



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

Name of medicine (INN):	Ketonalogues + Essential Amino Acids 600 mg film coated tablets
Indication:	For prevention and therapy of damages to faulty or deficient protein metabolism in chronic renal insufficiency in connection with limited protein in food of 40g per day (for adults) and less i.e. generally in patients with a glomerular filtration rate (GFR) between 5 and about 15mL/ minute
Date of deliberation:	01 July 2015 26 November 2015
Recommendation:	DISAPPROVAL
Clinical evidence:	<p>The use of ketoanalogues + essential amino acids for patients with chronic kidney disease is being justified to delay the need for dialysis. The Council noted however, that there is no formal study which validates this claim. Likewise, it was discussed that other interventions, such as diet modification or managing blood sugar level, may be done by the patient to delay the onset of dialysis. A concern was raised on the prescription of the drug in actual practice wherein the correct dosage regimen is not being followed due to high treatment cost, hence, leading to waste in treatment. Given this current practice, there will be a risk in including the drug in the Formulary because physicians may be able to prescribe the correct dose but patients may not be able to comply because of its prohibitive cost.</p> <p>Based on the report presented by the evidence review group (ERG), four (4) out of the five (5) considered studies showed lower glomerular filtration rate (GFR) decrease in the ketoanalogues + essential amino acids group ranging from 0.05-4.8 ml/min, compared with groups having no supplementation of this drug (ranging from 0.08-6.2 ml/min). He added that the drug is associated with lesser proteinuria (-9.8 vs. 0.2) after 12 months of therapy. Meanwhile, the meta-analysis did not show any significant difference between ketoanalogues + essential amino acids and low protein diet in terms of change in GFR (SMD 0.85; 95% CI - 2.01 and 3.71).</p> <p>The Council acknowledged the best evidence available which is a local meta-analysis which showed that there is no significant difference in terms of GFR and the onset of dialysis. It was likewise noted that the</p>

submitted evidence only showed effectiveness in terms of laboratory measures. The Council discussed if the delay in the onset of dialysis is actually a valid outcome because eventually, the patient will still require dialysis.

In summary, the Council noted that only surrogate laboratory measures were reported in the ERG evaluation and there are no available studies showing hard outcomes. It was likewise noted that there is no significant difference between low-protein diet and supplementation with ketoanalogues + essential amino acids. The prohibitive cost of the drug was also highly considered by the FEC in their decision-making.

(See Attachment for the full ERG evaluation)

Cost data:

The Council considered that given the Philhealth adjusted coverage for dialysis of Php 2,500 per session, the approximated treatment cost of Php 10,000 per month with ketoanalogues + essential amino acids will already be equivalent to four (4) dialysis sessions. As earlier discussed, chronic kidney disease (CKD) can be prevented in several ways which include the adequate management of diabetes and hypertension through lifestyle and diet modification among others. Hence, instead of spending for the treatment with the drug, the patient's resources may be used efficiently to better manage these secondary causes of CKD.

The Council acknowledged the cost of treatment presented in the report. It was estimated that the monthly cost of treatment with ketoanalogues + essential amino acids is Php 13,050. *(See Attachment)*

Remarks:

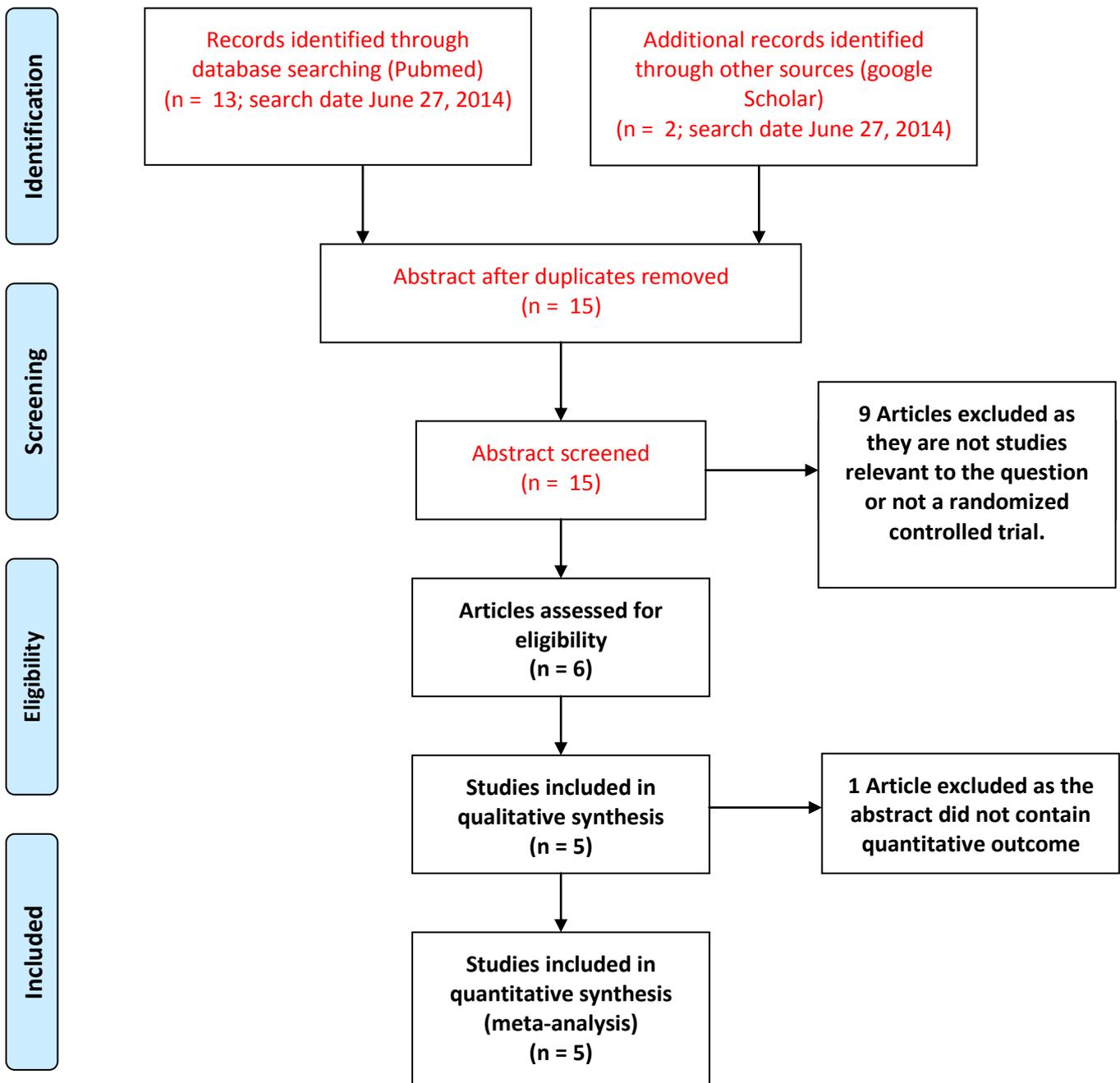
The ERG evaluated the documents submitted by the proponent to support their appeal and it was noted that most of the randomized controlled trials submitted in the appeal were already included in the previous review. The message of the appeal was also confirmed in the review, i.e., ketosteril provided benefits in terms of laboratory parameters (surrogate outcomes), hence the ERG still maintain its original findings and recommendation.

The Council concurred to this and 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.

The Secretary of Health has officially disapproved the proposal to include ketoanalogues + essential amino acids in the PNF.

PRISMA Table

PubMed search strategy was MESH search of “ketosteril” OR “ketoanalogues”. This resulted to 80 articles. When limited to randomized controlled trials and studies on human subjects. The yield was 13 articles. The 13 articles were independently reviewed by two reviewers. After abstract review a total of 3 articles were retrieved for full text review.



Among patients with CKD, how effective is Ketoanalogues + Essential Amino Acids 600 mg film coated tablets (Ketosteril) compared to placebo (or usual care) in preventing deterioration of renal function in terms of

- a. Proteinuria (mean difference)
- b. Worsening of GFR
- c. Dialysis

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Ketoanalogues		Placebo			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
	Mou, 2013	RCT	17 patients with CGN and HBV infection	Ketosteril + diet vs. diet	Change in GFR after treatment Change in serum creatinine	+4.9 mL/min -9.8 umol/L	8	+0.6 mL/min +0.2 umol/L	9	Can't tell	Abstract
	Milovanov et al, 2013	RCT (3 arms)	46 CKD with autoimmune disorder	Ketosteril + diet vs. diet	Change in GFR after treatment	-4.8 mL/min	18	-6.2 mL/min	18	Moderate	Values are reviewer's computation as the article presented mean values instead of change
	Mircescu, et al, 2007	RCT	53 CKD patients	Ketosteril + diet vs. Diet	Change in GFR after treatment	-0.05 mL/Min	27	-0.08 mL/min	26	Can't tell	Abstract
	Prakash et al. J Ren Nutr. 2004	RCT	34 Chronic renal failure patients	Ketosteril + diet vs. diet	Change in GFR after treatment Change in serum creatinine	- 0.5 mL/min - 0.19 mg/dL	18	- 6.1 mL/min + 0.88 mg/dL	16	Can't tell	Abstract
	Teplan et al. Wien Klin Wochenschr. 2001	RCT	38 Chronic renal failure patients	Ketosteril + diet vs diet alone	Change in GFR after treatment	- 1.8 mL/min	20	- 6.2 mL/min	18	Can't tell	Abstract

*group means with standard deviations may be reported if the data are continuous

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: Decrease in GFR from baseline												
1	Meta-analysis	No	No	No	No		Ketosteril	Low protein diet		0.85 (95% CI; -2.01 and 3.71)	High	Critical

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS

Among patients with CKD, how cost-effective is Ketoanalogues + Essential Amino Acids 600 mg film coated tablets (Ketosteril) compared to placebo (or usual care) in preventing deterioration of renal function.

<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 36.25 per 600 mg tablet</p>		<p>RCTs are placebo controlled</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>12 tablets daily</p>		
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>Php 13,050 monthly course</p>		
<p>ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (in PhP)</p>			
<p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>	<p>Php 13,050</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 search PubMed using the free text search with the term “ketosteril”. The search yielded to 80 articles, then we limit to publication type “clinical trial” and yielded 13 articles. We reviewed the articles and included 5 for this review. However only one full text is available.
- One local meta-analysis obtained via google search was included in this review.
- A total of 5 RCTs and 1 meta-analysis among patients with chronic kidney diseases were included in this review.

Effectiveness

- Among the 5 studies with chronic kidney disease or chronic renal insufficiency patients, 4 studies reported lesser GFR decrease in ketosteril group ranging from 0.05-4.8 ml/min, compared to groups with no ketosteril supplementation ranging from 0.08-6.2 ml/min (Teplan, et al, 2001; Prakash, et al, 2001; Mircescu, et al, 2013 and Milovanov, 2013). while 1 study reported greater GFR increase (+4.9 ml/min) in ketosteril + low protein diet group compared to low protein diet (Mou, 2013).
- There was only one study with proteinuria outcome, but this was among patients with chronic glomerulonephritis and HBV infection. Ketosteril is associated with lesser proteinuria (-9.8 vs. 0.2) after 12 months of therapy (Mou, et al, 2013).
- Of the two studies with serum creatinine outcome, 2 studies reported a decrease in serum creatinine (Prakash, 2004 and Mou, 2013) after ketosteril supplementation. Ketosteril had greater decrease in serum creatinine ranging from 0.19-9.8 umol/L.
- The meta-analysis did not show any significant difference between ketosteril and low protein diet in terms of change in GFR (SMD 0.85; 95% CI -2.01 and 3.71).

Overall Recommendation

- Based on our findings which measured surrogate outcomes (laboratory measures) as required by the research question given to the reviewers, ketosteril may be included in the PNDF. However, the articles reviewed were abstracts and clinical trials that included small number of subjects. In addition a local meta-analysis did not show any significant advantage by ketosteril. Because of the cost being prohibitive, we recommend to NCPAM to balance the cost and effectiveness to patients with CKD. In this regard, inclusion to the PNDF may have to be deferred.

References

1. Teplan V, Schüch O, Votruba M, Poledne R, Kazdová L, Skibová J, Malý J. 2001. Metabolic effects of keto acid--amino acid supplementation in patients with chronic renal insufficiency receiving a low-protein diet and recombinant human erythropoietin--a randomized controlled trial. *Wien Klin Wochenschr.* 2001 Sep 17;113(17-18):661-9.
2. Prakash S, Pande DP, Sharma S, Sharma D, Bal CS, Kulkarni H. 2004. Randomized, double-blind, placebo-controlled trial to evaluate efficacy of ketodiet in predialytic chronic renal failure. *J Ren Nutr.* 2004 Apr;14(2):89-96.
3. Mircescu G, Gârneață L, Stancu SH, Căpușă C. 2007. Effects of a supplemented hypoproteic diet in chronic kidney disease. *J Ren Nutr.* 2007 May;17(3):179-88.
4. Milovanov YS, Milovanova LY, Mikhailov AA, Aleksandrova II. 2013. Influence of Diet Balanced with Essential Amino Acids / Keto Acid Analogs and High-Nutrient Blend on the Progression of Renal Failure in Patients in the Pre-Dialysis Stage of Chronic Kidney Disease Caused by Systemic Autoimmune Diseases. *International Journal of BioMedicine* 3(3) (2013) 184-187.

5. Mou S, Li J, Yu Z, Wang Q and Ni Z. 2013. Keto acid-supplemented low-protein diet for treatment of adult patients with hepatitis B virus infection and chronic glomerulonephritis. *Journal of International Medical Research* 41(1) 129–137.
6. Pancho GA, Paningbalan JC and Shiu LA. A meta-analysis on keto analogues and low protein diet in the retardation of progression of kidney failure in chronic kidney disease. *Phil J Int Med* 2013; 51 (3): 1-4.

Response to appeal on the reviewers' recommendation on Ketosteril

We reviewed the articles submitted to support the appeal on ketosteril. We found out that most of the randomized controlled trials submitted in the appeal were already included in our review. The message of the appeal was also confirmed in our review i.e. ketosteril provided benefits in terms of laboratory parameters (surrogate outcomes). Thus we still maintain our recommendation:

“However, the articles reviewed were abstracts and clinical trials that included small number of subjects. In addition a local meta-analysis did not show any significant advantage by ketosteril. Because of the cost being prohibitive, we recommend to FEC to balance the cost and effectiveness to patients with CKD. In this regard, inclusion to the PNF may have to be deferred.”

Because cost is significant issue for PNF, it is recommended that the manufacturer decrease the cost of ketosteril for it to be reconsidered for inclusion in the PNF.