



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

Name of medicine (INN):	Remifentanil IV injection
Indication:	Used for analgesia/anesthesia
Date of deliberation:	01 July 2015
Recommendation:	DISAPPROVAL
Clinical evidence:	<p>In terms of pain at rest, patients given remifentanil has lesser pain score compared with those who were given fentanyl (SMD= -5.97; 95% CI -16.21 and 4.56). The difference however, was NOT statistically significant. Likewise, mechanical ventilation and hospital stay were also lesser in the remifentanil group compared with the fentanyl group. On the other hand, higher morphine consumption and higher need for rescue analgesic were seen among those patients given with remifentanil. Based on the evaluation, if the drug is compared with meperidine, remifentanil has statistically significant lower pain scores (SMD=-25.25 (95%CI; -31.24 and -19.25). However, when compared with other opioids, remifentanil has statistically significant higher pain scores (SMD=3.26 95%CI; 0.51 and 6.1).</p> <p>As for its safety, studies showed statistically insignificant higher incidence of nausea (RR=1.03 (95%CI; 0.97 and 1.09) and vomiting (RR=1.06 (95%CI; 0.96 and 1.17)) and lower incidence of respiratory depression RR=0.32 (95%CI; 0.09 and 1.16).</p> <p>.</p> <p><i>(See Attachment for the full ERG evaluation)</i></p>
Cost data:	<p>It was noted that remifentanil is not available in the local market. Likewise, considering its price in other countries, the total cost per patient is considerably higher with remifentanil (Php 2,634) compared to fentanyl which only costs Php 85 per ampule.</p> <p>The Council acknowledged the cost of treatment presented in the report</p>

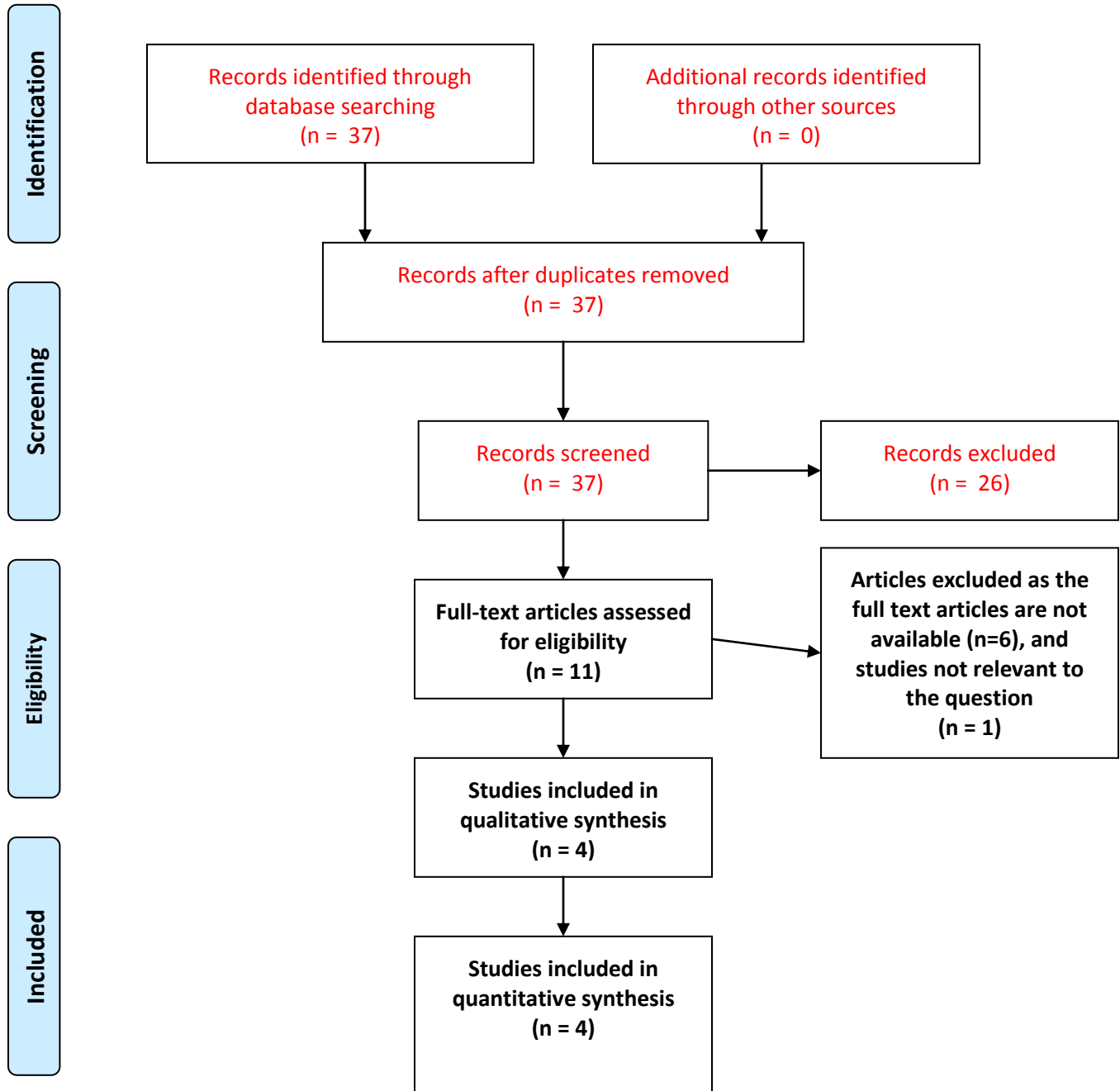
of the Evidence Review Group (*See Attachment*).

Remarks:

The Secretary of Health has officially disapproved the proposal to include remifentanyl in the PNF. There was no appeal received within the set deadline, thus the recommendation of the Council still remains.

PRISMA Table

PubMed search strategy using the terms “Remifentanyl“ limited to “meta-analysis” was conducted February 2015. The yield was 37 articles.



1. Among postoperative patients with moderate to severe pain, is remifentanil as effective as fentanyl, nalbuphine or tramadol in providing 24-hour pain relief?

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Remifentanil		Control			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
	Fletcher and Martinez. Br J Anaesth. 2014	Meta-analysis	Subgroup analysis of 853 patients undergoing surgery in 15 trials Subgroup analysis of 30 patients undergoing surgery in 1 trial	Remifentanil vs control Remifentanil vs. fentanyl iv	Pain at rest in 24 hrs Morphine consumption Pain at rest in 24 hrs Morphine consumption	Raw mean score not available in text		Raw mean score not available in text		SMD=3.26 (95%CI; 0.51 and 6.1) SMD=0.68 (95%CI; 0.32 and 1.03) SMD=-5.97 (95%CI; -16.21 and 4.26) SMD=0.67 (95%CI; -0.07 and -1.41)	
	Leong et al. Anesth Analg. 2011	Meta-analysis	349 women in labor included in 7 trials	Remifentanil vs. meperidine	0-100 visual pain scale	Raw mean score not available in text		Raw mean score not available in text		SMD=-25.25 (95%CI; -31.24 and -19.25)	
	Greco et al. J Cardiothorac Vasc Anesth. 2012	Meta-analysis	1473 cardiac surgery patients in 16 randomized controlled trials	Remifentanil vs. fentanyl	Mechanical ventilation Hospital stay Troponin-I release	Raw mean score not available in text		Raw mean score not available in text		SMD=-138.49 (95%ci; -244.28 and -32.71) SMD=-1.08 (95%CI; -1.60 and -0.57) SMD=-2.08 (95%CI; -3.93 and -0.24)	
	Komatsu et al. Anaesthesia. 2007		1694 patients in 30 RCTs	Remifentanil vs. other opioids	Post-operative analgesia Nausea					RR=1.36 (95%CI; 1.21 and 1.53) RR=1.03 (95%CI; 0.97 and 1.09)	

				Remifentanil vs. fentanyl	Vomiting						RR=1.06 (95%CI; 0.96 and 1.17)
					Respiratory depression						RR=0.32 (95%CI; 0.09 and 1.16)
					Need for naloxone						RR=0.25 (95%CI; 0.14 and 0.47)
					Need for rescue analgesia						RR=1.30 (95%CI; 1.07 and 1.59)
					Nausea						RR=1.09 (95%CI; 0.99 and 1.12)
					Shivering						RR=2.13 (95%CI; 1.65 and 2.74)
					Need for naloxone						RR=0.10 (95%CI; 0.03 and 0.37)

EVIDENCE TABLE 2: GRADE EVIDENCE PROFILE TABLE

QUALITY ASSESSMENT							SUMMARY OF FINDINGS					Importance
							No. of patients		Effect		Over-all Quality	
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute MD		
Outcome: Pain at rest in 24 hrs												
1	Meta-analyses	None	None	None	None		Remifentanyl	Other opioids		3.26 (95%CI; 0.51 and 6.1)	High	Critical
Outcome: Pain at rest in 24 hrs												
1	Meta-analyses	None	None	None	None		Remifentanyl	Fentanyl		-5.97 (95%CI; -16.21 and 4.26)	High	Critical
Outcome: Nausea												
1	Meta-analyses	None	None	None	None		Remifentanyl	Other opioids	1.03 (95%CI; 0.97 and 1.09)		High	Critical
Outcome: Nausea												
1	Meta-analyses	None	None	None	None		Remifentanyl	Fentanyl	1.09 (95%CI; 0.99 and 1.12)		High	Critical

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS (Attach EvidenceTables)

<p>PARAMETER (Indicate information for intended recipient) * <i><u>INTENDED RECIPIENT:</u></i></p>	<p>NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</p>	<p>CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF <i>(*where there is no comparator medicine in the formulary, use the cost of the best existing standard of care)</i></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>Remifentanil 1 mg/3ml = \$59.19 (not available locally)</p>	<p>Fentanyl 50mcg in 2 ml ampule (P85)</p>	<p>Remifentanil is not available locally. Price is internet price. Fentanyl is DPRI price</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>1 ampule post-operative</p>	<p>1 ampule post-operative</p>	
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>P 2,634</p>	<p>P 85</p>	<p>At 44.5; \$-Peso exchange rate</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>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>			
<p>ESTIMATED NUMBER OF PATIENTS WITH THE DISEASE/CONDITION WHO WILL USE THE MEDICINE</p>			
<p>QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			
<p>DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			

REVIEWERS' RECOMMENDATIONS

Literature Search

- We searched PubMed database last February 2015 using the terms “remifentanil” and “meta-analysis” which yielded 37 articles. We reviewed the 37 abstracts and considered 11 studies for full text retrieval. Only 5 full text articles are available. Four of these articles are included in the review.
 - Fletcher D(1), Martinez V(2). Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth.* 2014 Jun;112(6):991-1004. doi: 10.1093/bja/aeu137.
 - Leong WL(1), Sng BL, Sia AT. A comparison between remifentanil and meperidine for labor analgesia: a systematic review. *Anesth Analg.* 2011 Oct;113(4):818-25. doi: 10.1213/ANE.0b013e3182289fe9. Epub 2011 Sep 2.
 - Greco M(1), Landoni G, Biondi-Zoccai G, Cabrini L, Ruggeri L, Pasculli N, Giacchi V, Sayeg J, Greco T, Zangrillo A. Remifentanil in cardiac surgery: a meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth.* 2012 Feb;26(1):110-6. doi: 10.1053/j.jvca.2011.05.007. Epub 2011 Aug 5.
 - Komatsu R(1), Turan AM, Orhan-Sungur M, McGuire J, Radke OC, Apfel CC. Remifentanil for general anaesthesia: a systematic review. *Anaesthesia.* 2007 Dec;62(12):1266-80.

Effectiveness/Efficacy

- We considered the presence of pain and other visual measurement of pain as the main clinical outcomes.
 - In terms of pain at rest, patients given remifentanil has lesser pain score compared to patients given fentanyl (SMD= -5.97; 95% CI -16.21 and 4.56) but this difference was not statistically significant. In addition, mechanical ventilation, hospital stay were also lesser in the remifentanil group compared to fentanyl group. There was however a higher morphine consumption among those given remifentanil. The need for rescue analgesic was also higher in remifentanil in the meta-analysis conducted by Komatsu et al.
 - Compared to meperidine, remifentanil has significantly lower pain scores (SMD=-25.25 (95%CI; -31.24 and -19.25) and this was statistically significant.
 - Compared to other opioids however, remifentanil had higher pain scores (SMD=3.26 95%CI; 0.51 and 6.1) and this was statistically significant.

Safety

- In terms of safety, there was a higher incidence of nausea (RR=1.03 (95%CI; 0.97 and 1.09), vomiting RR=1.06 (95%CI; 0.96 and 1.17) and lower incidence of respiratory depression RR=0.32 (95%CI; 0.09 and 1.16) among patients given remifentanil than among patients given other opioids. These however were not statistically significant. This observation of higher side effects was also similarly higher in remifentanil when it was compared to fentanyl.

Summary of Review

- In summary, remifentanil is as effective as fentanyl and less effective than other opioids. It also has more side effects but the difference was not statistically significant.

Cost Data

- Remifentanil is not yet available in local market. We obtained the internet price. In terms of price we found remifentanil to be a lot more expensive than fentanyl (P2,634 vs. P85 per dose).

Overall Recommendation

- Overall we found remifentanil to be more effective than meperidine but as effective as fentanyl. However it is a lot more expensive than fentanyl. There is not enough evidence and justification to include remifentanil in the PNF.

References

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2. Kim SH(1), Stoicea N(2), Soghomonyan S(2), Bergese SD(3). Intraoperative use of remifentanyl and opioid induced hyperalgesia/acute opioid tolerance: systematic review. *Front Pharmacol.* 2014 May 8;5:108. doi: 10.3389/fphar.2014.00108. eCollection 2014.
3. Fletcher D(1), Martinez V(2). Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth.* 2014 Jun;112(6):991-1004. doi: 10.1093/bja/aeu137.
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11. Komatsu R(1), Turan AM, Orhan-Sungur M, McGuire J, Radke OC, Apfel CC. Remifentanyl for general anaesthesia: a systematic review. *Anaesthesia.* 2007 Dec;62(12):1266-80.
12. Vassiliou T(1), Putzke C, Geldner G, Eberhart L. Cost analyses of remifentanyl, mivacurium and ropivacaine - a systematic review. *Expert Opin Pharmacother.* 2004 Feb;5(2):415-25.