



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

Name of medicine (INN): Tramadol hydrochloride + Paracetamol 37.5mg/325mg tablet;
18.75mg/162.50mg tablet

Indication: Indicated for the management of moderate to severe pain.

Date of deliberation: 23 October 2015

Recommendation: **DISAPPROVAL**

Clinical evidence: The results of the ERG output showed that the fixed dose had better efficacy in terms of pain relief for 6-8 hours duration than its individual component i.e. RR=2.7; 95%CI: 1.8 and 4.0 for tramadol/paracetamol; RR=1.9; 95%CI: 1.2 and 2.9 for tramadol and RR=1.7; 95%CI: 1.1 and 2.6 for paracetamol.

It was also shown to be better than any of its individual component with smaller NNTs when compared to tramadol alone (2.5 for tramadol/paracetamol vs. 4 for tramadol) and paracetamol alone (2.5 for tramadol/paracetamol vs. 5 for paracetamol).

As regards its safety, similar incidence of withdrawals due to adverse event was observed but it was noted that compared to placebo, tramadol/paracetamol (13% vs. 2%) and tramadol alone (12% vs. 2%) have higher incidence of nausea or vomiting.

(See Attachment for the full ERG evaluation)

Cost data: For a one week course, tramadol/paracetamol fixed dose combination will cost Php 599.76 (tramadol 18.75 mg + paracetamol 162.50 mg) to Php 923.16 (tramadol 37.5 mg + paracetamol 325 mg) compared to just Php 5.88 for paracetamol or Php 50.61 for tramadol at the DPRI price. The Council noted that even the cheapest generic counterpart in the market of the fixed dose combination is still more expensive than the total cost of the single dose preparations of paracetamol and tramadol.

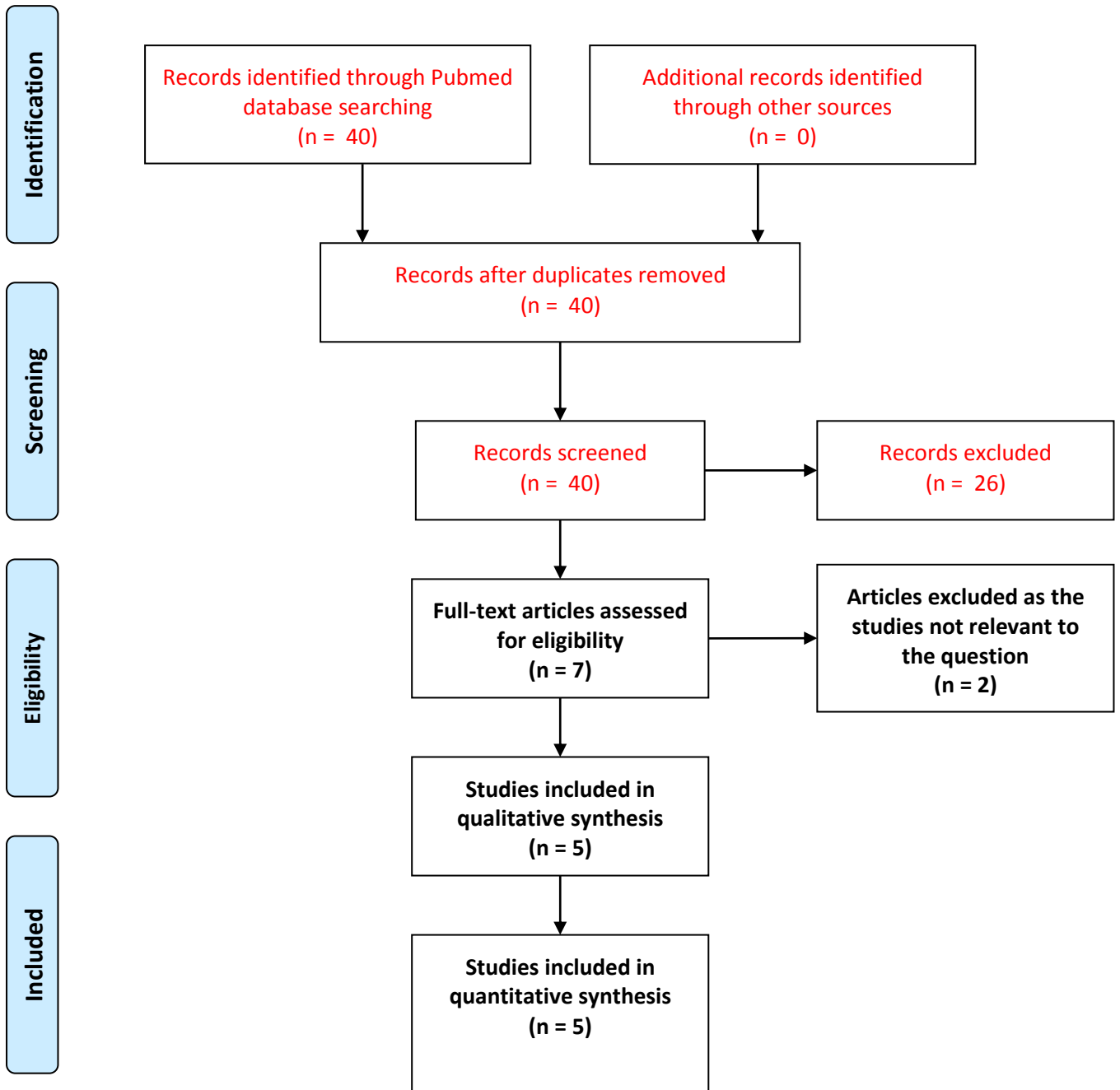
(See Attachment for the full ERG evaluation)

Remarks: The ERG evaluated the documents submitted by the proponent to support their appeal for reconsideration and it was noted that the same advantage can be achieved by taking the separate formulation. The ease

of dosing is only about swallowing a tablet once instead of twice with the separate preparation. Likewise, the cost is a lot more for the fixed dose for a simple act of swallowing two reasonably sized tablets.

The Council concurred to this and it was observed that the only advantage of the FDC is in terms of decreasing the adverse drug reactions related to high dose tramadol, e.g., dizziness and nausea. Hence, given that the product has prohibitive cost and the proponent did not give a lower price offer, the initial recommendation to disapprove its inclusion still remains.

PRISMA Table



1. Among patients aged 20 – 40 complaining of acute musculoskeletal pain, would the use of combination tramadol plus paracetamol prove better than tramadol alone in controlling symptoms? (Include question on safety: nausea, vomiting and dizziness including syncopal attacks)

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS	Tramadol/Pracetamol		Control			
					(including adverse events)	No. of events *	Total # of patients	No. of events *	Total # of patients		
1	Whittle et al. Cochrane, 2011	Meta-analysis	11 RCTs with 672 patients with rheumatoid arthritis	Tramadol/paracetamol plus standard treatment vs. standard treatment	Mean daily pain intensity	47.23	SD 19.96	53.81	SD 16.59	High	MD=-6.58; 95% CI: -11.55 and -1.61
					Mean daily pain relief	1.04	SD 0.89	0.78	SD 0.8		MD=0.26; 95%CI: 0.03 and 0.49
					Global improvement	109	201	27	66		RR=1.33; 95%CI: 0.97 and 1.82
					Withdrawals	1	201	1	66		RR=0.33; 95%CI: 0.02 and 5.18
2	Roskell et al. Pain Pract, 2011	Meta-analysis	21 RCTs on patients with fibromyalgia	Tramadol/paracetamol plus standard vs. standard treatment	50% Improvement in pain response	54	156	29	157	High	RR=1.87; 95%CI: 1.26 and 2.78
					Withdrawal due to adverse event	29	156	18	157		RR=1.62; 95%CI: 0.94 and 2.80
3	McQuay et al.	Meta-analysis	RCTs on post-surgical patients	Tramadol/paracetamol vs. tramadol	NNT for at least 50% pain relief (lower NNT is better-Figure 2)	2.5	95%CI; 1.5 and 5-8	4	95%CI: 2 and 15	High	Tramadol/paracetamol was more effective than either of its two component
				Tramadol/paracetamol vs. tramadol		2.5	95%CI; 1.5 and 5-8	5	95%CI: 2 and 30		
4	Edwards et al. J Pain Symptom Management,	Meta-analysis	7 RCTs on post-surgical patients	Tramadol/paracetamol vs. placebo	Pain relief data (6 hrs)	58	101	22	100	High	RR=2.6; 95%CI: 1.7 and 3.9
				Tramadol vs.		45	98	22	100		RR=2.1; 95%CI: 1.4 and

	2002			placebo							3.2
				Paracetamol vs. placebo		40	100	22	100		RR=1.8; 95%CI: 1.2 and 2.8
				Tramadol/paracetamol vs. placebo	Pain relief data (8 hrs)	59	101	22	100		RR=2.7; 95%CI: 1.8 and 4.0
				Tramadol vs. placebo		40	98	22	100		RR=1.9; 95%CI: 1.2 and 2.9
				Paracetamol vs. placebo		37	100	22	100		RR=1.7; 95%CI: 1.1 and 2.6
				Tramadol/paracetamol vs. placebo	Adverse event (nausea or vomiting)	13	101	2	100		
				Tramadol vs. placebo		12 (12%)	99	2	100		
				Tramadol/paracetamol vs. placebo	Withdrawals (dental pain arm)	31 (9%)	340	124 (37%)	337		
				Tramadol vs. placebo		83 (24%)	340	124 (37%)	337		
				Paracetamol vs. placebo		30 (9%)	340	124 (37%)	337		
5	Medve et al. Anesth Prog, 2001	RCT	1,197 patients who undergone dental extraction	Tramadol/paracetamol vs. tramadol alone	Patient global assessment (higher score is better)	3.0	SD 1.31	2.0	SD 1.27	High	p=0.0001
				Tramadol/paracetamol vs. paracetamol alone		3.0	SD 1.31	2.7	SD 1.26		p=0.0040

				Tramadol/para cetamol vs. placebo		3.0	SD 1.31	1.6	SD 0.98		p=0.0001
--	--	--	--	---	--	-----	---------	-----	---------	--	----------

EVIDENCE TABLE 2: GRADE EVIDENCE PROFILE TABLE

QUALITY ASSESSMENT							SUMMARY OF FINDINGS					Importance
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Over-all Quality	
							Intervention	Control	Relative (95% CI)	Absolute MD		
Outcome: Mean daily pain intensity												
1	Meta-analysis	None	None	None	None		Tramadol/paracetamol plus standard treatment	Standard treatment		MD=-6.58; 95% CI: -11.55 and -1.61	High	Critical
Outcome: At least 50% improvement in pain												
1	Meta-analysis	None	None	None	None		Tramadol/paracetamol plus standard treatment	Standard treatment	1.87; 95%CI: 1.26 and 2.78		High	Critical
Outcome: Pain relief at 8 hrs (indirect comparison)												
1	Meta-analysis	None	None	None	None	Indirect comparison	Tramadol/paracetamol	Placebo	2.7; 95%CI: 1.8 and 4.0		Moderate	Critical
1	Meta-analysis	None	None	None	None	Indirect comparison	Tramadol	Placebo	1.9; 95%CI: 1.2 and 2.9		Moderate	Critical
1	Meta-analysis	None	None	None	None	Indirect comparison	Paracetamol	Placebo	1.7; 95%CI: 1.1 and 2.6		Moderate	Critical

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS

<p align="center">PARAMETER (Indicate information for intended recipient)^x <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)</p> <p>a. Proposed list price to the government</p> <p>b. Current prevailing market price</p>	<p>¹Tramadol 37.5 /paracetamol 325 (Dolcet): PhP 43.96/tab</p> <p>¹Tramadol 18.75 /paracetamol 162.50 (Dolcet Mini): PhP 28.56/tab</p>	<p>²Paracetamol 500mg tablet PhP 0.21</p> <p>Tramadol 50mg capsule P 2.41</p>	<p>¹company submission</p> <p>²DPRI MIMS</p> <p>DPRI</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>For 1 week course</p> <p align="center">21</p>	<p>For 1 week course</p> <p align="center">28 (paracetamol) or 21 (tramadol)</p>	
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>¹Tramadol 37.5 /paracetamol 325 (Dolcet): PhP 923.16</p> <p>¹Tramadol 18.75 /paracetamol 162.50 (Dolcet Mini): PhP 599.76</p>	<p>²Paracetamol 500mg tablet PhP 5.88</p> <p>Tramadol 50mg capsule P 50.61</p>	
<p>ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (n PhP)</p> <p>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>¹Tramadol 37.5 /paracetamol 325 (Dolcet): PhP 923.16</p> <p>¹Tramadol 18.75 /paracetamol 162.50 (Dolcet Mini): PhP 599.76</p>	<p>²Paracetamol 500mg tablet PhP 5.88</p> <p>Tramadol 50mg capsule P 50.61</p>	
<p>ESTIMATED NUMBER OF PATIENTS WITH THE DISEASE/CONDITION</p>			

WHO WILL USE THE MEDICINE			
QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)			
DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)			

REVIEWERS' RECOMMENDATIONS

Literature Search

- We searched Pubmed last April 2015 using the terms “tramadol” AND “paracetamol” OR “acetaminophen” and limited the search to meta-analysis articles only. The yield was 14. The latest meta-analysis was 2012 so we updated our search with “tramadol” AND “paracetamol” OR “acetaminophen” and limited the search to randomized controlled trials published from January 2012 to present. The yield was 26 articles. We reviewed the 40 articles and considered 7 for full text retrieval.
- Of the 7 full text we reviewed we included 5 in this review as it answer the questions by NCPAM:
 - Whittle SL(1), Richards BL, Husni E, Buchbinder R. Opioid therapy for treating rheumatoid arthritis pain. *Cochrane Database Syst Rev.* 2011 Nov 9;(11):CD003113. doi: 10.1002/14651858.CD003113.pub3.
 - Roskell NS(1), Beard SM, Zhao Y, Le TK. A meta-analysis of pain response in the treatment of fibromyalgia. *Pain Pract.* 2011 Nov-Dec;11(6):516-27. doi: 10.1111/j.1533-2500.2010.00441.x. Epub 2010 Dec 28.
 - McQuay H(1), Edwards J. Meta-analysis of single dose oral tramadol plus acetaminophen in acute postoperative pain. *Eur J Anaesthesiol Suppl.* 2003;28:19-22.
 - Edwards JE(1), McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. *J Pain Symptom Manage.* 2002 Feb;23(2):121-30.
 - Medve RA(1), Wang J, Karim R. Tramadol and acetaminophen tablets for dental pain. *Anesth Prog.* 2001 Summer;48(3):79-81.

Effectiveness/Efficacy

- Among patients with rheumatoid arthritis, tramadol/paracetamol was more effective than standard treatment alone in terms of decrease pain intensity (MD = -6.58; 95% CI: -11.55 and -1.61) and mean daily pain relief (MD=0.26; 95%CI: 0.03 and 0.49). The advantage of the combination over standard treatment was also shown among patients with fibromyalgia where at least 50% improvement in pain was seen in more than 80% of patients (RR=1.87; 95%CI: 1.26 and 2.78).
- Tramadol/paracetamol combination was also shown to be better than any of its individual component with smaller NNTs when compared to tramadol alone (2.5 for tramadol/paracetamol vs. 4 for tramadol) and paracetamol alone (2.5 for tramadol/paracetamol vs. 5 for paracetamol).
- A meta-analysis that used indirect comparisons of the fixed dose and individual components showed that the fixed dose had better efficacy for 6-8 hours duration than its individual component i.e. RR=2.7; 95%CI: 1.8 and 4.0 for tramadol/paracetamol ; RR=1.9; 95%CI: 1.2 and 2.9 for tramadol and RR=1.7; 95%CI: 1.1 and 2.6 for paracetamol.

Safety

- In terms of safety, the withdrawals from treatment because of side effect were similar between tramadol/paracetamol plus standard treatment vs. standard treatment alone. This was shown in two meta-analyses i.e. Whittle et al, 2011 and Roskell et al, 2011.
- Tramadol/paracetamol and tramadol alone has higher incidence of nausea or vomiting than paracetamol or placebo.

Summary of Review

- Tramadol/paracetamol was found to be more effective than its single component by at least 50% vs. tramadol and 80% vs. paracetamol. Withdrawals due to adverse event were similar but the tramadol component had more nausea and vomiting as side effect.

Cost Data (Cost-comparison table)

- For a one week course, tramadol/paracetamol fixed dose combination will cost Php 599.76 (tramadol 18.75 mg + paracetamol 162.50 mg) to Php 923.16 (tramadol 37.5 mg + paracetamol 325 mg) compared to just Php 5.88 for paracetamol or Php 50.61 for tramadol at DPRI price. Even at MIMS price the fixed dose combination will still be 2.5 times the single preparation. Taking the separate preparation together will also turn out to be more affordable than the fixed dose combination.

Final Recommendation

- Overall we found the fixed dose combination to be more effective than placebo or the individual component. However it is a lot more expensive. Taking the individual components at the same time may be more affordable. At present, there is not enough justification to include the fixed dose combination of tramadol/paracetamol in the formulary.

References

1. Chaparro LE(1), Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev.* 2012 Jul 11;7:CD008943. doi: 10.1002/14651858.CD008943.pub2.
2. Whittle SL(1), Richards BL, Husni E, Buchbinder R. Opioid therapy for treating rheumatoid arthritis pain. *Cochrane Database Syst Rev.* 2011 Nov 9;(11):CD003113. doi: 10.1002/14651858.CD003113.pub3.
3. Roskell NS(1), Beard SM, Zhao Y, Le TK. A meta-analysis of pain response in the treatment of fibromyalgia. *Pain Pract.* 2011 Nov-Dec;11(6):516-27. doi: 10.1111/j.1533-2500.2010.00441.x. Epub 2010 Dec 28.
4. Cepeda MS(1), Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis: a systematic review and metaanalysis. *J Rheumatol.* 2007 Mar;34(3):543-55.
5. McQuay H(1), Edwards J. Meta-analysis of single dose oral tramadol plus acetaminophen in acute postoperative pain. *Eur J Anaesthesiol Suppl.* 2003;28:19-22.
6. Edwards JE(1), McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. *J Pain Symptom Manage.* 2002 Feb;23(2):121-30.
7. Medve RA(1), Wang J, Karim R. Tramadol and acetaminophen tablets for dental pain. *Anesth Prog.* 2001 Summer;48(3):79-81.

Response to appeal on the reviewers' recommendation on tramadol/paracetamol fixed dose combination

We tried to update the review by examining the articles included in the appeal by the manufacturer. The two articles (Pergolizzi et al and Dhillon) were review articles coming from publications that may have also been included in our review. We agree on the findings of clinical effectiveness of the combination.

However, we stand firm on our conclusion that the same advantage can be achieved by taking the separate formulation. We don't agree with the contention by the manufacturer based on Dhillon's opinion that synergism of the drugs' action can be achieved only by the fixed dose combination. The ease of dosing is only about swallowing a tablet once instead of twice with the separate preparation. The cost is a lot more for the fixed dose for a simple act of swallowing two reasonably sized tablets.

Thus, we stand by our conclusion that at present, there is not enough justification to include the fixed dose combination of tramadol/paracetamol in the formulary. If the manufacturer can decrease the price approximately similar to the separate preparation, FEC may reconsider its decision.