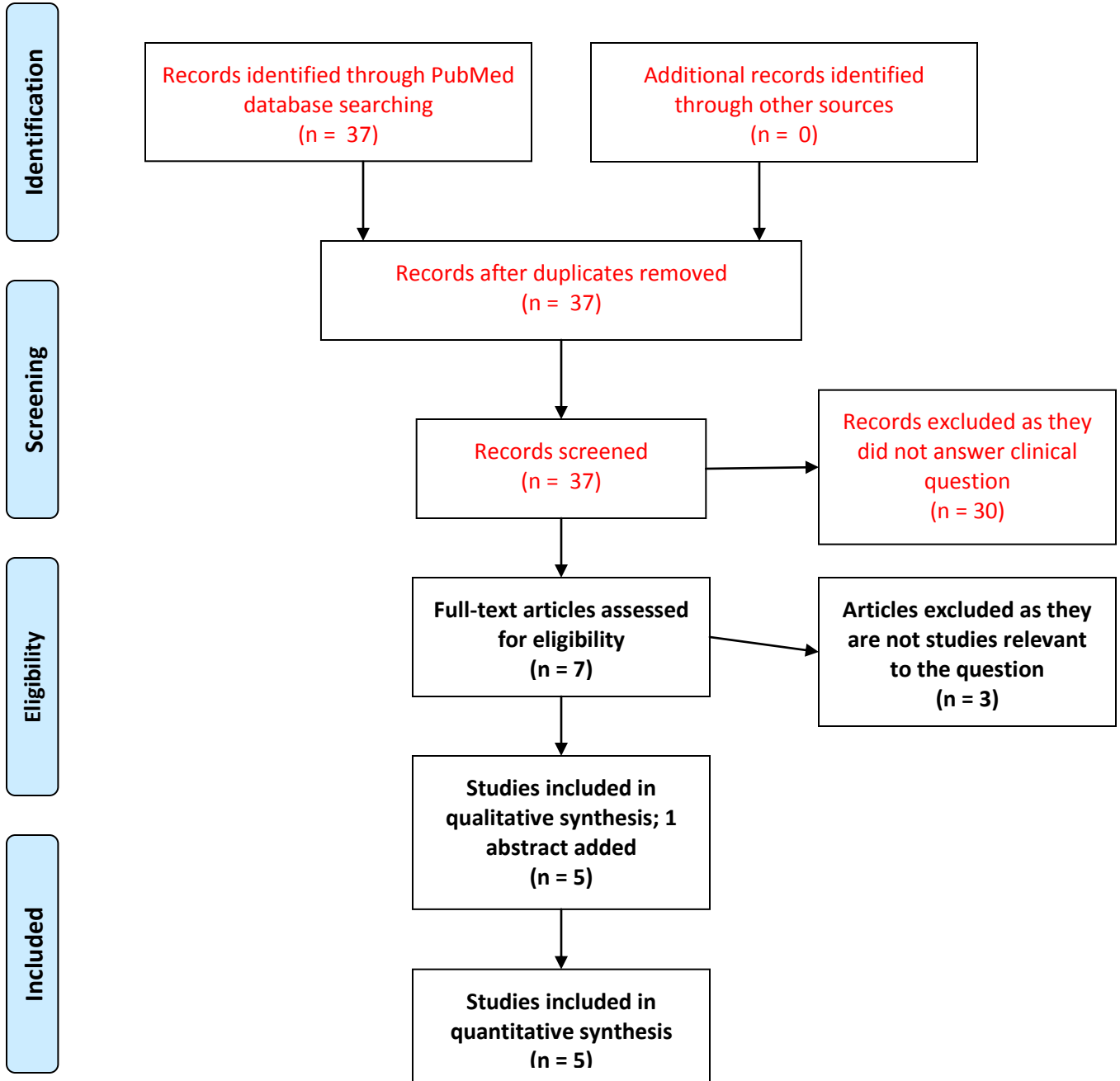




Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

| | |
|--------------------------------|--|
| Name of medicine (INN): | Cerebrolysin 215.2 mg/mL concentrate solution for IV infusion |
| Indication: | For the treatment of acute ischemic stroke |
| Date of deliberation: | 26 November 2015 |
| Recommendation: | DISAPPROVAL |
| Clinical evidence: | <p>Large randomized controlled trials (RCTs), graded as high quality (GRADEPRO), on patients with acute stroke (1,070 patients) overall showed no significant advantage of cerebrolysin over placebo in terms of NIH Stroke Scale (6 vs. 5), Barthel's index (30 vs 30), Rankin score (2 vs. 2), overall mortality (5.3% vs. 6.6%) and adverse event (242 vs 243).</p> <p>Smaller studies have shown some benefit for cognitive ability and aphasia but no benefit on overall stroke status, deaths or adverse event.</p> <p><i>(See Attachment for the full ERG evaluation)</i></p> |
| Cost data: | <p>The total treatment cost for cerebrolysin is Php 24,000.00 but with no clinically significant advantage over placebo.</p> <p><i>(See Attachment).</i></p> |
| Remarks: | <p>No appeal for reconsideration was received within the set deadline, thus the recommendation of the Council to disapprove the medicine still remains.</p> <p>The Secretary of Health has officially disapproved the proposal to include cerebrolysin in the PNF.</p> |

PRISMA Table



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

EVIDENCE TABLE 1

| NO | TITLE/ AUTHOR YEAR/JOURNAL | STUDY DESIGN | PARTICIPANT DESCRIPTION | INTERVENTION | RESULTS/OUTCOMES | | | | | GRADE OF EVIDENCE | REMARKS |
|----|---------------------------------------|--------------|------------------------------|---|---|-----------------|---------------------|-----------------|---------------------|-------------------|--|
| | | | | | EVENTS | Cerebrolysin | | Control | | | |
| | | | | | (including adverse events) | No. of events * | Total # of patients | No. of events * | Total # of patients | | |
| 1 | Heiss et al. Stroke. 2012 | RCT | 1,070 acute ischemic stroke | Cerebrolysin vs. placebo within 12 hrs. Both groups received standard treatment | National Institute of Health Stroke Scale median improvement | 6 | 527 | 5 | 540 | High | ITT population |
| | | | | | Barthel's Index | 30 | | 30 | | | |
| | | | | | Modified Rankin Scale median score | 2 | | 2 | | | |
| | | | | | Mortality | 5.3% | | 6.6% | | | |
| | | | | | Adverse events | 242 | | 243 | | | |
| | | | | | Mortality | 10.5% | | 20.2% | | | |
| 2 | Ladurner et al. J Neural Transm. 2005 | RCT | 146 acute stroke | Cerebrolysin vs. placebo within 24 hrs. (Standard treatment given to both) | Canadian Neurologic Scale | | | | | | No significant difference in CNS score |
| | | | | | Death | 8.0% | 78 | 10.0% | 68 | | |
| | | | | | All adverse event | 6 | 78 | 7 | 68 | | |
| 3 | Chen et al. Br J Neurosurg. 2013 | RCT | 32 patients with head injury | Cerebrolysin vs. placebo within 24 hrs. All patients received standard care for traumatic | Mini-mental State Examination change from baseline to week 12 | 6.8 | SD 6.5 | 3.5 | SD 3.8 | High | p=0.11 |
| | | | | | Cognitive Abilities Screening | 21.0 | SD 20.4 | 7.6 | SD 12.2 | | p=0.04 |

| | | | | | | | | | | | |
|---|--|-----|--|---|---|-------|----|-------|-----|----------|---|
| | | | | brain injury without craniotomy. | Instrument change from baseline to week 12 | | | | | | |
| 4 | Jianu et al. J Med Life. 2010 | RCT | 425 Left middle cerebral artery infarction | Cerebrolysin plus standard therapy vs. placebo plus standard therapy vs. standard therapy alone | Aphasia quotient, spontaneous speech, repetition and naming Broca's aphasia No aphasia Death Adverse events | 57.7% | 52 | 73.1% | 104 | Moderate | Cerebrolysin group had a significant improvement (p<0.05) over the placebo group. p=1.0 p=0.38 |
| 5 | Bajenaru et al. J Med Life. 2010 | RCT | 100 hemorrhagic stroke | Cerebrolysin vs. placebo (10 days daily administration) | Unified Neurological Stroke Scale, Barthel Index, and Syndrome Short Test | | | | | Abstract | No statistically significant group effects were observed based on single average comparisons at the individual visits |

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS

| <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>Php 800 per 215.2 mg/mL concentrate solution for IV infusion, 10mL ampule</p> | | <p>Company submission</p> |
| <p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p> | <p>30mL daily for 10 days (Heiss)</p> | | |
| <p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p> | <p>Php 24,000</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>none</p> | | |
| <p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p> | <p>Php 24,000</p> | | |

REVIEWERS' RECOMMENDATIONS

Literature Search

- We conducted PubMed search last June 2015 using the term “cerebrolysin” and limit our search to meta-analysis which yielded 3 results. We updated our search with “cerebrolysin” and limit to randomized controlled trials and yielded 34 results. We reviewed all the 37 abstracts and considered 9 articles for full text retrieval.
- Only 8 full text articles are available and of the 8 articles, 5 are included in this review. They are the following:
 - Chen CC(1), Wei ST, Tsaia SC, Chen XX, Cho DY. Cerebrolysin enhances cognitive recovery of mild traumatic brain injury patients:double-blind, placebo-controlled, randomized study. *Br J Neurosurg.* 2013 Dec;27(6):803-7. doi: 10.3109/02688697.2013.793287. Epub 2013 May 8.
 - Heiss WD(1), Brainin M, Bornstein NM, Tuomilehto J, Hong Z; Cerebrolysin Acute Stroke Treatment in Asia (CASTA) Investigators. Cerebrolysin in patients with acute ischemic stroke in Asia: results of a double-blind, placebo-controlled randomized trial. *Stroke.* 2012 Mar;43(3):630-6. doi: 10.1161/STROKEAHA.111.628537. Epub 2012 Jan 26.
 - Jianu DC(1), Muresanu DF, Bajenaru O, Popescu BO, Deme SM, Moessler H, Meinzingen SZ, Petrica L. Cerebrolysin adjuvant treatment in Broca's aphasics following first acute ischemic stroke of the left middle cerebral artery. *J Med Life.* 2010 Jul-Sep;3(3):297-307.
 - Ladurner G(1), Kalvach P, Moessler H; Cerebrolysin Study Group. Neuroprotective treatment with cerebrolysin in patients with acute stroke: a randomised controlled trial. *J Neural Transm.* 2005 Mar;112(3):415-28. Epub 2004 Dec 7.

Effectiveness/Efficacy

- Large RCTs on patients with acute stroke (1,070 patients) overall showed no significant advantage of cerebrolysin over placebo in terms of NIH Stroke Scale (6 vs. 5), Barthel's index (30 vs 30), Rankin score (2 vs. 2), overall mortality (5.3% vs. 6.6%) and adverse event (242 vs 243) (Heiss et al, 2012).
- Smaller studies have shown some benefit for cognitive ability and aphasia but no benefit on overall stroke status, deaths or adverse event.

Summary of Review

- Our review did not show advantage of cerebrolysin over placebo for clinically relevant outcomes like overall stroke status, adverse events or deaths.

Cost Data

- In terms of cost, the total treatment cost for cerebrolysin is Php 24,000.00 but with no clinically significant advantage over placebo.

Overall Recommendation

- There is not enough evidence or justification for inclusion of cerebrolysin in the PNDP.

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.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. Chen N(1), Yang M, Guo J, Zhou M, Zhu C, He L. Cerebrolysin for vascular dementia. *Cochrane Database Syst Rev.* 2013 Jan 31;1:CD008900. doi: 10.1002/14651858.CD008900.pub2.
4. Wei ZH(1), He QB, Wang H, Su BH, Chen HZ. Meta-analysis: the efficacy of nootropic agent Cerebrolysin in the treatment of Alzheimer's disease. *J Neural Transm.* 2007;114(5):629-34. Epub 2007 Feb 23.

5. Chen CC(1), Wei ST, Tsaia SC, Chen XX, Cho DY. Cerebrolysin enhances cognitive recovery of mild traumatic brain injury patients:double-blind, placebo-controlled, randomized study. *Br J Neurosurg.* 2013 Dec;27(6):803-7. doi: 10.3109/02688697.2013.793287. Epub 2013 May 8.
6. Lang W(1), Stadler CH, Poljakovic Z, Fleet D; Lyse Study Group. A prospective, randomized, placebo-controlled, double-blind trial about safety and efficacy of combined treatment with alteplase (rt-PA) and Cerebrolysin in acute ischaemic hemispheric stroke. *Int J Stroke.* 2013 Feb;8(2):95-104. doi: 10.1111/j.1747-4949.2012.00901.x. Epub 2012 Sep 26.
7. Heiss WD(1), Brainin M, Bornstein NM, Tuomilehto J, Hong Z; Cerebrolysin Acute Stroke Treatment in Asia (CASTA) Investigators. Cerebrolysin in patients with acute ischemic stroke in Asia: results of a double-blind, placebo-controlled randomized trial. *Stroke.* 2012 Mar;43(3):630-6. doi: 10.1161/STROKEAHA.111.628537. Epub 2012 Jan 26.
8. Bajenaru O(1), Tiu C, Moessler H, Antochi F, Muresanu D, Popescu BO, Novak P. Efficacy and safety of Cerebrolysin in patients with hemorrhagic stroke. *J Med Life.* 2010 Apr-Jun;3(2):137-43.
9. Jianu DC(1), Muresanu DF, Bajenaru O, Popescu BO, Deme SM, Moessler H, Meinzingen SZ, Petrica L. Cerebrolysin adjuvant treatment in Broca's aphasics following first acute ischemic stroke of the left middle cerebral artery. *J Med Life.* 2010 Jul-Sep;3(3):297-307.
10. Hong Z(1), Moessler H, Bornstein N, Brainin M, Heiss WD; CASTA-Investigators. A double-blind, placebo-controlled, randomized trial to evaluate the safety and efficacy of Cerebrolysin in patients with acute ischaemic stroke in Asia--CASTA. *Int J Stroke.* 2009 Oct;4(5):406-12. doi: 10.1111/j.1747-4949.2009.00340.x.
11. Ladurner G(1), Kalvach P, Moessler H; Cerebrolysin Study Group. Neuroprotective treatment with cerebrolysin in patients with acute stroke: a randomised controlled trial. *J Neural Transm.* 2005 Mar;112(3):415-28. Epub 2004 Dec 7.