



		EMLc	Codes ATC: En attente
Indication	Acute malnutrition in infants, children or adolescents	Code ICD11: 5B52	
Type de médicament	Plant-derived medicine		
Type de liste	Liste de base (EML) (EMLc)		
Formulations	Biscuit or paste of nutritional composition as determined by the UN joint statement on the community-based management of severe acute malnutrition and Codex alimentarius guidelines.		
Historique des statuts LME	Demande refusée en 2017 (TRS 1006) Demande refusée en 2019 (TRS 1021) Ajouté en 2023 (TRS 1049)		
Sexe	Tous		
Âge	Enfants (1 mois - 12 ans)		
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique		
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.		
Wikipédia	Ready to use therapeutic food		

Recommandation du comité d'experts

The Expert Committee noted that severe acute malnutrition in children continues to be a considerable global health burden, affecting about 13.6 million children every year. Severe acute malnutrition is associated with metabolic dysregulation, impaired gluconeogenesis, disrupted amino acid or lipid metabolism, and increased risk of illness and mortality. Low- and middle-income countries are most affected and treatment services are estimated to reach less than 15% of undernourished children. The Committee noted that use of RUTF is currently recommended for use in several WHO guidelines and it is already included in national EMLs of a number of countries. The Committee also noted that the use of RUTF for the treatment of severe acute malnutrition in children aged 6 months to 5 years is supported by evidence from clinical trials showing benefits in improved recovery from malnutrition and weight gain compared with standard care. The Committee also noted that the effects of RUTF on relapse and mortality were still uncertain, and RUTF treatment was not associated with severe adverse events. The Committee noted that although data were limited, available cost-effectiveness studies indicate RUTF to be a cost-effective intervention as part of community-based management programmes for severe acute malnutrition, and more cost-effective than inpatient treatment. The Committee was satisfied with the information provided by the applicants addressing the specific concerns of the 2019 Expert Committee about the potential consequences of including RUTF on the Model List and associated risk-mitigation measures. The Committee was also reassured by the publication of the Codex Alimentarius guidelines which define the nutritional composition, production and labelling standards for RUTF as a food for special medical purposes. Potential risks of contamination are minimized by following good manufacturing processes which are also outlined the Codex Alimentarius guidelines. Based on these considerations, the Expert Committee recommended the inclusion of RUTF on the core list of the EMLc, in a new section on therapeutic foods, for treatment of severe acute malnutrition in children aged 6 months to 5 years.

Contexte

Applications requesting inclusion of RUTF on the EMLc for prevention of severe acute malnutrition have been considered on two previous occasions by the Expert Committee. On each occasion, listing was not recommended. In 2017, the Expert Committee

acknowledged the effectiveness of RUTF in the outpatient treatment of uncomplicated severe acute malnutrition in children aged 6–59 months. The Committee agreed that improving access to RUTF in health facilities at the country level for the outpatient treatment of severe acute malnutrition is essential. However, at that time, the Committee considered that listing RUTF on the EMLc may have had implications for the availability of alternative products or formulations, including decreasing availability at the country level because of increased regulation and requirements on the production and supply chain. The Committee recommended further analysis of the implications and impacts of including RUTF in the EMLc addressing the following aspects: • country regulatory requirements if RUTF is included in the national EML (medicine/pharmaceutical versus food) and ability of local and international producers to comply with those requirements; • cost and access implications if RUTF is listed as a medicine/pharmaceutical rather than a food; • guidelines on appropriate use of RUTF, that is, only for uncomplicated cases of severe acute malnutrition and not for other children; • progress by the Codex Committee on Nutrition and Foods for Special Dietary Uses) on the development of RUTF guidelines; and • outcome of ongoing systematic reviews of the effectiveness and safety of RUTF (1). Following a resubmission in 2019, the Expert Committee acknowledged once again the efficacy of RUTF for the dietary management of uncomplicated severe acute malnutrition in children younger than 5 years, many in non-hospitalized settings. However, a new report prepared in response to the request of the previous Expert Committee accompanying the application highlighted the divided opinions and ongoing uncertainty of the country-level implications of including RUTF as a medicine on the Model List. Some concerns initially raised in 2017 were still valid: the report highlighted that adding RUTF to the Model List could have unknown or unintended consequences such as more restricted access and increased costs and could potentially hinder local production. The Committee noted that, at that time, the work to establish standards and guidelines for RUTF under the Codex Alimentarius, regarding production, nutritional aspects and labelling to facilitate harmonization of the requirements of RUTF at an international level, was not yet finalized. In the absence of such standards, and without a clear indication of the potential consequences and implications at the country level of including RUTF on the Model List, and without the reassurance of a risk-mitigation plan to address any consequences, the Expert Committee did not recommend the addition of RUTF to the core list of the EMLc. In 2019, the Committee recommended that a comprehensive risk-mitigation plan for potential consequences of the addition of RUTF on the Model List would be highly relevant for any future consideration of the inclusion of this product (2).

Pertinence pour la santé publique

Public health relevance Severe acute malnutrition in children aged 6–59 months is defined anthropometrically using any one or combination of the following criteria: a mid-upper arm circumference < 115 mm or a weight-for-height < –3 Z-scores of the WHO growth standards, or bilateral nutritional oedema (3). This target population is identified through passive and active screening at health facilities and at the community level and this screening is integrated into national health systems using the community management of acute malnutrition model. Children detected as having severe acute malnutrition and presenting specific and severe medical complications or with complete anorexia are referred for inpatient care treatment. Children detected with severe acute malnutrition but not needing inpatient treatment and with a preserved appetite are admitted into outpatient care and given RUTF alongside the appropriate medical treatment and follow-up. Rates of severe acute malnutrition in children have remained persistently high and progress towards the Sustainable Development Goal (SDG) target of reducing the prevalence of child wasting to less than 5% by 2025 has been limited (4). Severe acute malnutrition affects about 13.6 million children younger than 5 years on an annual basis in low- and lower middle-income countries (5). Some of the highest prevalence of the condition is reported in countries in east and west Africa, however, more than half of all children suffering from severe acute malnutrition live in southern Asia. While severe acute malnutrition has typically been linked to humanitarian crises, three out of four children suffering from severe acute malnutrition do not live in areas affected by such crises, demonstrating that this condition is a widespread public health concern (4). In the context of climate change, persistent drought, elevated food prices and COVID-19, the rates of severe acute malnutrition are rising in many countries. In 2022, 260 000 additional children suffered from severe acute malnutrition in 15 of the highest burden countries (6). In some countries, Afghanistan for example, rates of severe acute malnutrition have doubled in the last 5 years (7).

Bénéfices

The evidence of benefits presented in the current application remained largely unchanged from the application submitted in 2019. Two systematic reviews on the use of RUTF were published in 2013. A 2013 Cochrane systematic review included three quasi-

randomized trials comparing RUTF with a standard flour porridge diet for the treatment of severe acute malnutrition. The meta-analysis found that RUTF improved recovery (risk ratio (RR) 1.32, 95% confidence interval (CI) 1.16 to 1.50) but the evidence was too limited to draw definitive conclusions on relapse, mortality or weight gain (8). This review was updated in 2019 with an additional 11 studies included, bringing the total number of studies to 15. RUTF was associated with improvements in recovery (RR 1.33, 95% CI 1.16 to 1.54; six studies, 1852 participants; moderate-quality evidence) and in weight gain (mean difference (MD) 1.12 g/kg a day, 95% CI 0.27 to 1.96 g/kg a day; four studies, 1450 participants; low-quality evidence). Results were less certain for relapses (RR 0.55, 95% CI 0.30 to 1.01; four studies, 1505 participants; very low-quality evidence) and mortality (RR 1.05, 95% CI 0.51 to 2.16; four studies, 1505 participants; very low-quality evidence). A meta-analysis of two quasi-randomized cluster trials showed that standard RUTF meeting total daily nutritional requirements may improve recovery (RR 1.41, 95% CI 1.19 to 1.68; low-quality evidence) and reduce relapse (RR 0.11, 95% CI 0.01 to 0.85; low-quality evidence) compared with RUTF given as a supplement to the usual diet. The effects were imprecise for mortality (RR 1.36, 95% CI 0.46 to 4.04; very low-quality evidence) and rate of weight gain (MD 1.21 g/kg a day, 95% CI -0.74 to 3.16 g/kg a day; very low-quality evidence). The updated review concluded that RUTF likely contributed to improved recovery and weight gain, however the effects on relapse and mortality were still unknown. Different formulations of RUTF were compared with the current evidence not favouring a particular formulation over another for most outcomes (9). A 2013 systematic review, meta-analysis and Delphi process on the treatment of severe and moderate acute malnutrition compared children who received RUTF with those who received standard care (in-patient treatment with therapeutic milks followed by provision of corn soy blend food for feeding at home). The review included largely the same studies used in the Cochrane review and the evidence was also considered to be of low quality. The meta-analysis found that children given RUTF were 51% more likely to achieve nutritional recovery (weight-for-height Z score ≥ -2) than the standard care group (RR 1.51, 95% CI 1.04 to 2.20). Weight gain in the RUTF group was also higher: this difference was statistically significant but small (MD 1.27 g/kg a day, 95% CI 0.16 to 2.38 g/kg a day). No significant differences were found in mortality between the two groups. Because of the limited number of high-quality comparative trials evaluating community-based treatment using RUTF, the authors 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 severe acute malnutrition using RUTF, the Delphi process estimated a case fatality rate of 4% (range: 2–7%) and a recovery rate of 80% (range: 50–93%). Overall, the review argued that the management of uncomplicated severe acute malnutrition in children aged 6–59 months using RUTF is backed by a wealth of observational and programmatic data, despite the limited number of impact studies (10). The application also summarized the results of additional studies documenting the acceptability of RUTF formulation and programme evaluation. One randomized control trial in India of 26 children with severe acute malnutrition found that children who received RUTF in addition to standard supplementary nutrition (roughly 500 kcal of energy and 12–15 g of protein) had 10 times higher odds of recovery compared the control group (odds ratio (OR) 10.28, 95% CI 1.02 to 103.95) (11). Another study was conducted to assess the effects of different types of RUTF (soybean, maize and sorghum RUTF with and without added milk (high iron and vitamin C arms) and peanut and milk standard RUTF (low iron arm)) on anaemia, iron deficiency and recovery. The study was characterized by high attrition, with missing data for about 30% of children in both arms. Soybean, maize and sorghum RUTF with and without added milk was associated with the lowest prevalence of anaemia and iron deficiency, and the highest recovery rate (12).

Torts

The 2019 Cochrane systematic review evaluated the safety of RUTF compared with standard flour porridge diet for mortality, frequency of diarrhoea and adverse outcomes. No difference was seen in mortality between the children who received RUTF and those who received standard diets (RR 0.97, 95% CI 0.46 to 2.05; three studies, 599 participants). Similarly, there was no difference in the frequency of diarrhoea (number of days of diarrhoea in the first 2 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; one study, 352 participants) (9). The other systematic review reported did not include adverse events among considered outcomes (10). Peanuts, chickpeas and soybeans – the main raw foods used in lipid-based RUTF formulations – contain a wide range of naturally occurring microorganisms, some capable of causing human diseases. Therefore, even low-moisture foods with sufficiently low water content to prevent the growth of bacteria can be vehicles for pathogens. Children with acute malnutrition may be more susceptible to foodborne illnesses because changes caused by malnutrition may affect their immune system and their ability to defend against pathogens (13,14). For peanut-based RUTFs, the largest safety concern is contamination by *Salmonella* spp. Salmonellosis is a health risk even in very low doses in some foods (e.g. foods with high lipid content) and its link to foodborne disease outbreaks is well established (14).

Aflatoxin, a family of toxins produced by certain mushrooms, may be present in peanuts and milk. Chronic consumption of high levels of aflatoxin in early life can affect children's growth and development, and their immune and hepatic systems (13). Vitamin toxicity is a theoretical concern for fat-soluble vitamins A, D and E as these are present in RUTF in doses higher than the recommended daily intakes because these high doses are necessary to resolve vitamin deficiencies in children with severe acute malnutrition. If RUTF is consumed by a child without malnutrition, they may be at risk of toxicity of fat-soluble vitamins. The Codex Alimentarius guidelines for RUTF include appropriate food safety guidance on microbiological, chemical and physical hazards associated with RUTF and its production (15).

Rapport coût/efficacité

A 2020 review by Action Against Hunger and Save the Children United Kingdom brought together all the existing literature on cost and cost-effectiveness of treatment of severe acute malnutrition. The review identified 21 studies, of which 20 reported the cost per treated child, and 11 cost-effectiveness data reports. The studies spanned countries in Africa and south Asia and were conducted between 2009 and 2019. Total costs per treated child ranged from US\$ 76 in Niger to US\$ 805 in Ghana, with a median cost of US\$ 196. These costs included RUTF procurement and transportation, as well as costs of delivery (e.g. infrastructure, health worker time, additional drugs delivered with the treatment package and community outreach) (18). The wide range in cost per child reflects the varying treatment methods, contexts, scale and models of implementation. For example, in the Ghana study, only 40 children were treated which is likely to have driven up the cost per child treated. Another factor influencing the large variation in costs is linked to the method used and the sources of cost information included, which differed across studies. While total cost of treatment varied significantly, the absolute cost of RUTF was more consistent across programmes. In programmes with higher total costs, RUTF accounts for a smaller portion of the total cost (RUTF was 13% of the total cost of treatment in Ghana) and vice versa (RUTF was 46% of the total cost of treatment in Niger). The total treatment cost is largely driven by the context, scale and characteristics of the programme and, to a lesser extent, by the cost of RUTF. While the evidence on the cost-effectiveness of treatment of severe acute malnutrition is limited, treatment with RUTF using the community-based model is considered a highly cost-effective intervention. Six studies included in the review assessed the cost per disability-adjusted life year (DALY) averted. The cost per DALY averted ranged from US\$ 26 in Bangladesh to US\$ 53 in Zambia. Given that these estimates are lower than the gross domestic product per capita in the countries where implemented, the intervention is considered to be cost effective (18). UNICEF, the main procurer of RUTF, reported that the weighted average price per carton of RUTF decreased from US\$ 52 in 2006 to US\$ 41 in 2021 (19). One carton of RUTF includes 150 sachets, sufficient to treat a child for 68 weeks (20). The application noted that RUTF price reductions achieved over the past 16 years risk being reversed due to the current global situation (disruption of supply chains due to COVID-19 and armed conflicts) where prices are rising for ingredients, packaging, energy and international freight.

Directives de l'OMS

The use of RUTF for the outpatient treatment of severe acute malnutrition in children aged 6–59 months has been a recommended treatment approach for more than 15 years. The 2007 Joint Statement issued by the WHO, the World Food Programme, the United Nations System Standing Committee on Nutrition and UNICEF highlighted the importance of community-based treatment of severe acute malnutrition with RUTF and recommended this approach for uncomplicated cases of this condition (3). The Joint Statement further advocates the importance of national protocols and provision of RUTF for the management of severe acute malnutrition. The 2013 WHO guidelines for the management of severe acute malnutrition recommend outpatient treatment for children who 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 (16). More recently, RUTF has been included in the WHO guidelines on the dairy protein content in RUTF for treatment of uncomplicated severe acute malnutrition. This guidance document on the appropriate use of RUTF clarifies which cases of severe acute malnutrition are eligible for RUTF (17). It addresses the concerns raised by previous Expert Committees on the lack of recommendations on when and how to use RUTF.

Disponibilité

Over the past decade, UNICEF has been focusing efforts on integrating RUTF in national supply chains and securing domestic funding for this product. Modest gains have been made by governments in high-burden countries, although UNICEF continues to procure 75–80% of RUTF for the treatment of severe acute malnutrition. The availability of recognized international guidelines will

support the integration process by providing national governments with a regulatory framework which can be applied at the country level to ensure quality and standards. These guidelines will be able to orient governments in the procurement process and will also be an essential tool to assist in building regulatory capacity within national governments to establish their own regulatory framework for RUTF.

Autres considérations

A recent mapping exercise by UNICEF identified 71 countries with national clinical guidelines on the management of severe acute malnutrition which includes treatment with RUTF. A further 10 countries have draft or interim guidance on the management of severe acute malnutrition using RUTF (21). The application reported that, as of November 2021, 25 countries with programmes to treat severe acute malnutrition with RUTF had included RUTF in their country's national EML. The number of countries with RUTF in the national EML was considerably higher in the African region than elsewhere. Only 18% of countries in the region of the Americas and 10% of countries in the western Pacific region included RUTF in the national EML. No countries in the Eastern Mediterranean, European or South-East Asia regions included RUTF in their national EMLs. Of the 25 countries with RUTF in the national EML, 11 classified RUTF as a medicine, seven as a food for special medical purposes and seven as other. In most countries RUTF is regulated by medicines regulatory authorities. The mapping exercise did not find any impediments or issues from regulatory agencies or in procuring RUTF when it was included in the national EML as a medicine instead of a food. In 2022, the Codex Alimentarius guideline for RUTF was finalized, thus providing the first international reference document detailing the composition and manufacturing standards for RUTF (15). This guideline is expected to support procurement processes and provide governments with a regulatory framework which can be applied at the country level to ensure quality and standards of RUTF products. The guideline also clarifies the regulatory status of RUTF as a food for special medical purposes. One of the key concerns in listing RUTF on the EML raised in stakeholder consultations in 2018 was that this listing might lead to the application of pharmaceutical standards to the manufacturing process (22). The Codex Alimentarius guideline has determined that RUTF sits within the regulatory framework of food production, with a focus on the fact that this product is for specific medical purposes. Classifying RUTF as a food for special medical purpose will help countries by clarify that these products are specially processed or formulated, highlighting that they are only for use in the treatment of severe acute malnutrition, not for general consumption. The guidelines provide a set of quality standards for suppliers and limiting definitions and nutrient compositions of RUTF. These standards can also be used as importation requirements. Unlike therapeutic milk products, RUTF formulas are not water-based, thus limiting bacterial growth. They can be transported and stored without refrigeration and in areas where hygiene conditions are suboptimal (3), making RUTF an ideal candidate to treat severe acute malnutrition at the community level in areas afflicted by poverty, lack of access to food, disease, and humanitarian emergencies.

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