Application for inclusion of Ready-to-Use Therapeutic Food (RUTF) on the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc)

GENERAL ITEMS

1. Summary statement of the proposal for inclusion, change or deletion.

The proposed inclusion of Ready-to-Use Therapeutic Food (RUTF) in the Essential Medicines List and in the Essential Medicines List for Children (Section 26. "Solutions Correcting Water, Electrolyte and Acid-based Disturbances", under 26.3 Miscellaneous) is based on existing evidence of its efficacy in the management of Severe Acute Malnutrition (SAM) in children from 6 to 59 months of age.

RUTF is part of a larger treatment protocol for in- and outpatient SAM management commonly known as Community-Based Management of Acute Malnutrition (CMAM). The use of RUTF is mainly for outpatient (ambulatory) management of uncomplicated Severe Acute Malnutrition.

This proposal is based on the following evidence and considerations, described in detail below:

These recommendations are based on a substantial body of observational and programmatic data but limited impact studies of high quality.

Two reviews published in 2013 found a 32-51% improved nutritional recovery in children who received RUTF compared to standard diet (unfortified porridge) for the community-based treatment of SAM in children 6-59 months.

The use of RUTF for the outpatient treatment of uncomplicated SAM in children 6-59 months of age is well established. RUTF is recommended for outpatient treatment (for children with and without diarrhea) as well as during the rehabilitation phase of inpatient treatment. Children given RUTF for the community-based management of SAM are more likely to achieve nutritional recovery than children receiving unfortified porridge.

RUTF is essential to be able to treat most of the 16 million children with SAM, of which many are at immediate risk of dying. Within a community-based management of acute malnutrition programme (CMAM), it is a cost-effective and life-saving intervention.

2. Name of the WHO technical department and focal point supporting the application (where relevant).
3. Name of organization(s) consulted and/or supporting the application.

**Consultations:**
Action Against Hunger (ACF) consulted various stakeholders from the following organisations:
- WHO
- UNICEF
- Nutriset
- Valid International
- Médécins sans frontières (MSF)
- Helen Keller international (HKI)
- Baby Milk Action, a member of *International Baby Food Action Network* (IBFAN)
- Society for International Development (SID)
- ACF itself.

In addition, stakeholders which worked formerly at WFP and at IRD were interviewed.

**Feedback:**
Stakeholders were interviewed on the relevance of adding RUTF to the WHO EML, and on the compatibility with the Codex Alimentarius guidelines for RUTF, which is currently being discussed at the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU).

WHO expressed formal support to this initiative.

Most of the consulted stakeholders expressed willingness to collaborate.

The findings from this consultation are available and can be consulted on the CMAM forum website (soon to be transferred to the No Wasted Live website) from December 2016.

**Affiliation:**
ACF is in official relationship with WHO, an observer member of the CCNFSDU and member of advocacy coalitions including HKI, IBFAN and SID.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

**International Nonproprietary Name (INN):**
The product generic name is Ready-To-Use Therapeutic Food (RUTF). It is developed based on WHO recommendations for dietary management of SAM. There is no explicit INN for the product itself however here is the list of the INNs of the molecular names of the actives molecules in the product (vitamins and minerals):
Retinol, Thiamine, Riboflavin, Niacin, Pantothenic acid, Pyridoxine, Biotin, Folic acid, Cyanocobalamin, Ascorbic acid, Cholecalciferol, Tocopherol, Phytonadione, Sodium, Potassium, Calcium, Phosphorous, Magnesium, Iron, Zinc, Copper, Selenium, Iodine.

Anatomical Therapeutic Chemical (ATC) code of the medicine:
No ATC code for the product described. RUTF is intended to cover the special nutrient needs (macronutrient and micronutrients) of children with severe acute malnutrition.

5. Formulation(s) and strength(s) proposed for inclusion; including adult and paediatric (if appropriate).

Formulation:
RUTF is a lipid-based nutrient-rich product.
It consists of a lipid matrix with a complex of vitamins and minerals.
The lipid-based matrix is constituted of peanut paste (or chickpea paste), vegetable oil, sugar and milk powder and a complex of vitamins and minerals.
The following is the nutrient content of 100g of the product (RUTF):
- Energy content is between 520-550 kcal/100 g
- Proteins content 10-12% total energy (equivalent to 12.8-16.2% by weight)
- Lipids content: 45-60% total energy (equivalent to 25.8-36.3% by weight)
- N-6 fatty acids represent 3 to 10% of total energy
- N-3 fatty acids represent 0.3 to 2.5% of total energy
- Trans-fatty acids represent less than 3% of total fat
- Fibres content is below 5%
- Vitamin A (retinol) between 0.8 and 1.2mg RE
- Vitamin D (Cholecalciferol) between 15 and 20 mcg
- Vitamin C (Ascorbic acid) 50 mg minimum
- Vitamin E (Tocopherol) 20 mg minimum
- Vitamin K (Phytonadione) between 15 and 30 mcg
- Vitamin B1 (thiamine) 0.5 mg minimum
- Vitamin B2 (riboflavin) 1.6 mg minimum
- Vitamin B6 Pyridoxine 0.6 mg minimum
- Vitamin B12 Cyanocobalamin 1.6 mcg minimum
- Vitamin B9 (folic acid) 200 mcg minimum
- Vitamin B3 (niacin) 5 mg minimum
- Vitamin B5 (pantothenic acid) 3 mg minimum
- Vitamin B7 (biotin) 60 mcg minimum
- Sodium below 290 mg
- Potassium between 1100 and 1400 mg
- Calcium between 300 and 600 mg
- Phosphorous between 300 and 600 mg
- Magnesium between 80 and 140 mg
- Iron between 10 and 14 mg
Zinc between 11 and 14 mg
Copper between 1.4 and 1.8 mg
Selenium between 20 and 40 mcg
Iodine between 70 and 140 mcg

**Strength:**
The recommendation is 150 to 220 kcal/kg body weight/day of RUTF for young children from 6 months of age who have SAM without medical complications.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.
The listing is requested as an individual medicine.

TREATMENT DETAILS, PUBLIC HEALTH RELEVANCE AND EVIDENCE APPRAISAL AND SYNTHESIS

7. Treatment details (requirements for diagnosis, treatment and monitoring).

**Therapeutic dosage regimen and duration of treatment:**
The WHO guideline Management of severe malnutrition: a manual for physicians and other senior health workers [1] recommended the use of a liquid formulation (F-100) for the rehabilitation phase of SAM treatment (Transition and Phase 2). F-100 was exceptionally used in hospital conditions, till full recovery, as associated microbiological risk with use of F-100 for home or ambulatory treatment is great.
In the current practice RUTF has replaced liquid F-100 in a variety of settings where SAM is treated. Most RUTF are lipid-based pastes, combining milk powder, electrolytes and micronutrients to meet recommended nutritional values [2]. RUTF offers the malnourished child the same nutrient intake as F-100, with the addition of 10–14 mg/100 g of iron, and without the free water, when consumed in isoenergetic amounts.
The recommendation is 150 to 220 kcal/kg body weight/day of RUTF for young children from 6 months of age who have SAM without medical complications.
The recommendation to stop treatment with RUTF is when children from 6-59 months of age have a:

- Weight-for-height/length ≥−2 Z-score and no oedema for at least 2 weeks, or
- Mid-upper-arm circumference ≥125 mm and no oedema for at least 2 weeks.

Although the recommended duration is between 6 and 8 weeks, many national SAM management protocols recommend a maximum duration of 8 weeks.

SAM can be detected in the community, by community-based healthcare actors as well as in primary health-care facilities and hospitals. Health-care workers should assess the mid-upper arm circumference or the weight-for-height/weight-for-length status of infants and children who
are 6–59 months of age and also examine them for bilateral oedema. Infants and children who are 6–59 months of age and have a mid-upper arm circumference <115 mm or a weight-for-height/length ≤−3 Z-scores of the WHO growth standards [4], or have bilateral oedema, should be immediately admitted to a programme for the management of severe acute malnutrition. Children who are identified as having SAM should first be assessed with a full clinical examination to confirm whether they have medical complications and whether they have an appetite. Children who have appetite (pass the appetite test) and are clinically well and alert should be treated as outpatients. Children who have medical complications, severe oedema, or poor appetite (fail the appetite test) or present with one or more IMCI danger signs should be treated as inpatients. The treatment with RUTF is recommended for use in the rehabilitation phase of the treatment of SAM (Phase 2 in in-patients) and where the SAM cases do not require inpatient care and are managed as outpatients [3].

**Listing in the core list:**
RUTF should be added to the core list because of its impact on child survival, and because of its cost-effectiveness.
SAM is a disease, included in the International Classification of diseases (ICD-10 Version: 2010, Chapter IV Endocrine, nutritional and metabolic diseases, E40-E46 Malnutrition, and in ICD 11 to be published in 2018).
It is estimated currently that about 16-17 million children suffer from this disease and one million children die each year because of it [2].
SAM has a significant impact on rates and severity of disease, since malnutrition compromises the immune system and increases vulnerability to infectious disease. Children with SAM are at higher risk of dying from common childhood illnesses (risk increases by 11.6 times in the case of severe wasting [5]). SAM should thus be considered as a priority condition.
Community-based management of acute malnutrition (CMAM) delivered by community health workers (CHWs) and using RUTF is a cost-effective strategy compared with inpatient treatment, and compares well with the cost-effectiveness of other common child survival interventions [6].

8. Information supporting the public health relevance.

**Epidemiological information on disease burden:**
The UNICEF, WHO & World Bank Group Joint Child Malnutrition Estimates (2016 Edition) [7] estimated 2.5 % of the children under-five suffering of severe wasting (representing WHZ<-3 Z-Scores from WHO 2006 Growth Reference [4]) in the world, corresponding to a global burden of 17 million. Africa (4.3 million) and Asia (11.9 millions) are the most affected continents accounting for about 95% of the global burden. The global wasting levels (WHZ<-2 z-scores) in Southern and South-Central Asia are above WHO Public Health Emergency cut-off of 10%.

**Assessment of current use**
Precise data on use of RUTF is not available. However, it is estimated that only 15-20%of the children with SAM currently receive adequate treatment [8].
**Target population(s)**
Infants and children who are 6–59 months of age and have a mid-upper arm circumference <115 mm or a weight-for-height/length <−3 Z-scores of the WHO growth standards, or have bilateral oedema.

**Likely impact of treatment on the disease**
As part of the larger protocol of SAM management, the proper use of RUTF is likely to contribute to the rehabilitation of minimum 75 % [9] of the children 6-59 months of age having severe acute malnutrition. More on the effectiveness of RUTF for treatment of SAM in children 6-59 months of age can be found in Section 9.


The use of RUTF for the outpatient treatment of uncomplicated SAM in children 6-59 months of age is well established and has been a recommended treatment approach for over a decade.

The 2006 Joint Statement issued by the WHO, WFP, UNICEF and the UNSSC on Nutrition highlighted the importance of community-based treatment of SAM with RUTF and recommended this approach for uncomplicated cases of SAM. The Joint Statement went further to advocate the importance of national protocols and provision of RUTF for the management of SAM [2]. The 2013 WHO guideline updates for the management of SAM recommend outpatient treatment for children who are diagnosed with SAM, have passed an appetite test and are clinically well. Despite the low quality of evidence identified, these guidelines include a strong recommendation for the use of RUTF for outpatient treatment (for children with and without diarrhea) as well as during the rehabilitation phase of inpatient treatment [3].

These recommendations are based on a substantial body of observational and programmatic data but limited impact studies of high quality. Two systematic reviews on the use of RUTF for the treatment of SAM in children from 6-59 months of age were published in 2013. Both reviews used GRADE criteria to assess the available evidence base and are included with this application. As was stated in the WHO guidelines, the available evidence is generally very low quality with only a small number of randomized controlled trials published. Very little on the effectiveness of RUTF has been published since these reviews in 2013.

The 2013 Cochrane Review included three quasi-randomized trials comparing RUTF with a standard flour porridge diet for the treatment of SAM. The definition of recovery varied across the 3 studies and included WHZ>-2, WHZ≥0 and reaching 100% weight for height. The meta-analysis found that RUTF improved recovery slightly (RR 1.32; 95% confidence interval 1.16 to 1.50) but the evidence was too limited to draw definitive conclusions on relapse, mortality or weight gain [10].
A systematic review, meta-analysis and Delphi process on the treatment of severe and moderate acute malnutrition was also published in 2013, comparing children who received RUTF with those who received standard care (in-patient treatment followed by provision of corn soy blend (CSB) food for feeding at home). The evidence was also noted as low quality and limited (largely the same as studies included in the Cochrane Review). However, the review and meta-analysis found that children given RUTF for the community-based treatment of SAM were 51% more likely to achieve nutritional recovery (WHZ ≥ -2) than the standard care group (RR: 1.51; 95% CI 1.04 – 2.20). Weight gain in the RUTF group was also higher, this was statistically significant but small (MD: 1.27; 95% CI 0.16 – 2.38). There were no significant differences in mortality between the two groups [11].

Due to the limited high quality comparative trials evaluating community-based treatment using RUTF, Lenters et al complemented the systematic review and meta-analysis with a Delphi process to gather and synthesize expert opinion on the plausible impact estimates of the intervention. For community-based treatment of uncomplicated SAM using RUTF, the Delphi process estimated case fatality rate to be at 4% (range: 2-7%), and a recovery rate of 80% (range: 50-93%). Overall, the review argues that the community-based management of uncomplicated SAM in children 6-59 months of age is backed by a wealth of observational and programmatic data, despite the limited number of impact studies [11].

Since these reviews were published in 2013, a handful of additional studies have been published documenting the acceptability of RUTF formulation and program evaluation. However, only one additional clinical trial was found, resulting in an evidence-based that remains of generally low quality and volume. The single additional clinical trial identified was a cluster randomized trial in India of 26 children with uncomplicated SAM. The study found that children who received RUTF in addition to standard supplementary nutrition (roughly 500 kcal of energy and 12-15g protein provided at Anganwadi centers under the Integrated Child Development Scheme) were 10 times more likely to recover (odds ratio 10.28; 95% CI1.02-104.95) [12].

As highlighted in the Lenters et al review, there are very few impact and effectiveness trials for RUTF published and none, as far as we are aware, currently underway. This reflects the broader community’s acceptance of strong programmatic data documenting high recovery rates and, just as importantly, higher coverage rates than are possible through in-patient treatment of severe acute malnutrition. Current research is focused on developing equally effective but cheaper formulas of RUTF that can be produced locally and improving program quality to increase coverage and quality.


RUTF are high-energy, fortified, ready-to-eat foods for the treatment of SAM in children 6-59 months of age. The evidence presented here on both effectiveness and harms is focused on the most commonly used formula, which is peanut-based with added milk powder among other ingredients.
Unlike F-100, all RUTF formulas are not water-based, meaning that bacteria cannot grow in them. They can be transported and stored without refrigeration and in areas where hygiene conditions are not optimal [2].

For peanut-based RUTFs, the largest safety concern for the product is aflatoxin. The 2006 Joint Statement published guidance on the nutritional composition and maximum toxin levels that are still safe for consumption, this is 10 ppb maximum for aflatoxin [2]. UNICEF Supply Division regularly tests for aflatoxin in RUTF they procure. In 2013-2014, 99.5% of RUTF tested had <5 ppb aflatoxin [UNICEF Supply Division 2015] [13].

The 2013 Cochrane Review included a review of the safety of RUTF, including a comparison of the mortality, frequency diarrhea, and adverse outcomes between RUTF and the standard flour porridge diet. There was no difference in mortality between the children who received RUTF and those who received standard diets (RR 0.97; 95% CI 0.46 – 2.05; n = 599). Similarly, there was no difference in the frequency of diarrhea (number of days of diarrhea in the first two weeks of treatment) between the children who received RUTF and those who received the standard diets (MD -0.6; 95% CI -1.30 to 0.10; n=352). In addition, the WHO guideline updates in 2013 stated that empirical data to suggest that RUTF either increases the incidence of diarrhea or worsens diarrhea among children with SAM [3]. There were no further reports of adverse outcomes, including allergic reactions reported [10].

11. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group.

**Cost of Treatment using RUTF**

The evidence on costs and cost-effectiveness of large-scale programs using RUTF for the outpatient treatment of uncomplicated cases of SAM in children 6-59 months of age is limited but growing.

A review of the published literature for non-emergency community-based programs treating SAM with RUTF found a range of $135 to $805 per child successfully treated (see table below). This range reflects the varying contexts, scale and models of implementation. While costing methodologies vary across studies, this represents the total cost of treatment including the RUTF product procurement and transportation, as well as costs of delivery including infrastructure, health worker, the additional drugs delivered with the treatment package, etc.
While total cost of treatment can vary significantly, the absolute cost of RUTF product procurement and transportation is more consistent across programs. In 2016, UNICEF procured RUTF from 19 international and local producers, with 1 carton of RUTF (containing 150 92-gram sachets[1]) costing $41-$52. Historical costs for RUTF procured by UNICEF are published each year [14]. In the published literature, the cost of RUTF product per child treated ranged from $39.6-$104.65 (if the Ghana trial is excluded, the cost of RUTF product per child treated ranges from $39.6-$55.5).

In all the studies found except one, RUTF was produced and procured internationally. In Zambia, RUTF was locally produced with internationally procured milk powder and peanuts. The authors of the study noted that alternative formulations using locally grown ingredients could be just as effective while significantly reducing costs. In Malawi, it was estimated that local production could reduce product costs from $55 per child treated to $22.67. However, beyond this, there is very little published evidence on costs for locally produced product and the evidence is weak.

In programs with larger total costs, RUTF accounts for a much smaller portion of the total cost (RUTF was 13% of the total cost of treatment in Ghana - $805) and vice versa (RUTF was 46% of the total cost of treatment in Nigeria - $106). This demonstrates that total treatment cost is largely driven, not by the cost of RUTF, but by the context, scale and quality of the program. For example, while product costs were relatively high in Ghana ($105 per child treated), the total cost of treatment ($805 per child treated) was largely due to high geographic coverage requiring high management costs coupled with a low number of cases detected and treated.

As noted in the WHO Guidelines Updates in 2013, no cost data is available to compare the cost of treatment using F-100 with RUTF [3].
**Cost-effectiveness of treatment with RUTF:**
The evidence on cost-effectiveness of large-scale programs using RUTF for the treatment of uncomplicated cases of SAM in children 6-59 months of age is similarly limited but growing. However, CMAM is considered a cost-effective intervention, both in terms of cost per death averted and cost per DALY.

A review of the published literature for non-emergency CMAM programmes found a range of $145 to $809 per child successfully treated (see the table above). The range reflects the varying contexts, scale and implementation.

In addition to cost-effectiveness per child treated, a small number of studies also included analysis of cost per DALY or life saved. The Malawi [Wilford 2011] [15] and Zambia [reference: Bachmann] studies estimated cost-effectiveness to be $42-$53 per DALY or $1,365-$1,760 per life saved. A recent cost-effectiveness analysis of a large-scale program in Nigeria found 30 US$ per DALY and 1117 US$ per life saved. These cost-effectiveness estimates demonstrate that the treatment of SAM is both cost-effective and comparable to the cost-effectiveness of other child survival interventions. Indeed, according to World Bank and WHO CHOICE [21] [22], these estimates fall within the benchmarks for attractive and cost-effective interventions. However, it is important to note that these estimates are dependent upon a number of factors and subsequently have wide confidence intervals.

As noted in the WHO Guidelines Updates in 2013, no cost data is available to compare the cost-effectiveness of treatment using F-100 with RUTF [3].

**REGULATORY INFORMATION**

**12. Summary of regulatory status of the medicine.**

**Regulatory status of RUTF:**
It is not recorded as a medicine in the following country regulatory authorities:
- US Food and Drug Administration (FDA)
- European Medicines Agency (EMA)
- Australian Government, Department of Health, Therapeutic Goods Administration
- Japanese Pharmaceuticals and Medical Devices Agency
- Health Canada

However, RUTF is registered by various health or food authorities in the following countries:
What is the status of RUTF in the following countries? [20]
(non-exhaustive, as of August 2016)

<table>
<thead>
<tr>
<th>Countries</th>
<th>On the essential medicines/drugs list*</th>
<th>Registered as a medicine or a drug*</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia</td>
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<td>x</td>
<td>Registration by Food Medicine and Healthcare administration and Control Authority (2010-2015)</td>
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<tr>
<td>Kenya, South Africa</td>
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<td>x</td>
<td>Registration by Ministry of Public Health and Sanitation (2010)</td>
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<tr>
<td>Niger</td>
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<td>x</td>
<td>Registration by the Health Authority (Department of Pharmaceutical and Medical Products)</td>
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<td>Zimbabwe</td>
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<td>South Africa</td>
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<td>x</td>
<td>Registration by the Department of Agriculture, Forestry and Fisheries</td>
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<tr>
<td>Sudan, South Sudan</td>
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<td></td>
<td>Registration by Health Authorities (not clear whether medicine status or not)</td>
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<td>Guinea-Conakry</td>
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<td>In the ‘Guide Thérapeutique National’ (synthesis of EML and national pharmaceutical protocols)</td>
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<td>Vietnam</td>
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<td>Registration by the Food Drugs Authority</td>
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<td>Haiti, Burkina Faso, Côte d’Ivoire, Uganda, Malawi</td>
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<tr>
<td>Nigeria, Ghana, Liberia</td>
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<td>On-going process to add RUTF to EML</td>
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*Note: in some countries, RUTF is registered as a medicine by national authorities, but not necessarily on the national Essential Medicines List.
13. **Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia).**

To date the product is not included in the International, British, United States or European Pharmacopoeia.

The FAO/WHO joint commission of the Codex Alimentarius (CCNFSDU) is currently undergoing the process of developing guidelines for RUTF. The Guidelines will include:

- Description of the product,
- Raw materials and ingredients,
- Nutritional composition and quality factors,
- Contaminants,
- Technologies for and effect for processing,
- Good manufacturing practices and good hygiene practices,
- Method of analysis and sampling,
- Packaging,
- Labelling

14. **Reference list**


Annex 1 - APPLICATION KEY INFORMATION SUMMARY, included in the application email

Annex 2 - Key articles from the literature, included in the application email

