



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

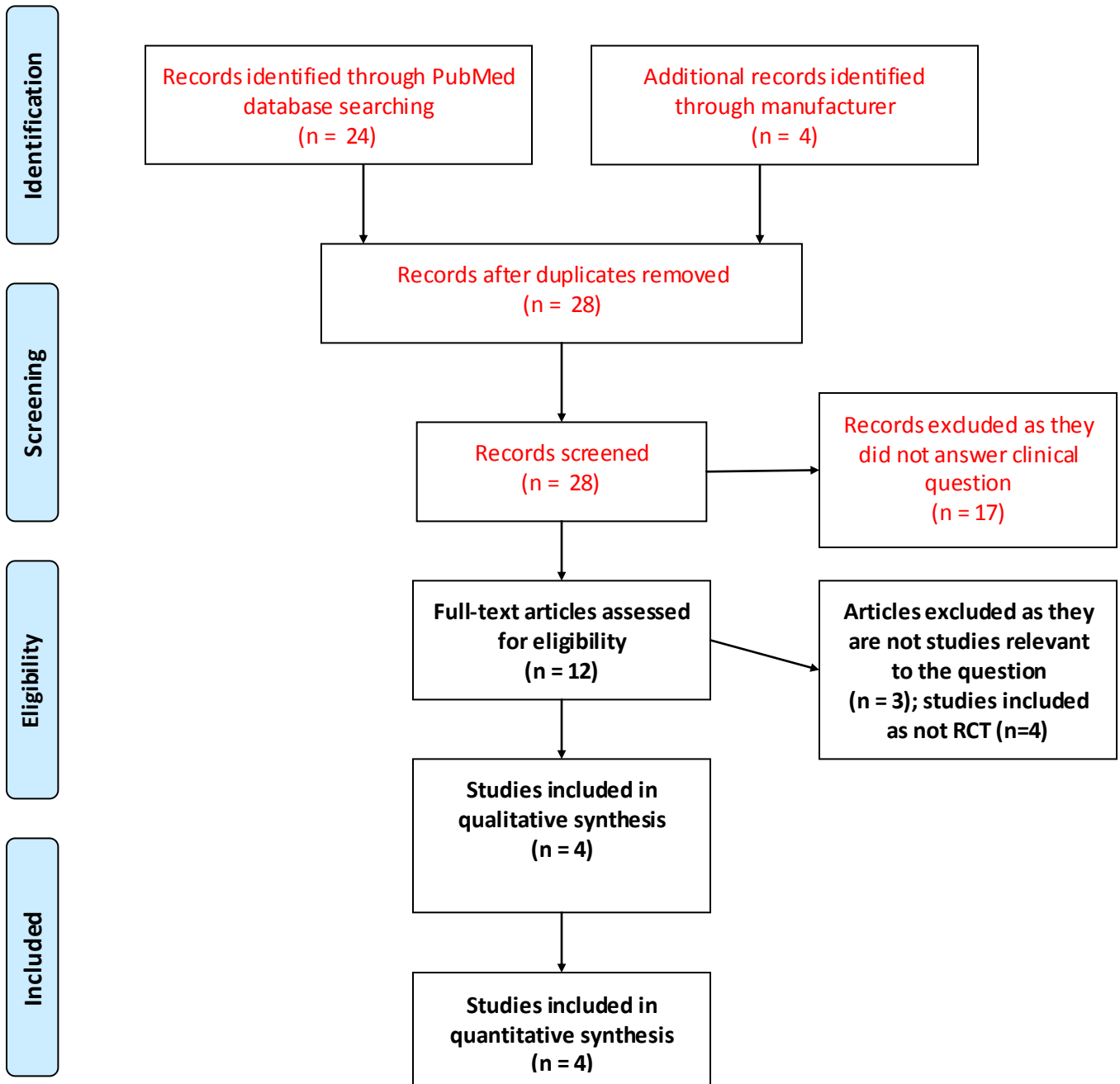
Name of medicine (INN):	Citicoline (as sodium) - 500 mg and 1000 mg tablet - 100 mg/mL adult solution - 125 mg/mL (500 mg/4 mL) solution for injection - 250 mg/mL (1000 mg/4 mL) solution for injection
Indication:	For the treatment of cerebrovascular disorders (including ischaemic stroke), parkinsonism and head injury
Date of deliberation:	26 November 2015 29 March 2016
Recommendation:	DISAPPROVAL
Clinical evidence:	<p>A pooled analysis of randomized controlled trial (RCTs), graded as moderate quality, conducted before 2002 showed significantly better recovery among stroke patients given citicoline compared to placebo. However more recent and robust RCTs, graded as high quality, showed no significant difference between citicoline and placebo in terms of mortality 19% vs 21%; global recovery OR=1.03 (95%CI: 0.86 and 1.25) and adverse event 93% vs. 94% (Davalos et al, 2012).</p> <p>Another study measured NIH Stroke Score and Rankin Score which showed no significant difference between citicoline and placebo (NIH Stroke score 6.41 vs. 7.08; Rankin score 1.95 vs. 2.08) (Mitta et al, 2012).</p> <p><i>(See Attachment for the full ERG evaluation)</i></p>
Cost data:	<p>The total treatment cost of citicoline was P 11,408.57 with no additional benefit.</p> <p><i>(See Attachment).</i></p>
Remarks:	<p>The proponent did not provide alternative evidence for review by the Evidence Review Group, instead the appeal was based on a critic of the overall results of the ICTUS trial. The Formulary Executive Council as well as the ERG have already considered the ICTUS</p>

trial in their previous evaluation and it was noted that there was no analysis done to determine whether or not citicoline will work in settings similar to the Philippines. They acknowledged the argument that citicoline was not seen to be effective in the ICTUS trial because the conditions were ideal such that thrombolytic agents were given to the stroke patients and since the setting in the country is not ideal, then citicoline might be helpful. However, this was just an assumption and there is not enough evidence to prove that it is indeed effective in the local setting.

The Council suggested conducting a local randomized controlled trial in order to establish the above assumption. In the mean time that the evidence is insufficient, the recommendation to disapprove citicoline still remains.

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

PRISMA Table



1. Will acute stroke patients given citicoline have better functional recovery at 3 months or longer?
2. What is the frequency of adverse events and mortality among acute stroke patients given citicoline compared to placebo?
3. What is the cost-effectiveness of citicoline?

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Cerebrolysin		Control			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
1	Dávalos et al. Lancet. 2012	RCT	2,298 acute stroke patients	Citicoline vs. placebo. All patients received standard care	Mortality	221 (19%)	1,148	242 (21%)	1,150	High	p=0.31 OR=1.03 (95%CI;0.86 and 1.25) p=0.27
					Global recovery at 90 days						
					NIH Stroke Score change from baseline	-1.54	SD 13.61	0.89	SD 14.34		
					Adverse events	1,064	1,148	1,080	1,150		
2	Mitta et al. J Assoc Physicians India. 2012	RCT	90 acute ischemic strokes	Citicoline vs. control (2 arms of 3 arm RCT)	National Institute of Health Stroke Score after 3 months	6.41	SD 7.62	7.08	SD 6.65		
					Modified Rankin Scale	1.95	SD 1.39	2.08	SD 1.49		
3	Alvarez-Sabín et al. Cerebrovasc Dis. 2013	RCT	347 ischemic stroke	Citicoline vs. control	No impairment at 12 months in terms of: Attention Language Memory Spatial perception Motor speed						OR=2.37 (95%CI; 1.26 and 4.46) OR=1.40 (95%CI; 0.74 and 2.65) OR=1.20 (95%CI; 0.65 and 2.23) OR=1.28 (95%CI; 0.66 and 2.46) OR=1.30 99%CI; 0.71 and 2.37)

					Temporal orientation						OR=2.15 (95%CI; 1.01 and 4.56)
4	Dávalos et al. Stroke. 2002	Pooled analysis of RCTs	1,652 stroke patients	Citicoline vs. placebo	Global recovery at 12 wks	27.9%		21.9%			OR=1.38 (95%CI; 1.10 and 1.72)
					Mortality	18.8%		17.8%			Overall adverse events were similar

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS

<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</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>Citicoline (Cholinerv) 250 mg/ml in 4ml amp P 191.1 per ampule Citicoline (Cholinerv) 500/tab 30s (P 1,749.92)</p>	<p>Citicolline studies are placebo controlled thus no cost comparison was made.</p>	
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>6 ampules (2 ampules daily for 3 days) 176 tabs (4 tabs daily for 39 days)</p>		
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>1,146.6 (amp) 10,261.97 (tabs) Total 11,408.57</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>Total 11,408.577</p>		

REVIEWERS' RECOMMENDATIONS

Literature Search

- We searched PubMed last June 2015 using the terms “citicoline” and limit our search to meta-analysis. This yielded 6 articles. We reviewed the articles and found the latest meta-analysis was published in 2009. We updated our search to “citicoline” and limit our search to randomized controlled trials published from 2009 to the present. This yielded 18 articles. We reviewed the 24 articles and considered 8 articles for full text retrieval. We also reviewed 4 full text articles from the manufacturer.
- We reviewed the full text and included the following 4 articles in this review:
 - Dávalos A(1), Alvarez-Sabín J, Castillo J, Díez-Tejedor E, Ferro J, Martínez-Vila E, Serena J, Segura T, Cruz VT, Masjuan J, Cobo E, Secades JJ; International Citicoline Trial on acUte Stroke (ICTUS) trial investigators. Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial). *Lancet*. 2012 Jul 28;380(9839):349-57. doi: 10.1016/S0140-6736(12)60813-7. Epub 2012 Jun 11.
 - Dávalos A(1), Castillo J, Alvarez-Sabín J, Secades JJ, Mercadal J, López S, Cobo E, Warach S, Sherman D, Clark WM, Lozano R. Oral citicoline in acute ischemic stroke: an individual patient data pooling analysis of clinical trials. *Stroke*. 2002 Dec;33(12):2850-7.
 - Mitta M(1), Goel D, Bansal KK, Puri P. Eदारवणे - citicoline comparative study in acute ischemic stroke (ECCS-AIS). *J Assoc Physicians India*. 2012 Nov;60:36-8
 - Alvarez-Sabín J(1), Ortega G, Jacas C, Santamarina E, Maisterra O, Ribo M, Molina C, Quintana M, Román GC. Long-term treatment with citicoline may improve poststroke vascular cognitive impairment. *Cerebrovasc Dis*. 2013;35(2):146-54. doi: 10.1159/000346602. Epub 2013 Feb 7.

Effectiveness/Efficacy

- A pooled analysis of RCTs conducted before 2002 showed significantly better recovery among stroke patients given citicoline compared to placebo. However more recent and robust randomized controlled trial showed no significant difference between citicoline and placebo in terms of mortality 19% vs 21%; global recovery OR=1.03 (95% CI;0.86 and 1.25) and adverse event 93% vs. 94% (Davalos et al, 2012).
- Another study measured NIH Stroke Score and Rankin Score which showed no significant difference between citicoline and placebo (NIH Stroke score 6.41 vs. 7.08; Rankin score 1.95 vs. 2.08)(Mitta et al, 2012)

Summary of Review

- Newer evidence does not show clinically and statistically significant benefit when citicoline was given to patients with acute stroke. The ICTUS trial (Davalos et al, 2012) was discontinued after 3 interim analyses for lack of benefit.

Cost Data

- The total cost of citicoline treatment was P 11,408.57 with no additional benefit.

Overall Recommendation

- There is no available evidence or justification to include citicoline in the PNF.

References

1. Navarro JC(1), 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.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. Dávalos A(1), Castillo J, Alvarez-Sabín J, Secades JJ, Mercadal J, López S, Cobo E, Warach S, Sherman D, Clark WM, Lozano R. Oral citicoline in acute ischemic stroke: an individual patient data pooling analysis of clinical trials. *Stroke*. 2002 Dec;33(12):2850-7.

4. Nomani F(1), Kamal AK(1). Citicoline in the treatment of acute ischaemic stroke: an international, randomized, multicentre, placebo-controlled study (ICTUS trial) is the use of Citicoline is beneficial for acute ischaemic stroke? *J Pak Med Assoc.* 2013 Nov;63(11):1445.
5. Hart T(1), Benn EK, Bagiella E, Arenth P, Dikmen S, Hesdorffer DC, Novack TA, Ricker JH, Zafonte R. Early trajectory of psychiatric symptoms after traumatic brain injury: relationship to patient and injury characteristics. *J Neurotrauma.* 2014 Apr 1;31(7):610-7. doi: 10.1089/neu.2013.3041. Epub 2014 Jan
6. Mitta M(1), Goel D, Bansal KK, Puri P. Edaravone - citicoline comparative study in acute ischemic stroke (ECCS-AIS). *J Assoc Physicians India.* 2012 Nov;60:36-8.
7. Alvarez-Sabín J(1), Ortega G, Jacas C, Santamarina E, Maisterra O, Ribo M, Molina C, Quintana M, Román GC. Long-term treatment with citicoline may improve poststroke vascular cognitive impairment. *Cerebrovasc Dis.* 2013;35(2):146-54. doi: 10.1159/000346602. Epub 2013 Feb 7.
8. Zafonte RD(1), Bagiella E, Ansel BM, Novack TA, Friedewald WT, Hesdorffer DC, Timmons SD, Jallo J, Eisenberg H, Hart T, Ricker JH, Diaz-Arrastia R, Merchant RE, Temkin NR, Melton S, Dikmen SS. Effect of citicoline on functional and cognitive status among patients with traumatic brain injury: Citicoline Brain Injury Treatment Trial (COBRIT). *JAMA.* 2012 Nov 21;308(19):1993-2000. doi: 10.1001/jama.2012.13256.
9. Dávalos A(1), Alvarez-Sabín J, Castillo J, Díez-Tejedor E, Ferro J, Martínez-Vila E, Serena J, Segura T, Cruz VT, Masjuan J, Cobo E, Secades JJ; International Citicoline Trial on acUte Stroke (ICTUS) trial investigators. Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial). *Lancet.* 2012 Jul 28;380(9839):349-57. doi: 10.1016/S0140-6736(12)60813-7. Epub 2012 Jun 11.

Response to appeal on the reviewers' recommendation on Citicoline

The appeal was based on a critic of the overall results of ICTUS trial. It did point out the benefit of citicoline to subgroups of patients which the ERG also noted. The subgroup benefits however need to be investigated further as this was not the original intention of the ICTUS trial. Thus, the subgroup results cannot be made as the basis for recommending the inclusion of citicoline in the PNF.

The appeal also pointed the analysis of the ERG based on the pooled analysis of clinical trials by Davalos in 2002. The ICTUS study was more rigorous clinical evidence than the pooled analysis. The ERG therefore placed more weight on the ICTUS trial for its decision.

Unfortunately, the appeal did not provide alternative evidence for review by the ERG. The ERG maintains its recommendation not to include citicoline in the PNDF.