



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

Name of medicine (INN):	Parecoxib (as sodium) 40 mg lyophilized powder for IM/IV injection + Sodium chloride 9mg/mL (0.9% w/v) (as diluent)
Indication:	For the short term treatment of post-operative pain i.e., oral surgery, abdominal hysterectomy, myomectomy, total knee replacement, total hip asthroplasty, laparoscopic cholecystectomy, inguinal hernia repair and general surgery like diagnostic laparoscopy, gastrectomy, hernioplasty, appendectomy, hemithyroidectomy and splenectomy.
Date of deliberation:	26 November 2015
Recommendation:	DISAPPROVAL
Clinical evidence:	<p>In a high quality meta-analysis by Lloyd et al, parecoxib given at 20 mg showed significant decrease by more than 50% in pain sensation compared to placebo (OR=5.11 (95%CI; 3.51 and 7.43)) while the overall adverse event was similar (OR=1.04 (95% CI; 0.89 and 1.22). Similar effectiveness and safety was shown in parecoxib 40 mg dose.</p> <p>In terms of any cardiovascular event, myocardial infarction or cerebrovascular event, there was no difference between parecoxib and placebo (RR=1.23 (95%CI; 0.48 and 3.17) for any cardiovascular event; RR=1.66 (95%CI; 0.27 and 10.10) for myocardial infarction; RR=1.45 (95%CI; 0.15 and 14.01) for cerebrovascular event.</p> <p>Compared to other intravenous NSAID like ketoprofen, parecoxib was shown to have similar efficacy in terms of pain intensity after 30 min of administration (33.84 vs. 35.16; $p>0.05$) and adverse event (25.9% vs. 28%) (Glina et al. 2011; high quality, GRADEPRO). Compared to celecoxib, intravenous parecoxib was associated with lower rescue morphine use but has similar side effects.</p> <p><i>(See Attachment for the full ERG evaluation)</i></p>
Cost data:	In terms of cost, intravenous parecoxib is almost 10 times more expensive than oral celecoxib when used as pre-medication. Other intravenous analgesic used after surgery like nalbuphine is more affordable than intravenous parecoxib.

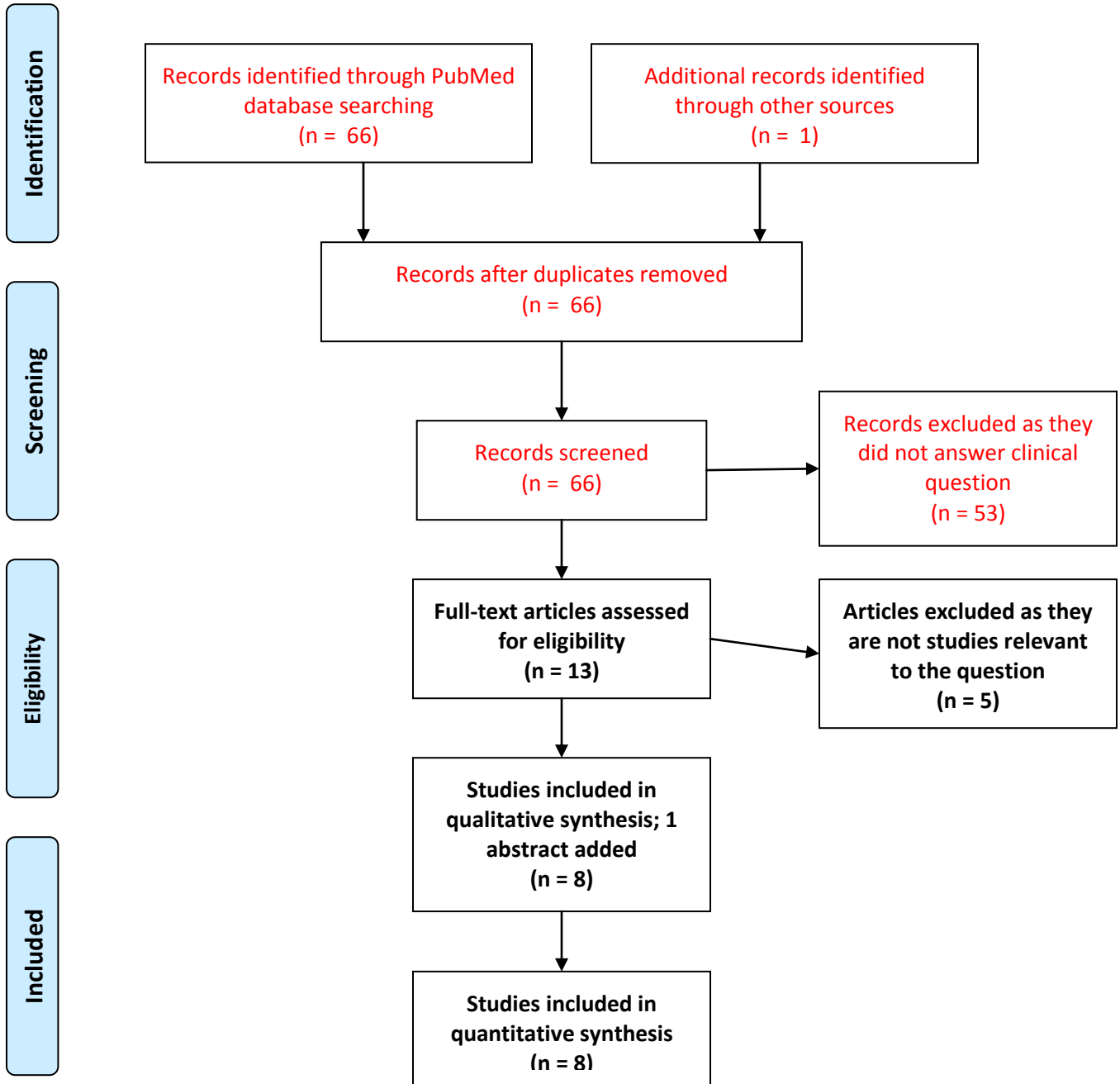
(See Attachment).

Remarks:

No appeal for reconsideration was received within the set deadline, thus the recommendation of the Council to disapprove the medicine still remains.

The Secretary of Health has officially disapproved the proposal to include parecoxib in the PNF.

PRISMA Table



- 1) What is the comparative clinical effectiveness of Parecoxib and other Cox-2 inhibitors (Valdecoxib, Rofecoxib, Celecoxib) in relieving pain due to inflammation?
- 2) How is Parecoxib compared with other Cox-2 inhibitors in terms of safety?
- 3) What is the cost-effectiveness of Parecoxib versus the other Cox-2 inhibitors?

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Parecoxib		Control			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
1	Lloyd et al. Cochrane Database Syst Rev. 2009	Meta- analysis	7 studies with 1,446 participants	Parecoxib 20 mg vs. placebo	Participants with more than 50% pain relief	169	320	29	271		OR=5.11 (95%CI; 3.51 and 7.43)
					Any adverse event	160	284	126	232		OR=1.04 (95% CI; 0.89 and 1.22)
				Parecoxib 40 mg vs. placebo	Participants with more than 50% pain relief	175	278	41	241		OR=3.89 (2.85 and 5.31)
					Any adverse event	130	243	114	202		OR=1.03 (95%CI; 0.88 and 1.21)
2	Schug et al. Anesth Analg. 2009	Pooled analysis	17 studies involving 4,881 noncardiac surgery patients	Parecoxib vs. placebo	Any CV event	13 (0.44%)	2,966	7 (0.37%)	1,915		RR=1.23 (95%CI; 0.48 and 3.17)
					Any myocardial event	4 (0.13%)		2 (0.10%)			RR=1.66 (95%CI; 0.27 and 10.10)
					Any cerebrovascular event	3 (0.10%)		1 (0.05%)			RR=1.45 (95%CI; 0.15 and 14.01)
3	Paech et al. Anaesth Intensive Care. 2014	RCT	111 women who underwent cesarean section	Parecoxib vs. paracetamol	Pain score at rest (24 hrs)	2	1-3	2	1-4		
					Supplementary tramadol	21 (70%)	30	18 (58%)	32		
4	Dahl et al. Acta Anaesthesiol	RCT	89 adult outpatient surgery for anterior	Parecoxib vs. steroid	Rescue opioids (parecoxib/valdcoxi b subgroup)	8.9	SD 9.6	8.7	SD 8.0	High	Data from subgroup analysis

	Scand. 2012		cruciate ligament								
5	Glina et al. Int Braz J Urol. 2011	RCT	338 patients with acute renal colic	Parecoxib IV vs. ketoprofen IV	Mean pain intensity difference at 30 min	33.84	SD 24.61	35.16	SD 26.01		NS
					Overall adverse event	25.9%	156	28%	141		NS
					Serious adverse events	4.6%		4.9%			NS
6	Kyriakidis et al. Hernia. 2011	RCT (3 arm)	510 patients for hernia surgery	Parecoxib vs. lornoxicam	Mean duration of analgesia	11 hrs		8 hrs			p<0.05
					Number of patients requiring escape analgesia	8 (3.1%)	260	19 (13.6%)	140		p<0.05
					Total adverse event	11 (4.2%)	260	7 (5%)	140		NS
				Parecoxib vs. diclofenac	Mean duration of analgesia	11 hrs		6 hrs			p<0.05
					Number of patients requiring escape analgesia	8 (3.1%)	260	36 (32.7%)	110		p<0.05
					Total adverse event	11 (4.2%)	260	6 (4.3%)	110		NS
7	Ittichaikulthol et al. J Med Assoc Thai. 2010	RCT (3 arm)	120 knee or hip surgery patients	Parecoxib vs. celecoxib	Mean 24 hr morphine use	10.73 mg	SD 3.20	25.28 mg	SD 5.39		p<0.01
					Side effects (sedation, nausea, vomiting, pruritus)	12 (30%)	40	9 (22.5%)	40		NS
				Parecoxib vs. placebo		10.73 mg	SD 3.20	37.5 mg	SD 6.78		p<0.01
8	Wei Wei et al. Experimental and	Meta-analyses	RCTs of parecoxib sodium from	Treatment Group: IV 40 mg parecoxib	Patients' global evaluation of study medication		N=1207 patients		N=732 patients		RR=0.99 (95%CI; 0.80 and 1.21)

	Therapeutic Medicine, 2013		January 1999 to January 2013	+ patient controlled analgesia Control: patient controlled analgesia alone	24 hours after surgery Patients' global evaluation of study medication 48 hours after surgery Incidence of Adverse Drug Events after surgery (fever, nausea, vomiting, respiratory depression, headache)							RR=0.98 (95%CI; 0.90 and 1.07) RR=1.03 (95%CI; 0.95 and 1.12)
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DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS

For acute pain after surgery

<p>PARAMETER (Indicate information for intended recipient)* <u>INTENDED RECIPIENT:</u></p>	<p>NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</p>	<p>CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF</p>	<p>REFERENCES</p>
<p>COST PER DOSAGE UNIT (in PhP) a. Proposed list price to the government b. Current prevailing market price</p>	<p>Parecoxib 40mg/5 ml Php 489.50</p>	<p>Nalbuphine 10 mg/ml, 1 ml ampule: Php 30/ampule</p>	
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>Acute pain: 40 mg initially followed by 20 or 40 mg every 6 -12 hour Max dose 80 mg/day 2 units</p>	<p>Acute pain: 1 ½ ampule for a 70 kg patient; followed every 6 hours 6 ampules/day 6 units</p>	
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>Php 979/day x 3 days (based on post-op studies) Php 2,937</p>	<p>Php 180/day If given for 3 days: Php 540.00</p>	
<p>ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (n PhP) a. Implementation costs: (cost of drug administration, monitoring, additional diagnostic services, additional equipment, travel, caregiver, etc.)</p>	<p>Vomiting Metochlopramide : DPRI Price Php 2.85 x 3 Php 8.55</p>	<p>Antidote: DPRI Price Naloxone 400 mcg/ml Php 392.00 2 mg/dose (Max of 10 mg) = 3 amps Php 1,176</p>	
<p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>	<p>Php 2,945.55</p>	<p>Php 1,716.00</p>	

For pre-medication

<p align="center">PARAMETER (Indicate information for intended recipient)* <u>INTENDED RECIPIENT:</u></p>	<p align="center">NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</p>	<p align="center">CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF</p>	<p align="center">REFERENCES</p>
<p>COST PER DOSAGE UNIT (in PhP) c. Proposed list price to the government d. Current prevailing market price</p>	<p>Parecoxib 40mg/5 ml Php 489.50</p>	<p>Celecoxib 400mg cap Php 25</p>	
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>Premedication 40 mg</p>	<p>Premedication 400 mg</p>	
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>Php 489.50/vial</p>	<p>Php 25</p>	
<p>ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (n PhP) b. Implementation costs: (cost of drug administration, monitoring, additional diagnostic services, additional equipment, travel, caregiver, etc.)</p>		<p>Rescue morphine Php 48</p>	
<p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>	<p>Php 489.50</p>	<p>Php 73</p>	

REVIEWERS' RECOMMENDATIONS

Literature Search

- We searched PubMed last April 2015 using the term “parecoxib” and limited the search yield to meta-analysis articles. The yield was 5 articles. We reviewed the 5 articles and found that the latest potentially useful meta-analysis was 2009. We updated our search with the term “parecoxib” and limited our search to randomized controlled trials published from January 2009 to present. The yield was 61 articles. We reviewed the 66 abstracts and considered 13 articles for full text retrieval. Of the 13 articles, we considered 8 for inclusion in this review.
 - Lloyd R(1), Derry S, Moore RA, McQuay HJ. Intravenous or intramuscular parecoxib for acute postoperative pain in adults. *Cochrane Database Syst Rev.* 2009 Apr 15;(2):CD004771. doi: 10.1002/14651858.CD004771.pub4.
 - Schug SA(1), Joshi GP, Camu F, Pan S, Cheung R. Cardiovascular safety of the cyclooxygenase-2 selective inhibitors parecoxib and valdecoxib in the postoperative setting: an analysis of integrated data. *Anesth Analg.* 2009 Jan;108(1):299-307. doi: 10.1213/ane.0b013e31818ca3ac.
 - Paech MJ(1), McDonnell NJ, Sinha A, Baber C, Nathan EA. A randomised controlled trial of parecoxib, celecoxib and paracetamol as adjuncts to patient-controlled epidural analgesia after caesarean delivery. *Anaesth Intensive Care.* 2014 Jan;42(1):15-22.
 - Glina S(1), Damiao R, Afif-Abdo J, Santa Maria CF, Novoa R, Cairoli CE, Wajsbrot D, Araya G. Efficacy and safety of parecoxib in the treatment of acute renal colic: a randomized clinical trial. *Int Braz J Urol.* 2011 Nov-Dec;37(6):697-705.
 - Dahl V(1), Spreng UJ, Waage M, Raeder JC. Short stay and less pain after ambulatory anterior cruciate ligament (ACL) repair: COX-2 inhibitor versus glucocorticoid versus both combined. *Acta Anaesthesiol Scand.* 2012 Jan;56(1):95-101. doi: 10.1111/j.1399-6576.2011.02584.x. Epub 2011 Nov 21.
 - Kyriakidis AV(1), Perysinakis I, Alexandris I, Athanasiou K, Papadopoulos Ch, Mpesikos I. Parecoxib sodium in the treatment of postoperative pain after Lichtenstein tension-free mesh inguinal hernia repair. *Hernia.* 2011 Feb;15(1):59-64. doi: 10.1007/s10029-010-0737-1. Epub 2010 Oct 19.
 - Ittichaikulthol W(1), Prachanpanich N, Kositchaiwat C, Intapan T. The post-operative analgesic efficacy of celecoxib compared with placebo and parecoxib after total hip or knee arthroplasty. *J Med Assoc Thai.* 2010 Aug;93(8):937-42.
 - Wei Wei et al. Efficacy and Safety of Parecoxib sodium for acute postoperative pain: A meta-analysis *Experimental and Therapeutic Medicine*, 2013; 6: 525-531

Effectiveness/Efficacy

- Parecoxib is an intravenous COX-2 inhibitor that has been proven to be effective. In a meta-analysis by Lloyd et al, parecoxib given at 20 mg showed significant decrease by more than 50% in pain sensation compared to placebo (OR=5.11 (95%CI; 3.51 and 7.43)) while the overall adverse event was similar (OR=1.04 (95% CI; 0.89 and 1.22)). Similar effectiveness and safety was shown in parecoxib 40 mg dose.
- In terms of any cardiovascular event, myocardial infarction or cerebrovascular event, there was no difference between parecoxib and placebo (RR=1.23 (95%CI; 0.48 and 3.17) for any cardiovascular event; RR=1.66 (95%CI; 0.27 and 10.10) for myocardial infarction; RR=1.45 (95%CI; 0.15 and 14.01 for cerebrovascular event). It has also been shown to be effective among women undergoing cesarean section.
- Compared to other intravenous NSAID like ketoprofen, parecoxib was shown to have similar efficacy in terms of pain intensity after 30 min of administration (33.84 vs. 35.16; p>0.05) and adverse event (25.9% vs. 28%)(Glina et al. 2011).
- Compared to celecoxib, intravenous parecoxib was associated with lower rescue morphine use but has similar side effects.

Summary of Review

- Overall, parecoxib is similar in efficacy and side effects compared with other intravenous NSAID. But compared with oral celecoxib, intravenous parecoxib has lower use for rescue morphine medication and with similar side effects.

Cost Data

- In terms of cost, intravenous parecoxib is almost 10 times more expensive than oral celecoxib when used as pre-medication. Other intravenous analgesic used after surgery like nalbuphine is more affordable than intravenous parecoxib.

Overall Recommendation

- The advantage of COX-2 inhibitors over the other NSAID is its less gastrointestinal side effect during long term use. For acute surgical conditions however, intravenous parecoxib is more expensive than other intravenous analgesic with similar efficacy and acceptable side effect profile.
- Thus, there is not enough evidence and justification to include intravenous parecoxib in the PNF.

References

1. Navarro JC, Baroque AC 2nd, Lokin JK, Venketasubramanian N. The real stroke burden in the Philippines. *Int J Stroke*. 2014 Jul;9(5):640-1. doi: 10.1111/ij.s.12287. Epub 2014 May 20.
2. Loo KW(1), Gan SH. Burden of stroke in the Philippines. *Int J Stroke*. 2013 Feb;8(2):131-4. doi: 10.1111/j.1747-4949.2012.00806.x. Epub 2012 May 9.
3. Lu H and Javier F. Prevalence and Treatment of Chronic Pain in the Philippines. *PJIM*, 2011; 49 (2): 61-69.