, weight 16 kg: 75mg of Naropin 7.5 mg/ml was administered as axillary brachial plexus block, after approx. 10 min generalised cerebral convulsion attack. Treatment with 2 doses of diazepam 2.5 mg and induction of general anaesthesia. Complete recovery. The administered dose of 4.7 mg/kg was higher as recommended, so systemic toxicity due to overdose is a reasonable explanation for the event, however, also accidental intravascular administration cannot be excluded.
2. Spontaneous report of a 12 year old female, weight 28 kg. An infraclavicular block was carried out with Naropeine 5 mg/ml. 10 ml was injected on the median nerve and 12 ml on the radial nerve (total of 22 ml = 110 mg). General convulsion after 10-15 min. After 2 mg of Hypnoval iv and ventilation via mask complete recovery after 30 min. The administered dose of 3.9 mg/kg was higher as recommended, so systemic toxicity due to overdose is a reasonable explanation for the event, however, also accidental intravascular administration cannot be excluded.
3. Spontaneous report of a 13 year old male, weight 40 kg with pseudocholinesterase deficiency. 15 ml of 7.5 mg/ml ropivacaine (2.8mg/kg) and 15 ml of 10 mg/ml lignocaine (3.8 mg/kg) for axillary brachial plexus block. Within one minute grand mal fit of approximately 4 min duration. After 5 mg midazolam iv and oxygen via face mask recovery. Considering the short time interval, an inadvertent intravascular injection is most likely.
4. Spontaneous report of a 6 year old male, weight 20 kg. Four episodes of convulsions occurring 8-10 min after injection of 20 ml Naropin 7.5 mg/ml for femoral block. Recovery after 30 min (therapeutic measures: intubation and intensive care) Blood level of total ropivacaine after 1 h: 4 µg/ml, which is higher than the threshold plasma concentration for adults. The administered dose of 7.5 mg/kg is higher than recommended, so systemic toxicity due to overdose is a reasonable explanation for the event.
5. Spontaneous report of a 6 year old male, unknown weight. For brachial plexus nerve block the patient received 112.5 mg of Ropivacaine 7.5 mg/ml. Convulsion within 5 min. Recovery after anticonvulsant. The event may be explained as an overdose, as a 6 year old child is likely to be below 37 kg.
6. Spontaneous report of a 4 year old male, weight 16 kg. Local anaesthesia at cervical level with 30 mg mepivacaine 20 mg/ml and 3 mg ropivacaine 2 mg/ml. Convulsive crisis after 3 min. Spontaneous recovery. Midazolam was administered. Considering the short

time interval an inadvertent intravascular injection is most likely, but also an accidental intrathecal injection cannot be ruled out.

7. Literature source: 13 year old female, 55 kg. After induction of general anaesthesia, PCB was performed with 10 ml of lidocaine 10mg/ml (1.8 mg/kg) with adrenaline and 10 ml of ropivacaine 7.5 mg/ml (1.4 mg/ml). After 15 min ventricular arrhythmia (HR 150 bpm and wide QRS) with increased BP (120/92 mmHg). Suspecting LA poisoning, Medialipid 20% was rapidly injected iv. Recovery within 30 min. Plasma concentrations of ropivacaine and lidocaine were 872 and 648 mg/ml after lipid injection. Plasma levels are not indicative of systemic toxicity. Information of possible contributing factors during anaesthesia are missing. Ventricular arrhythmia is listed as a rare AE for ropivacaine.
8. Spontaneous report of an 8 year old female, unknown weight. 150 mg (20 ml) Ropivacaine for axillary nerve block. Convulsion after 7-8min. Recovery after diazepam administration. An inadvertent intravascular injection cannot be ruled out. Concentrations of 7.5 mg/ml are not recommended in children.
9. Literature source 3 year old male, 14 kg. Bilateral ilioinguinal and iliohypogastric nerve block with Lidocaine 10mg/ml 100 mg and Ropivacaine 7.5 mg/ml 75 mg under general anaesthesia. Surgery for 28 min without any symptoms. After administration of muscle relaxant antagonist at the end of surgery generalized tonic-clonic convulsions 4-5 times. Recovery after 7 mg diazepam. Total dose of the local anaesthetics (5,4 mg/kg ropivacaine , 7,1 mg/kg lidocaine) is higher than recommended maximum doses for children, so systemic toxicity due to overdose is a reasonable explanation for the event.
10. Spontaneous report of a 7 year old male, unknown weight. Convulsions after perineural administration of lidocaine and ropivacaine. Recovery. No precise information about patient's weight, doses, indication, site of injection, concomitant diseases or medication.
11. Spontaneous report of a 4 year old female, unknown weight. Convulsions after perineural administration of lidocaine and ropivacaine. Recovery. No precise information about patient's weight, doses, indication, site of injection, concomitant diseases or medication.

In 7 of these spontaneous reports of convulsions after paediatric use of ropivacaine for PNB, ropivacaine 0,75% was administered, which should not be recommended for the use in children. In 5 reports an inadvertent intravascular injection was likely or could not be ruled out. In 4 reports the administered ropivacaine dose was higher (or suspected to be higher) than the recommended maximum dose. 2 case reports are not evaluable due to incomplete information. In conclusion, CNS symptoms were most commonly reported due to systemic toxicity as a result of overdose or inadvertent intravascular injection. Ventricular arrhythmia is listed as a rare AE to ropivacaine.

The MAH comes to the conclusion that no safety concerns regarding peripheral nerve blocks in children can be derived from the presented review. The review provides support for inclusion of the following paediatric posology for single and continuous peripheral nerve block in the prescribing information:

Overall Summary and Conclusion

Although in clinical practice PNB are not used in children to an extent comparable to adults, the presented database seems to give sufficient evidence that ropivacaine used for PNB in children > 1 year has the same efficacy and safety as in adults provided that doses and concentrations of ropivacaine do not exceed the recommended range. PNB should only be performed by experienced anesthetists in children.

Thus, the proposal of the MAH to include the proposed indication and dose recommendations can be accepted:

Section 4.1

Single peripheral nerve block: infants from 1 year and children up to and including 12 years (Ropivacaine 5mg/ml)

Single and continuous peripheral nerve block: infants from 1 year and children up to and including 12 years (Ropivacaine 2mg/ml)

Section 4.2

The proposed ropivacaine doses for peripheral block in infants and children provide guidelines for use in children without severe disease. Guidance on factors affecting the choice of local anaesthetic dose in children according to severity of disease (ASA classification) should be sought from standard textbooks.

Table 1 Doses for use in infants and children aged 1-12 years

	Concentration	Volume	Dose (mg/kg)
ACUTE PAIN MANAGEMENT (per- and postoperative)			
Single injection for peripheral nerve block (e.g. ilioinguinal nerve block, brachial plexus block)	5.0 mg/mL	0.5-0.6 mL/kg	2.5-3.0 mg/kg
Continuous infusion for peripheral nerve block ¹	2.0 mg/mL	0.1-0.3 mL/kg/h	0.2-0.6 mg/kg/h

¹Recommended duration of continued infusion: up to 72 hours

Question 3

The MAH is asked to provide the Final Assessment Report of the PSUR Worksharing Procedure if already available.

Summary of the MAH's response

The Final Assessment Report for the PSUR Worksharing has not yet been received.

Assessment of the Applicant's response

In the meantime the Final AR of NL/H/PSUR/0040/001 has become available. The final conclusion was:

The benefit-risk balance for ropivacaine remains favourable.

Commitments were given to monitor closely chondrolysis, off-label use, neurological disorders, cardiac disorders, hepatobiliary events, porphyria, vasoconstriction, muscular weakness, movement disorders, intrathecal administration and the use of ropivacaine in ilio-inguinal nerve blocks.

Overall Summary and Conclusion

No new safety signals regarding the paediatric population can be derived from the Final Assessment Report of NL/H/PSUR/0040/001.

Question 4

The MAH should provide a proposal for the SmPC wording regarding the paediatric population in accordance with the actual SmPC –Guideline (NTA Rev 2, Vol. 2c, September 2009).

Summary of the MAH's response

In an attempt to make the SmPC more in line with the guideline the MAH presents a proposal for an update of the currently approved MR SmPC.

In countries where Naropin has been nationally approved though, the texts differ from the MRP version.

Section 4.1 Therapeutic indications

Naropin is indicated for:

1. Surgical anaesthesia in adults and adolescents above 12 years of age:
 - Epidural blocks for surgery, including Caesarean section
 - Major nerve blocks
 - Field blocks
2. Acute pain management in adults and adolescents above 12 years of age:
 - Continuous epidural infusion or intermittent bolus administration during postoperative or labour pain
 - Field blocks
 - Continuous peripheral nerve block via a continuous infusion or intermittent bolus injections, e.g. postoperative pain management
3. Acute pain management in paediatrics: (per- and postoperative)
 - Caudal epidural block in neonates, infants and children up to and including 12 years
 - Continuous epidural infusion in neonates, infants and children up to and including 12 years
 - Single and continuous peripheral nerve block in infants from 1 year and children up to and including 12 years.

Section 4.2 Posology and Method of Administration

Adults and children adolescents above 12 years of age

The following table is a guide to dosage for the more commonly used blocks. The smallest dose required to produce an effective block should be used. The clinician's experience and knowledge of the patient's physical status are of importance when deciding the dose. Table X Adults and children adolescents above 12 years of age

Section 4.8 Undesirable effects

A specific paediatric population heading has been added before the following statement at the end of section 4.8: "In children, early signs of local anaesthetic toxicity may be difficult to detect since they may not be able to verbally express them".

Assessment of the Applicant's response

In general, therapeutic indications must be specified for each medicinal product. Ropivacaine is available in different strengths, but up to now, the originator's SPC is a common SPC for the 2 mg/ml, 7,5 mg/ml and 10 mg/ml strengths. According to section 4.2, indications should differ depending on the concentration of the product. At present, only the the SPC of the 5 mg/ml strength is specified.

Especially regarding the paediatric indications the concentration of the ropivacaine formulation has to be taken into account. Therefore, the MAH's proposal is not sufficient to bring the wording concerning the paediatric population SPC in line with the requirements of the SPC Guideline (2009).

At present paediatric information is given as follows in the MR-SmPC for Naropin:

Naropin 2, 7,5 and 10 mg/ml:

Section 4.1:

Naropin is indicated for:

1. *Surgical anaesthesia:*
Epidural blocks for surgery, including Caesarean section
Major nerve blocks
Field blocks
2. *Acute pain management:*
Continuous epidural infusion or intermittent bolus administration during postoperative or labour pain
Field blocks
Continuous peripheral nerve block via a continuous infusion or intermittent bolus injections, e.g. postoperative pain management
3. *Acute pain management in paediatrics:*
(per- and postoperative)
Caudal epidural block in neonates, infants and children up to and including 12 years
Continuous epidural infusion in neonates, infants and children up to and including 12 years

Section 4.2:

Adults and children above 12 years of age

The following table is a guide to dosage for the more commonly used blocks. The smallest dose required to produce an effective block should be used. The clinician's experience and knowledge of the patient's physical status are of importance when deciding the dose.

Table 1 Adults and children above 12 years of age

	Conc. Mg/ml	Volume ml	Dose Mg	Onset minutes	Duration hours
SURGICAL ANAESTHESIA					
Lumbar Epidural Administration					
Surgery	7.5	15-25	113-188	10-20	3-5
	10.0	15-20	150-200	10-20	4-6
Caesarean Section	7.5	15-20	113-150 ¹⁾	10-20	3-5
Thoracic Epidural Administration					
To establish block for post-operative pain relief	7.5	5-15 (dependent on the level of injection)	38-113	10-20	n/a ²⁾
Major Nerve Block*					
Brachial plexus block	7.5	30-40	225-300 ³⁾	10-25	6-10
Field Block (e.g. minor nerve blocks and infiltration)	7.5	1-30	7.5-225	1-15	2-6

- * With regard to major nerve block, only for brachial plexus block a dose recommendation can be given. For other major nerve blocks lower doses may be required. However, there is presently no experience of specific dose recommendations for other blocks.
- 1) Incremental dosing should be applied, the starting dose about 100 mg (97,5 mg = 13 ml; 105 mg = 14 ml) to be given over 3-5 minutes. Two extra doses, in total an additional 50 mg, may be administered as needed.
 - 2) n/a = not applicable
 - 3) The dose for a major nerve block must be adjusted according to site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used, (see section 4.4. Special warnings and special precautions for use).

ACUTE PAIN MANAGEMENT

Lumbar Epidural Administration

Bolus	2.0	10-20	20-40	10-15	0.5-1.5
Intermittent injections (top-up) (e.g. labour pain management)	2.0	10-15 (mini-mum interval 30 minutes)	20-30		
Continuous infusion e.g. Labour pain	2.0	6-10 ml/h	12-20 mg/h	n/a	n/a
Postoperative pain management	2.0	6-14 ml/h	12-28 mg/h	n/a	n/a

Thoracic Epidural Administration

Continuous infusion (postoperative pain management)	2.0	6-14 ml/h	12-28 mg/h	n/a	n/a
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Field Block

(e.g. minor nerve blocks and infiltration)	2.0	1-100	2.0-200	1-5	2-6
Peripheral nerve block (Femoral or interscalene block)					
Continuous infusion or intermittent injections (e.g. postoperative pain management)	2.0	5-10 ml/h	10-20 mg/h	n/a	n/a

Table 2 Paediatric patients 0 up to and including 12 years of age

	Conc. mg/ml	Volume ml/kg	Dose mg/kg
ACUTE PAIN MANAGEMENT			
(per- and postoperative)			
Single Caudal Epidural Block	2.0	1	2
Blocks below T12, in children with a body weight up to 25 kg			
Continuous Epidural Infusion			
In children with a body weight up to 25 kg			
<i>0 up to 6 months</i>			
Ropivacaine hydrochloride DE/W/027pdWS/001			

Table 2

Paediatric patients 0 up to and including 12 years of age

	Conc.	Volume	Dose
	mg/ml	ml/kg	mg/kg
Bolus dose ^a	2.0	0.5-1	1-2
Infusion up to 72 hours	2.0	0.1 mL/kg/h	0.2 mg/kg/h
<i>6 up to 12 months</i>			
Bolus dose ^a	2.0	0.5-1	1-2
Infusion up to 72 hours	2.0	0.2 mL/kg/h	0.4 mg/kg/h
<i>1 to 12 years</i>			
Bolus dose ^b	2.0	1	2
Infusion up to 72 hours	2.0	0.2 mL/kg/h	0.4 mg/kg/h

The dose in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. The volume for single caudal epidural block and the volume for epidural bolus doses should not exceed 25 mL in any patient. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

- a Doses in the low end of the dose interval are recommended for thoracic epidural blocks while doses in the high end are recommended for lumbar or caudal epidural blocks.
- b Recommended for lumbar epidural blocks. It is good practice to reduce the bolus dose for thoracic epidural analgesia

The use of ropivacaine in premature children has not been documented.

Section 4.4:

Paediatric patients:

Neonates may need special attention due to immaturity of metabolic pathways. The larger variations in plasma concentrations of ropivacaine observed in clinical trials in neonates suggest that there may be an increased risk of systemic toxicity in this age group, especially during continuous epidural infusion. The recommended doses in neonates are based on limited clinical data. When ropivacaine is used in this patient group, regular monitoring of systemic toxicity (e.g. by signs of CNS toxicity, ECG, SpO₂) and local neurotoxicity (e.g. prolonged recovery) is required, which should be continued after ending infusion, due to a slow elimination in neonates.

Section 4.8

In children, early signs of local anaesthetic toxicity may be difficult to detect since they may not be able to verbally express them. See also section 4.4.

Section 5.2

The pharmacokinetics of ropivacaine was characterized in a pooled population PK analysis on data in 192 children between 0 and 12 years. Unbound ropivacaine and PPX clearance and ropivacaine unbound volume of distribution depend on both body weight and age up to the maturity of liver function, after which they depend largely on body weight. The maturation of unbound ropivacaine clearance appears to be complete by the age of 3 years, that of PPX by the age of 1 year and unbound ropivacaine volume of distribution by the age of 2 years. The PPX unbound volume of distribution only depends on body weight. As PPX has a longer half-life and a lower clearance, it may accumulate during epidural infusion. Unbound ropivacaine clearance (Cl_U) for ages above 6 months has reached values within the range of those in adults. Total ropivacaine clearance (CL) values displayed in Table 3 are those not affected by the postoperative increase in AAG.

Table 3 Estimates of pharmacokinetic parameters derived from the pooled paediatric population PK analysis

Age Group	BW ^a kg	Clu ^b (L/h/kg)	Vu ^c (L/kg)	CL ^d (L/h/kg)	t _{1/2} ^e (h)	t _{1/2ppx} ^f (h)
Newborn	3.27	2.40	21.86	0.096	6.3	43.3
1m	4.29	3.60	25.94	0.143	5.0	25.7
6m	7.85	8.03	41.71	0.320	3.6	14.5
1y	10.15	11.32	52.60	0.451	3.2	13.6
4y	16.69	15.91	65.24	0.633	2.8	15.1
10y	32.19	13.94	65.57	0.555	3.3	17.8

a Median bodyweight for respective age from WHO database.

b Unbound ropivacaine clearance

c Ropivacaine unbound volume of distribution

d Total ropivacaine clearance

e Ropivacaine terminal half life

f PPX terminal half life

The simulated mean unbound maximal plasma concentration (Cu_{max}) after a single caudal block tended to be higher in neonates and the time to Cu_{max} (t_{max}) decreased with an increase in age (Table 4).

Simulated mean unbound plasma concentrations at the end of a 72 h continuous epidural infusion at recommended dose rates also showed higher levels in neonates as compared to those in infants and children. See also section 4.4.

Table 4 Simulated mean and observed range of unbound Cu_{max} after a single caudal block

Age group	Dose (mg/kg)	Cu_{max} ^a (mg/L)	t _{max} ^b (h)	Cu_{max} ^c (mg/L)
0-1m	2.00	0.0582	2.00	0.05 – 0.08 (n=5)
1-6m	2.00	0.0375	1.50	0.02 – 0.09 (n=18)
6-12m	2.00	0.0283	1.00	0.01 – 0.05 (n=9)
1-10y	2.00	0.0221	0.50	0.01 – 0.05 (n=60)

a Unbound maximal plasma concentration

b Time to unbound maximal plasma concentration

c Observed and dose-normalised unbound maximal plasma concentration

At 6 months, the breakpoint for change in the recommended dose rate for continuous epidural infusion, unbound ropivacaine clearance has reached 34% and unbound PPX 71% of its mature value. The systemic exposure is higher in neonates and also somewhat higher in infants between 1 to 6 months compared to older children, which is related to the immaturity of their liver function. However, this is partly compensated for by the recommended 50% lower dose rate for continuous infusion in infants below 6 months.

Simulations on the sum of unbound plasma concentrations of ropivacaine and PPX, based on the PK parameters and their variance in the population analysis, indicate that for a single caudal block the recommended dose must be increased by a factor of 2.7 in the youngest group and a factor of 7.4 in the 1 to 10 year group in order for the upper prediction 90% confidence interval limit to touch the threshold for systemic toxicity. Corresponding factors for the continuous epidural infusion are 1.8 and 3.8 respectively.

Naropin 5mg/ml:

Section 4.1:

Naropin 5 mg/ml is indicated for intrathecal administration for surgical anaesthesia.

Section 4.2:

Children (<12years): Intrathecal administration has neither been investigated in infants, toddlers nor children.

Section 4.4:

Paediatric patients: Intrathecal administration for use in infants, toddlers or children has not been documented.

Section 5.2

In children, aged between 1 and 12 years, ropivacaine pharmacokinetics after regional anaesthesia has been shown to be unrelated to age. In this group ropivacaine has a total plasma clearance in the order of 7.5 ml/min kg, an unbound plasma clearance of 0.15 l/min kg, a volume of distribution at steady state of 2.4 l/kg, an unbound fraction of 5% and a terminal half-life of 3 hours. Ropivacaine shows a biphasic absorption from the caudal space. The clearance related to body weight in this age group is similar to that in adults.

As outlined above, the RMS is of the opinion that paediatric indications must be specified for every medicinal product. A recommendation for a wording concerning the paediatric population is given below in Chapter VIII FINALRAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION:.

Ropivacaine 7,5 and 10 mg/ml:

No new information regarding the use of the 7,5 and 10 mg/ml strength in children can be derived from the documentation. Hence, to meet the requirements of the SPC Guideline (2009), the wording for the paediatric information should be clarified. Please refer to the recommendation under VIII.

Ropivacaine 5mg/ml and Ropivacaine 2mg/ml:

As outlined in the assessment of the answer to question 2, a paediatric indication for peripheral nerve block can be accepted. For children < 12 years the 5 mg/ml strength can only be indicated for single PNB, while the 2 mg/ml strength can be used for continuous PNB, single and continuous epidural blockade.

To meet the requirements of the SPC Guideline (2009), the wording for the paediatric information should be clarified and the wording for the new paediatric indication should be introduced. Please refer to the recommendation under VIII.

Ropivacaine all strengths

To get the SPC wording in line with the actual requirements for the paediatric population, additional information is required in section 4.8. The information in section 5.2 is already included for the 2, 7,5 and 10 mg/ml strength and should therefore be included for the 5 mg/ml strength as well.

VIII. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Comments on the overall Day 90 conclusion and on the recommendations were received from 3 MS: Agreement from SE and UK with endorsement of the NL comment.

The following comment from NL on the proposed wording for section 4.2 has been incorporated into the Final Recommendation (see below):

NL agrees with the overall conclusion of the Rapporteur. However, some comments were made on the wording proposed for section 4.2 of the SmPCs.

Ropivacaine 7,5 and 10 mg/ml:

Section 4.2

The following text is currently proposed for the paediatric population up to and including 12 years:

The safety and efficacy of Ropivacaine 7,5 and 10 mg/ml in children has not been established. Other strengths (2 mg/ml, 5 mg/ml) may be more appropriate for administration to this population.

NL comment:

It is not that a lack of data would compromise the use of higher concentrations in children, as suggested by the above text. There were several reports (n=7) of convulsions in children when a high concentration of 7.5 mg/ml was applied. A more strict warning should be included.

The following text is proposed:

Paediatric population up to and including 12 years

The use of Ropivacaine 7,5 and 10 mg/ml may be associated with central toxic events in children. Lower strengths (2 mg/ml, 5 mg/ml) are more appropriate for administration to this population.

Ropivacaine 5mg/ml:

Section 4.2

The following text is currently proposed for infants and children aged 1-12 years:

The proposed ropivacaine doses for peripheral block in infants and children provide guidelines for use in children without severe disease. Guidance on factors affecting the choice of local anaesthetic dose in children according to severity of disease (ASA classification) should be sought from standard textbooks.

NL comment:

It is unclear where such directions for dosing could be found. A more appropriate wording would be: *More conservative doses and close monitoring are recommended for critical ill children.*

The **MAH** sent a Response to Day 90 PdAR and Day 115 comments (NL):

- We agree with the comment from NL regarding the text for 7.5 and 10 mg/ml but suggest a minor amendment i.e.
"Paediatric population up to and including 12 years
The use of Ropivacaine 7,5 and 10 mg/ml may be associated with central systemic toxic events in children. Lower strengths (2 mg/ml, 5 mg/ml) are more appropriate for administration to this population."
- We also agree with the second comment from NL and suggest the following text as an introduction to the dosage table for Infants and children aged 1-12 years:
"The doses for peripheral block in infants and children provide guidance for use in children without severe disease. More conservative doses and close monitoring are recommended for ~~critical-ill~~ children with severe disease."

RMS comment:

As the most prevalent toxic events in children have been seizures, the wording "central toxic events" should be maintained, but it is acceptable to add also "systemic toxic events" to address also more clearly e.g. cardiovascular events.
 The suggestion to change "critical ill" to children " to "children with severe disease" can be accepted.

A delayed comment of FR presupposed an update of the Final AR with revision of the Final recommendations:

With regard to the above procedure, we partially endorse the overall conclusions of the assessment report of the RMS.

Ropivacaine 2 mg/ml

Based on provided data, we agree to add the paediatric indication *"Single and continuous peripheral nerve block" in infants from 1 year and children up to and including 12 years*".

Ropivacaine 5 mg/ml

We do not agree with the introduction of the indication *"Single peripheral nerve block in infants from 1 year and children up to and including 12 years"* as this formulation is not used in infants due to the risk of overdose with this concentration.

RMS comment: At this time point of the procedure further discussions are no more scheduled. It has to be concluded that no agreement was reached between MS concerning the indication *"Single peripheral nerve block in infants from 1 year and children up to and including 12 years" for the 5 mg/ml solution.*

Due to a MAH Response to the comment FR and the updated AR a second update is sensible to meet all requirements:

AstraZeneca is concerned that the 2 mg/mL ropivacaine concentration is insufficient to establish intraoperative pain control in infants and children.

Regulatory perspective: From a regulatory perspective it can be concluded that ropivacaine 5 mg/mL has been approved for about ten years in some countries for *single peripheral nerve*

block in children. From the literature it is also clear that this strength is used in infants and children.

Approval of Ropivacaine 5mg/ml for paediatric PNB exists since 2001 in Finland and Switzerland, since 2002 in Sweden and since 2003 in Iceland. Dose recommendations are given for children aged 1-12years as follows:

	Conc. mg/ml	Volume ml/kg	Dose mg/kg
ACUTE PAIN MANAGEMENT (per- and postoperative)			
Peripheral nerve block in children 1-12 years of age (e.g. ilioinguinal nerve block)	5.0	0.6	3

Clinical perspective: Regional anaesthesia is a cornerstone in paediatric anaesthesia to date. Many different regional techniques are today included in the everyday practice of paediatric anaesthesiologists in order to provide effective and long-lasting postoperative analgesia (Willschke 2010). The use of peripheral nerve block is currently an important component in this armamentarium. Generally, children are first given general anaesthesia before a regional anaesthetic block is established. From many clinicians' point of view it is essential, in all patients, to early prevent any painful stimuli that might be generated by the surgical procedure. Use of the 2 mg/mL concentration of ropivacaine may not fully establish a successful nerve block and may require the use of increased amounts of general anaesthetics, including opioids and volatiles. The use of a more adequate ropivacaine concentration (5 mg/mL) for peripheral nerve blockade is considered to be sufficient to prevent nociceptive receptor input during the surgical procedure. Moreover, it is common practice to commence the postoperative analgesia as early as possible by using an effective concentration of the local anaesthetic for e.g. a peripheral nerve block.

In an editorial Ivani et al recommend a bolus dose of 0.5–1.0 mL/kg (depending on the nerve to be blocked) and the authors conclude that the same volume of the 5 mg/mL concentration is to be used if intraoperative pain control is necessary (Ivani and Mosetti 2005). If no intraoperative pain control is necessary the same volume of 2 mg/mL ropivacaine is recommended.

In the Clinical Overview 2011 (Single and continuous peripheral nerve block with ropivacaine in paediatrics) prepared during the Article 45 procedure, the published studies encompass different concentrations used, varying from 2 mg/mL to 7.5 mg/mL ropivacaine. In those studies, as well as in the AstraZeneca study SPROA 0014 (5 mg/mL, 0.6 mL/kg), there was no sign of systemic toxicity reported in any patient.

The Clinical Overview 2011 indicates that clinical investigators used ropivacaine 5 mg/ml successfully for peripheral block without signs of systemic toxicity in more than 300 patients aged up to and including 12 years.

Type of peripheral block	No. of infants and children
Brachial plexus block	215
Ilioinguinal-iliohypogastric block	88
Total	303

Table: Number of paediatric patients aged 1-12 years administered ropivacaine 5 mg/ml for PNB, (Data from Clinical Overview 2011, only studies where all patients were given 5 mg/mL solutions are included)

Pharmacokinetic perspective: Pharmacokinetic modelling was performed using a model generated from data in more than 190 paediatric patients exposed to ropivacaine in previous AstraZeneca studies, including patients exposed to 5 mg/mL for single peripheral block in study

SP-ROA-0014. Plasma concentrations were simulated every 0.1 hours for 1000 subjects. Subject covariates were re-sampled from the population of 1 to 12 year old infants and children in the comprehensive PopPK analysis (2005, previously submitted). For single peripheral block, using a dose of 3 mg/kg, the simulations indicate that the median unbound peak concentration reached after 0.8 h is 0.0347 mgEq/L (ropivacaine + 1/12 of active metabolite concentration), one-tenth of the toxicity threshold (0.34 mg/L). In the same paediatric population the upper 90% confidence interval for the maximum unbound plasma concentration is 0.074 mgEq/L, one-fifth of the toxicity threshold (Population PK Analysis 2011).

Consequently, the proposed effective dose (2.5-3.0 mg/kg) of ropivacaine 5 mg/mL for paediatric single peripheral nerve block is associated with a 5-10 fold safety margin with regard to the potential occurrence of systemic events, as evidenced by pharmacokinetic modelling (Population PK Analysis 2011).

Conclusion: AstraZeneca considers that the 5 mg/mL concentration is an important part of an effective anaesthetic regimen with a positive benefit risk ratio for single peripheral nerve block in infants and children.

References:

- Clinical Overview. NAROPIN™ (ropivacaine) – Solution for Injection or Infusion. Single and Continuous Peripheral Nerve Block with Ropivacaine in Paediatrics. 7 March 2011. [PAIN.000-184-613]
- Exploration of postmenstrual age as a covariate in a population pharmacokinetic model of ropivacaine (Naropin®) in neonates, infants and children and simulation of maximum unbound ropivacaine and PPX plasma concentrations after single (3 mg/kg) and continuous (0.6 mg/kg/hour) peripheral nerve block. 18 August 2011. [PAIN.000-200-756.2.0]
- Ivani G, Mossetti V. Continuous peripheral nerve blocks. Pediatric Anesthesia 2005 15: 87–90. [PAIN.000-188-380]
- Willschke H, Marhofer P, Machata A M, Lönngqvist P A. Current trends in paediatric regional anaesthesia. Anaesthesia, 2010, 65 (Suppl. 1): 97-4. Willschke, Anaesthesia 2010 65 (Suppl. 1):97-4[PAIN.000-187-948]

Overall conclusion

The RMS endorses the argumentation of the MAH.

However, as there is no consensus between MS, no all agreeing recommendation can be given regarding the introduction of the new indication for the 5 mg/ml solution. On the other hand, in three MS (Finland, Sweden, Iceland) and other European countries (Switzerland) Ropivacaine 5 mg/ml is already approved for peripheral nerve blocks in children > 1 year since 2001, 2002 and 2003. Dosing recommendations given are in line with those proposed during this procedure.

From the data discussed in the assessment above we cannot derive a potential risk to public health regarding this indication. In contrast, we agree that there is a well established use.

Final updated Recommendation

Type IB variation to be requested from the MAH by 13th December 2011 to introduce the following wording for the paediatric population in the SmPCs of the different strengths:

Ropivacaine 7,5 and 10 mg/ml:

Section 4.1

Ropivacaine 7,5 and 10 mg/ml is indicated in adults and children above 12 years for:

Surgical anaesthesia:

- Epidural blocks for surgery, including Caesarean section
- Major nerve blocks
- Field blocks

Section 4.2

Adults and children above 12 years of age

The following table is a guide to dosage for the more commonly used blocks. The smallest dose required to produce an effective block should be used. The clinician's experience and knowledge of the patient's physical status are of importance when deciding the dose.

	Conc. Mg/ml	Volume ml	Dose Mg	Onset minutes	Duration hours
SURGICAL ANAESTHESIA					
Lumbar Epidural Administration					
Surgery	7.5	15-25	113-188	10-20	3-5
	10.0	15-20	150-200	10-20	4-6
Caesarean Section	7.5	15-20	113-150 ¹⁾	10-20	3-5
Thoracic Epidural Administration					
To establish block for post-operative pain relief	7.5	5-15 (dependent on the level of injection)	38-113	10-20	n/a ²⁾
Major Nerve Block*					
Brachial plexus block	7.5	30-40	225-300 ³⁾	10-25	6-10
Field Block (e.g. minor nerve blocks and infiltration)	7.5	1-30	7.5-225	1-15	2-6

* With regard to major nerve block, only for brachial plexus block a dose recommendation can be given. For other major nerve blocks lower doses may be required. However, there is presently no experience of specific dose recommendations for other blocks.

- 1) Incremental dosing should be applied, the starting dose about 100 mg (97,5 mg = 13 ml; 105 mg = 14 ml) to be given over 3-5 minutes. Two extra doses, in total an additional 50 mg, may be administered as needed.
- 2) n/a = not applicable
- 3) The dose for a major nerve block must be adjusted according to site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used, (see section 4.4. Special warnings and special precautions for use).

Paediatric population up to and including 12 years

The use of Ropivacaine 7,5 and 10 mg/ml may be associated with systemic and central toxic events in children. Lower strengths (2 mg/ml, 5 mg/ml) are more appropriate for administration to this population.

Section 4.4

Paediatric patients:

The safety and efficacy of Ropivacaine 7,5 and 10 mg/ml in children up to and including 12 years has not been established.

Neonates may need special attention due to immaturity of metabolic pathways. The larger variations in plasma concentrations of ropivacaine observed in clinical trials in neonates suggest that there may be an increased risk of systemic toxicity in this age group.

Ropivacaine 5mg/ml:

Section 4.1

Ropivacaine 5 mg/ml is indicated for

- Intrathecal administration for surgical anaesthesia in adults

Section 4.2

Paediatric population:

Intrathecal administration has neither been investigated in infants, toddlers nor in children.

Section 4.4

Paediatric population

The safety and efficacy of intrathecal administration of ropivacaine has not been established in children.

Neonates may need special attention due to immaturity of metabolic pathways. The larger variations in plasma concentrations of ropivacaine observed in clinical trials in neonates suggest that there may be an increased risk of systemic toxicity in this age group.

Ropivacaine 5mg/ml:

No all agreeing recommendation can be given for the following wording as there is no consensus between MS:

Section 4.1

- Single peripheral nerve block in infants from 1 year and children up to and including 12 years

Section 4.2

Table 1 **Doses for use in infants and children aged 1-12 years**

	Concentration	Volume	Dose (mg/kg)
ACUTE PAIN MANAGEMENT (per- and postoperative)			
Single injection for peripheral nerve block (e.g. ilioinguinal nerve block, brachial plexus block)	5.0 mg/mL	0.5-0.6 mL/kg	2.5-3.0 mg/kg
Continuous infusion for peripheral nerve block ¹	2.0 mg/mL	0.1-0.3 mL/kg/h	0.2-0.6 mg/kg/h

¹Recommended duration of continued infusion: up to 72 hours

Section 4.4

The safety and efficacy of ropivacaine 5 mg/ml for peripheral nerve blocks has not been established in infants < 1 year.

Ropivacaine 2mg/ml:

Section 4.1

Ropivacaine 2mg/ml: is indicated for acute pain management

In adults and children above 12 years of age for

- Continuous epidural infusion or intermittent bolus administration during postoperative or labour pain
- Field blocks

- Continuous peripheral nerve block via a continuous infusion or intermittent bolus injections, e.g. postoperative pain management

In infants from 1 year and children up to and including 12 years for

- Single and continuous peripheral nerve block

In neonates, infants and children up to and including 12 years for (per- and postoperative)

- Caudal epidural block
- Continuous epidural infusion

Section 4.2

Adults and children above 12 years of age

The following table is a guide to dosage for the more commonly used blocks. The smallest dose required to produce an effective block should be used. The clinician's experience and knowledge of the patient's physical status are of importance when deciding the dose.

	Conc. Mg/ml	Volume ml	Dose Mg	Onset minutes	Duration hours
Lumbar Epidural Administration					
Bolus	2.0	10-20	20-40	10-15	0.5-1.5
Intermittent injections (top-up) (e.g. labour pain management)	2.0	10-15 (mini-mum interval 30 minutes)	20-30		
Continuous infusion e.g. Labour pain	2.0	6-10 ml/h	12-20 mg/h	n/a	n/a
Postoperative pain management	2.0	6-14 ml/h	12-28 mg/h	n/a	n/a
Thoracic Epidural Administration					
Continuous infusion (postoperative pain management)	2.0	6-14 ml/h	12-28 mg/h	n/a	n/a
Field Block					
(e.g. minor nerve blocks and infiltration)	2.0	1-100	2.0-200	1-5	2-6
Peripheral nerve block (Femoral or interscalene block)					
Continuous infusion or intermittent injections (e.g. postoperative pain management)	2.0	5-10 ml/h	10-20 mg/h	n/a	n/a
n/a = not applicable					

Paediatric patients 0 up to and including 12 years of age

	Concentration mg/ml	Volume ml/kg	Dose mg/kg
Single Caudal Epidural Block			
Blocks below T12, in children with a body weight up to 25 kg	2.0	1	2
Continuous Epidural Infusion			

Paediatric patients 0 up to and including 12 years of age

	Concentration	Volume	Dose
	mg/ml	ml/kg	mg/kg
In children with a body weight up to 25 kg			
<i>0 up to 6 months</i>			
Bolus dose ^a	2.0	0.5-1	1-2
Infusion up to 72 hours	2.0	0.1 mL/kg/h	0.2 mg/kg/h
<i>6 up to 12 months</i>			
Bolus dose ^a	2.0	0.5-1	1-2
Infusion up to 72 hours	2.0	0.2 mL/kg/h	0.4 mg/kg/h
<i>1 to 12 years</i>			
Bolus dose ^b	2.0	1	2
Infusion up to 72 hours	2.0	0.2 mL/kg/h	0.4 mg/kg/h

The dose in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. The volume for single caudal epidural block and the volume for epidural bolus doses should not exceed 25 mL in any patient. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

- a Doses in the low end of the dose interval are recommended for thoracic epidural blocks while doses in the high end are recommended for lumbar or caudal epidural blocks.
- b Recommended for lumbar epidural blocks. It is good practice to reduce the bolus dose for thoracic epidural analgesia

Infants and children aged 1-12 years:

The proposed ropivacaine doses for peripheral block in infants and children provide guidelines for use in children without severe disease. More conservative doses and close monitoring are recommended for children with severe disease.

Single injections for peripheral nerve block (e.g. ilioinguinal nerve block, brachial plexus block) should not exceed 2,5-3,0 mg/kg.

Continuous infusion for peripheral nerve block are recommended at 0,2-0,6 mg/kg/h (0,1-0,3 ml/kg/h) up to 72 h.

The use of ropivacaine in premature children has not been documented.

Section 4.4

Paediatric patients:

Neonates may need special attention due to immaturity of metabolic pathways. The larger variations in plasma concentrations of ropivacaine observed in clinical trials in neonates suggest that there may be an increased risk of systemic toxicity in this age group, especially during continuous epidural infusion. The recommended doses in neonates are based on limited clinical data. When ropivacaine is used in this patient group, regular monitoring of systemic toxicity (e.g. by signs of CNS toxicity, ECG, SpO₂) and local neurotoxicity (e.g. prolonged recovery) is required, which should be continued after ending infusion, due to a slow elimination in neonates. The safety and efficacy of ropivacaine 2 mg/ml for peripheral nerve blocks has not been established for infants < 1 year.

The safety and efficacy of ropivacaine 2 mg/ml for field blocks has not been established for children <12 years.

Ropivacaine all strengths

Section 4.8

Paediatric population:

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults except for hypotension which happens less often in children (< 1 in 10) and vomiting which happens more often in children (> 1 in 10).

In children, early signs of local anaesthetic toxicity may be difficult to detect since they may not be able to verbally express them.

Section 5.2

The pharmacokinetics of ropivacaine was characterized in a pooled population PK analysis on data in 192 children between 0 and 12 years. Unbound ropivacaine and PPX clearance and ropivacaine unbound volume of distribution depend on both body weight and age up to the maturity of liver function, after which they depend largely on body weight. The maturation of unbound ropivacaine clearance appears to be complete by the age of 3 years, that of PPX by the age of 1 year and unbound ropivacaine volume of distribution by the age of 2 years. The PPX unbound volume of distribution only depends on body weight. As PPX has a longer half-life and a lower clearance, it may accumulate during epidural infusion.

Unbound ropivacaine clearance (Cl_u) for ages above 6 months has reached values within the range of those in adults. Total ropivacaine clearance (CL) values displayed in the table **Table 3** are those not affected by the postoperative increase in AAG.

Estimates of pharmacokinetic parameters derived from the pooled paediatric population PK analysis

Age Group	BW^a kg	Cl_u^b (L/h/kg)	V_u^c (L/kg)	CL^d (L/h/kg)	t_{1/2}^e (h)	t_{1/2ppx}^f (h)
Newborn	3.27	2.40	21.86	0.096	6.3	43.3
1m	4.29	3.60	25.94	0.143	5.0	25.7
6m	7.85	8.03	41.71	0.320	3.6	14.5
1y	10.15	11.32	52.60	0.451	3.2	13.6
4y	16.69	15.91	65.24	0.633	2.8	15.1
10y	32.19	13.94	65.57	0.555	3.3	17.8

a Median bodyweight for respective age from WHO database.

b Unbound ropivacaine clearance

c Ropivacaine unbound volume of distribution

d Total ropivacaine clearance

e Ropivacaine terminal half life

f PPX terminal half life

The simulated mean unbound maximal plasma concentration (Cu_{max}) after a single caudal block tended to be higher in neonates and the time to Cu_{max} (t_{max}) decreased with an increase in age. Simulated mean unbound plasma concentrations at the end of a 72 h continuous epidural infusion at recommended dose rates also showed higher levels in neonates as compared to those in infants and children. See also section 4.4.

Simulated mean and observed range of unbound Cu_{max} after a single caudal block

Age group	Dose (mg/kg)	Cu_{max}^a (mg/L)	t_{max}^b (h)	Cu_{max}^c (mg/L)
0-1m	2.00	0.0582	2.00	0.05 – 0.08 (n=5)
1-6m	2.00	0.0375	1.50	0.02 – 0.09 (n=18)
6-12m	2.00	0.0283	1.00	0.01 – 0.05 (n=9)
1-10y	2.00	0.0221	0.50	0.01 – 0.05 (n=60)

a Unbound maximal plasma concentration

b Time to unbound maximal plasma concentration

c Observed and dose-normalised unbound maximal plasma concentration

At 6 months, the breakpoint for change in the recommended dose rate for continuous epidural infusion, unbound ropivacaine clearance has reached 34% and unbound PPX 71% of its mature value. The systemic exposure is higher in neonates and also somewhat higher in infants between 1 to 6 months compared to older children, which is related to the immaturity of their liver function. However, this is partly compensated for by the recommended 50% lower dose rate for continuous infusion in infants below 6 months.

Simulations on the sum of unbound plasma concentrations of ropivacaine and PPX, based on the PK parameters and their variance in the population analysis, indicate that for a single caudal block the recommended dose must be increased by a factor of 2.7 in the youngest group and a factor of 7.4 in the 1 to 10 year group in order for the upper prediction 90% confidence interval limit to touch the threshold for systemic toxicity. Corresponding factors for the continuous epidural infusion are 1.8 and 3.8 respectively.

Likewise the following wording for the paediatric population is to be introduced in the PLs of the different strengths:

Ropivacaine 7,5 and 10 mg/ml:

1. What /../ is and what it is used for

/../ is used in adults and children above 12 years to numb (anaesthetise) parts of the body. It is used to stop pain happening or to provide pain relief. It can be used to:...

- Numb parts of the body during surgery, including having a baby by Caesarean section.
- Relieve pain during childbirth, after surgery, or after an accident.

2. Before /../ is given to you

Take special care with /../:

In children up to and including 12 years. Other strengths (2 mg/ml, 5 mg/ml) may be more appropriate.

Ropivacaine 5mg/ml:

1. What /../ is and what it is used for

- /../ is used in adults to numb (anaesthetise) the area of the body where surgery is going to be performed. It is injected into the lower part of your spine. This quickly stops pain from your waist down for a limited period of time (usually 1 to 2 hours). This is known as a “spinal block” (or “spinal”).

2. Before /../ is given to you

Take special care with /./:

- In children as injections of /./ into the lower part of the spine are not established in children.

Ropivacaine 5mg/ml:

No all agreeing recommendation can be given for the following wording as there is no consensus between MS:

1. What /./ is and what it is used for

/./ is used in children aged 1-12 years to numb (anaesthetise) parts of the body. It is used to stop pain happening or to provide pain relief.

2. Before /./ is given to you**Take special care with /./:**

In children < 1 year as injections of /./ in order to numb parts of the body are not established in younger children.

Ropivacaine 2mg/ml:**1. What /./ is and what it is used for**

/./ is used in adults and children of all ages for acute pain management. It numbs (anaesthetises) parts of the body e.g. after surgery.

2. Before /./ is given to you**Take special care with /./:**

- In newborn children as they are more susceptible to /./.
- In children < 12 years as some injections of /./ in order to numb parts of the body are not established in younger children.

Ropivacaine all strengths**3. Possible side effects****Children**

In children, the side effects are the same as in adults except for low blood pressure which happens less often in children (affecting less than 1 in 10 children) and being sick which happens more often in children (affecting more than 1 in 10 children).

IX. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Naropin 2 mg/ml solution for infusion
Naropin 2 mg/ml solution for injection
Naropin 5 mg/ml solution for injection
Naropin 7,5 mg/ml solution for injection
Naropin 10 mg/ml solution for injection

AstraZeneca UK Ltd
AstraZeneca UK AB Sweden