

# MODULE III

## ORAL REHYDRATION

# ORAL REHYDRATION SOLUTION

## GENERAL PRODUCT INFORMATION

Oral rehydration solution (ORS) is an oral powder-containing mixture of glucose sodium chloride, potassium chloride, and sodium citrate. After being dissolved in the requisite volume of water they are intended for the prevention and treatment of dehydration due to diarrhea, including maintenance therapy.

ORS and zinc are recommended by the WHO and UNICEF to be used collectively to ensure the effective treatment of diarrhea.<sup>1,2</sup> ORS replaces the essential fluids and salts lost through diarrhea. Zinc decreases the duration and severity of an episode and reduces the risk of recurrence in the immediate short term. ORS and zinc are highly effective and affordable products for treatment of childhood diarrhea that could prevent deaths in up to 93% of diarrhea cases.

ORS is included in WHO's Essential Medicines List, and Priority Medicines for Mothers and Children, as well as national EMLs and treatment guidelines for childhood diarrhea treatment in many high-burden countries. ORS is also listed as a lifesaving commodity identified and targeted for scale-up and access by the UN Commission on Life-Saving Commodities for Women and Children.

Note: In 2005, WHO and UNICEF recommended a switch from the standard ORS to an improved lower-osmolarity formulation, to be combined with zinc supplementation.

<sup>1</sup> World Health Organization. 2005. *The Treatment of Diarrhea: A Manual for Physicians and other Senior Health Workers*. Geneva: WHO. Available at [http://www.who.int/maternal\\_child\\_adolescent/documents/9241593180/en/](http://www.who.int/maternal_child_adolescent/documents/9241593180/en/).

<sup>2</sup> World Health Organization. 2006. *Implementing the New Recommendations on the Clinical Management of Diarrhea: Guidelines for Policy Makers and Programme Managers*. Geneva: WHO. Available at [http://www.who.int/maternal\\_child\\_adolescent/documents/9241594217/en/](http://www.who.int/maternal_child_adolescent/documents/9241594217/en/).



## KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers approved by UNICEF and those with a proven record of quality products.
2. Procure only ORS that is manufactured as a pharmaceutical product following all GMP requirements. ORS is considered a medicine by inclusion in the WHO EML; therefore, procurement should be based on product quality.
3. Procurers need to focus on product quality to ensure that it is safe for patient use.



## KEY QUALITY CONSIDERATIONS

### Product specification

ORS that is procured should have a product composition in line with that described in the “[Product Specification](#)” section below. WHO and UNICEF currently recommend the use of low-osmolarity ORS with a total osmolarity of 245 mOsm/L, instead of the previous standard ORS with a total osmolarity of 311 mOsm/L, due to greater effectiveness.

ORS that is procured should contain only four ingredients, glucose, sodium chloride, potassium chloride, and trisodium citrate, in the concentrations described in the “[Product Specification](#)” section below. The addition of other ingredients, such as other minerals (especially zinc) or vitamins, has not been shown to improve the solution’s efficacy. For this reason, neither UNICEF nor WHO approve or provide ORS with additives for use in the treatment of the childhood diarrhea. Any additional ingredients should be clearly described on the packet. Manufacturers must demonstrate their clinical value, safety, and chemical stability.

### Packaging and labeling

ORS should be packaged in multi-ply laminated aluminum foil sachets, as product can be affected by highly humid environmental conditions. A compound of polyethylene (inside), aluminum (middle), and polyester or any other suitable coating compound (outside) has proven to be a satisfactory combination for packing ORS. However, product stability also depends on these conditions: the raw material is dry, the sealing is perfect, and the final product is stored appropriately.

ORS should be procured with packaging designated with: (1) the total net mass and the mass of the contents of each constituent, both expressed in grams; (2) the required volume of water to reconstitute the solution; (3) directions for the preparation of the solution and its administration; and (4) a warning that any solution that remains unused 24 hours after preparation is to be discarded.

**Storage, transportation, and distribution**

ORS is stable at room temperature and does not require cold chain storage.

<b>Name of the Medicinal Product</b>	Low-osmolarity oral rehydration salts																													
<b>Pharmaceutical Form</b>	Oral powder A white, crystalline powder; odorless Note: The recommended formulations of ORS can be produced in three dosage forms: powder, tablet, and liquid. This document deals only with the production of ORS in powder form, which also is the dosage form on the WHO EML.																													
<b>Qualitative and Quantitative Composition</b>	<b>Product Composition of ORS</b> <table border="1"> <thead> <tr> <th>COMPONENT</th> <th>CHEMICAL FORMULA</th> <th>CONCENTRATION (g/L)</th> </tr> </thead> <tbody> <tr> <td>Sodium chloride</td> <td>NaCl</td> <td>2.6</td> </tr> <tr> <td>Glucose, anhydrous</td> <td>C<sub>6</sub>H<sub>12</sub>O<sub>6</sub></td> <td>13.5</td> </tr> <tr> <td>Potassium chloride</td> <td>KCl</td> <td>1.5</td> </tr> <tr> <td>Trisodium citrate, dihydrate</td> <td>C<sub>6</sub>H<sub>5</sub>Na<sub>3</sub>O<sub>7</sub>,2H<sub>2</sub>O</td> <td>2.9</td> </tr> </tbody> </table> <b>Concentrations Yielded from Dissolution in Drinking Water</b> <table border="1"> <thead> <tr> <th>COMPONENT</th> <th>CONCENTRATION</th> </tr> </thead> <tbody> <tr> <td>Sodium</td> <td>75 mmol/L</td> </tr> <tr> <td>Chloride</td> <td>65 mmol/L</td> </tr> <tr> <td>Glucose, anhydrous</td> <td>75 mmol/L</td> </tr> <tr> <td>Potassium</td> <td>20 mmol/L</td> </tr> <tr> <td>Citrate</td> <td>10 mmol/L</td> </tr> </tbody> </table> <b>Total osmolarity:</b> 245 mOsm/L			COMPONENT	CHEMICAL FORMULA	CONCENTRATION (g/L)	Sodium chloride	NaCl	2.6	Glucose, anhydrous	C <sub>6</sub> H <sub>12</sub> O <sub>6</sub>	13.5	Potassium chloride	KCl	1.5	Trisodium citrate, dihydrate	C <sub>6</sub> H <sub>5</sub> Na <sub>3</sub> O <sub>7</sub> ,2H <sub>2</sub> O	2.9	COMPONENT	CONCENTRATION	Sodium	75 mmol/L	Chloride	65 mmol/L	Glucose, anhydrous	75 mmol/L	Potassium	20 mmol/L	Citrate	10 mmol/L
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<ul style="list-style-type: none"> <li>– Glucose facilitates the absorption of sodium (and hence water) on a 1:1 molar basis in the small intestine.</li> <li>– Sodium and potassium are needed to replace the losses of these essential ions during diarrhea (and vomiting).</li> <li>– Citrate corrects the acidosis that occurs as a result of diarrhea and dehydration.</li> </ul> ORS may contain suitable pharmaceutical aids (e.g., suitable flow agent in minimal quantities to improve the flow characteristics) and/or the flavoring agents.																														
Some papers describe that a number of mild to moderately dehydrated children refuse to drink ORS because of its strong salty taste. <sup>3</sup> The WHO																														

<sup>3</sup> Loo, D. M. I., F. van der Graaf, and W. T. Ten. 2004. "The Effect of Flavoring Oral Rehydration Solution on Its Composition and Palatability." *J Pediatric Gastroenterology and Nutrition* 39(5):545–8.

Control of Diarrhoeal Diseases (CDD) Programme conducted a safety/efficacy study in Egypt and an acceptability study in the Philippines of flavored and colored ORS solutions.<sup>4</sup> The results of these studies showed neither an advantage nor disadvantage for the flavored and colored ORS when compared to the standard ORS with regard to safety, acceptability, and correct use. For this reason, and with the aim of making an essential drug available at low price in the public health system, UNICEF and WHO recommend that governments use the ORS composition that contains only the four basic ingredients needed to effectively treat dehydration due to diarrhea. ORS produced for use in the private sector (commercial sales) and indicated for the prevention and treatment of dehydration due to diarrhea, may contain flavoring or coloring agents. In practice, two or more types of flavoring are often needed, and saccharine is added to increase their effect. The ingredients used for flavoring ORS must be among those listed as “generally recognized as safe” for their intended use by the US Food and Drug Administration (FDA) or by the US Flavor Extract Manufacturer’s Association. The responsibility for demonstrating the clinical efficacy, safety, and chemical stability of such products remains with the manufacturer.

### Packaging and Presentation

ORS is a powder for dilution in 200 mL, 500 mL, and 1 L. Products are packed in hermetically sealed, laminated sachets. The sachets may be made of multi-ply laminations with aluminum foil or polyethylene foil.

The multi-ply laminated aluminum foil sachet is usually recommended for ORS. A compound of polyethylene (inside), aluminum (middle), and polyester or any other suitable coating compound (outside) has proved to be a satisfactory combination for packing ORS.

The packaging configurations for ORS procured by UNICEF are:

- ORS low osmolarity, 20.5 g/1 L
- ORS low osmolarity, 10.2 g/0.5 L

ORS and zinc are recommended by WHO for combination use to ensure the effective treatment of diarrhea; in order to improve compliance, a co-package of ORS and zinc in accordance with WHO treatment protocol guidelines is offered by some manufacturers to improve treatment regimen adherence.

The packaging configurations for ORS procured by UNICEF are:

- ORS low osmolarity, 2 sachets for 1 L + zinc 20-mg dispersible tablets, blister pack of 10, packed together in a kit
- ORS low osmolarity, 4 sachets for 0.5 L + zinc 20-mg dispersible tablets, blister pack of 10, packed together in a kit

<sup>4</sup> Available at

[http://apps.who.int/iris/bitstream/handle/10665/69227/WHO\\_FCH\\_CAH\\_06.1.pdf;jsessionid=A426B006186DD09F4F593604F6D66435?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/69227/WHO_FCH_CAH_06.1.pdf;jsessionid=A426B006186DD09F4F593604F6D66435?sequence=1)

## SUPPLY



Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment, as described in [Module II](#).

### WHO-prequalified products

ORS is not included in the WHO PQP. Therefore, no WHO-prequalified ORS products are available.

### SRA-approved products

As of February 2018, there are no ORS products approved in SRA countries in the same formulation and strength as that described in the “[Product Specifications](#)” section.<sup>5</sup>

When manufacturers claim that products are approved by an SRA, they should provide the following information/documents to verify the SRA approval.

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, patient information leaflet, and the labeling by the reference SRA)
- A statement confirming that the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross-check the submitted information with the corresponding NMRA websites:

- US FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>
- EU regulatory authorities: [https://ec.europa.eu/health/documents/community-register/regca\\_en](https://ec.europa.eu/health/documents/community-register/regca_en)
- Swissmedic:  
<https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html>
- Health Canada: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>
- TGA, Australia: <https://www.tga.gov.au/australian-register-therapeutic-goods>

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<sup>5</sup> The ORS products approved in SRA countries are of different formulations and strengths. Furthermore, ORS is considered to be an over-the-counter medicine, which some SRAs do not include in the databases of approved drugs published on their websites, making it difficult to find SRA-approved ORS products.

## Trusted sources

ORS from the following manufacturers is listed by UNICEF as approved sources for procurement<sup>6</sup>:

- CHI Pharmaceuticals, Nigeria
- FDC Ltd, India
- KBI, Germany
- Renata Ltd, Bangladesh
- Universal Corporation Ltd, Kenya

It is recommended to check for updated information on the UNICEF website at the time of procurement.

## Related products

ORS products approved in the UK<sup>7</sup> contain glucose monohydrate 17.9 g/L, sodium chloride 2.35 g/L, potassium chloride 1.5 g/L, sodium citrate dihydrate 1.95 g/L, and citric acid anhydrous 0.64 g/L. It is available in a sachet for 200 mL. When dissolved in 200 mL of water, each ORS sachet will give the equivalent of: glucose 90 mmol/L, sodium 60 mmol/L, potassium 20 mmol/L, chloride 60 mmol/L, and citrate 10 mmol/L.

ORS products approved in Australia<sup>8</sup> contain glucose monohydrate 17.8 g/L, sodium chloride 2.35 g/L, potassium chloride 1.5 g/L, and sodium acid citrate 2.65 g/L. It is available in a sachet for 200 mL. When dissolved in 200 mL of water, each ORS sachet will give the equivalent of: glucose 90 mmol/L, sodium 63 mmol/L, potassium 20 mmol/L, chloride 60 mmol/L, and citrate 11 mmol/L.

Although the ORS formulation in the “Product Specification” section below is recommended, the above formulations approved in the UK and Australia also meet the WHO and UNICEF’s criteria for acceptable ORS formulations.<sup>9</sup> These criteria are listed below; they refer to the desired characteristics of the solution after it has been prepared according to the instructions on the packet:

- Total substance concentration (including that contributed by glucose) should be within the range of 200–310 mmol/L.
- Individual substance concentration:
  - Glucose should at least equal that of sodium but should not exceed 111 mmol/L.
  - Sodium should be within the range of 60–90 mEq/ or mmol/L.
  - Potassium should be within the range of 15–25 mEq/ or mmol/L.
  - Citrate should be within the range of 8–12 mmol/L.
  - Chloride should be within the range of 50–80 mEq/ or mmol/L.

<sup>6</sup> Available at

[https://www.unicef.org/supply/files/Amoxicillin\\_DT\\_Product\\_Profile\\_and\\_Supply\\_Update.pdf](https://www.unicef.org/supply/files/Amoxicillin_DT_Product_Profile_and_Supply_Update.pdf).

<sup>7</sup> <http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1512713009284.pdf>

<sup>8</sup> <http://tga-search.clients.funnelback.com/s/search.html?query=oral+rehydration+salt&collection=tga-artg&profile=record>.

<sup>9</sup> World Health Organization. 2002. “New Formula Oral Rehydration Solution.” In *WHO Drug Information*. Vol. 16, No. Geneva: WHO. Available at <http://apps.who.int/medicinedocs/en/d/Js4950e/2.4.html>.

Other formulations of ORS that exist in the market include:

ORS-hydrogen carbonate (bicarbonate)

- Trisodium citrate dihydrate may be replaced by 2.5 g/L of sodium hydrogen carbonate,  $\text{NaHCO}_3$  (sodium bicarbonate). However, as the stability of the latter formulation under tropical conditions is very poor, it is recommended only in ORS manufactured for immediate use, or where sodium hydrogen carbonate is packaged in separate packets.
- This formulation would also allow the use of 14.85 g/L of glucose monohydrate,  $\text{C}_6\text{H}_{12}\text{O}_6\text{H}_2\text{O}$ , instead of anhydrous glucose.
- The title of the two formulations could be distinguished by: “ORS-citrate” or “ORS-hydrogen carbonate” (bicarbonate). The title ORS used without qualification implies the product is the citrate formulation.

## STORAGE, STABILITY, AND DEGRADATION



ORS containing citrate (as opposed to bicarbonate containing ORS) is stable at ambient temperatures/humidity and is unlikely to undergo any significant degradation as a result of heat/humidity if it is properly manufactured, packaged, and sealed.

Shelf life: 2–3 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: ORS should be kept in a sealed packet; if a free-flowing powder is required, it should be kept in an airtight packet, preferably made of aluminum laminate. The USP monograph for ORS recommends preservation in a tight container and avoiding exposure to temperatures in excess of 30°C.

ORS does not need to be maintained in the cold chain.

Discard any solution that remains unused 24 hours after preparation.

## PRODUCT SPECIFICATIONS



The product must meet pharmacopoeial specifications, such as those of the International Pharmacopoeia, US Pharmacopoeia, and British Pharmacopoeia, depending on the quality assurance policy of the procurement agency or the equivalent thereof.

The testing parameters and acceptance criteria of the pharmacopoeias are similar. USP and BP monographs are applicable for ORS formulations containing sodium bicarbonate or sodium citrate, whereas International Pharmacopoeia is applicable only for ORS formulations containing trisodium citrate.

## Oral Rehydration

Table ORS-I. International Pharmacopoeia Specifications for ORS

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification		
a) Sugar	Melts when heated; first becomes yellow then brown, swells up and burns, evolving an odor of burnt sugar.	As per IP monograph of ORS
b) Sodium	The test solution yields reaction A described under 2.1 General identification tests as characteristic of sodium.	2.1 General identification tests
c) Potassium	A yellow-orange precipitate is produced.	As per IP monograph of ORS
d) Chlorides	A 5-mL aliquot of the test solution yields reaction A described under 2.1 General identification tests as characteristic of chlorides.	2.1 General identification tests
e) Citrates	A 5-mL aliquot of the test solution after neutralization yields reaction A described under 2.1 General identification tests as characteristic of citrates.	2.1 General identification tests
f) Glucose	A copious red precipitate is produced (glucose).	As per IP monograph of ORS
Uniformity of mass	Not more than two of the individual masses deviate from the average mass by more than 5% and none deviates by more than 10%.	As per IP monograph of ORS
Loss on drying	At 50°C it loses not more than 20 mg/g.	As per IP monograph of ORS
pH of the reconstituted solution	7.0–8.8	As per IP monograph of ORS
Assays		
a) Sodium	90–110%	1.8 Atomic spectrometry: emission and absorption
b) Potassium	90–110%	1.8 Atomic spectrometry: emission and absorption
c) Chloride	90–110%	Titration, as per IP monograph of ORS
d) Citrate	90–110%	2.6 Non-aqueous titration, Method A
e) Glucose	90–110%	Optical rotation, as per IP monograph of ORS

## Oral Rehydration

Table ORS-2. US Pharmacopoeia Specifications for ORS

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification		
a) Sodium	The sample imparts an intense yellow color to a nonluminous flame.	As per USP Monograph of ORS
b) Potassium	The sample imparts a violet color to a nonluminous flame. Since the presence of small quantities of sodium masks the color, screen out the yellow color produced by sodium by viewing through a blue filter that blocks the emission at 589 nm (sodium), but is transparent to emission at 404 nm (potassium).	As per USP Monograph of ORS
c) Chloride	Meet the requirements.	USP<191>
d) Bicarbonate (if present)	Where it contains sodium bicarbonate, it dissolves with effervescence, and the collected gas so obtained meets the requirements.	USP<191>
e) Citrate	Where it contains sodium citrate, it meets the requirements.	USP<191>
f) Dextrose (Glucose)	Where it contains dextrose, a copious red precipitate of cuprous oxide is formed.	As per USP monograph of ORS
Assay		
a) Dextrose	90–110%	USP<781A>, Angular rotation
b) Sodium and Potassium	90–110%	Photometry, as per USP monograph of ORS
c) Chloride	90–110%	Titration, as per USP monograph of ORS
d) Bicarbonate (if present)	90–110%	Titration, as per USP monograph of ORS
e) Citrate (if present)	90–110%	USP<345>, Assay for citric acid/citrate and phosphate
Minimum Fill	The average net weight of the contents of the 10 containers is NLT the labeled amount, and the net weight of the contents of any single container is NLT 95% and not more than (NMT) 105% of the labeled amount. If the contents of NMT 1 container are less than 95% but NLT 90% of the labeled amount, or more than 105% but NMT 110% of the labeled amount, determine the net weight of the contents of 20 additional containers. The average net weight of the contents of 30 containers is NLT the labeled amount, and the net weight of the contents of NMT 1 of the 30 containers is less than 95% but	USP<755>

## Oral Rehydration

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
	NLT 90% of the labeled amount, or more than 105% but NMT 110% of the labeled amount.	
pH of the reconstituted solution	7.0–8.8	USP<791>
Loss on drying	At 50°C, NMT 1.0%	USP<731>

Table ORS-3. British Pharmacopoeia Specifications for ORS

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification		
a) Glucose	When heated with cupri-tartaric solution R I a copious precipitate of copper (II) oxide is produced.	As per BP monograph of ORS
b) Potassium	Yields reaction B characteristic of potassium salts.	Appendix VI
c) Sodium	Yields reaction A characteristic of sodium salts.	Appendix VI
d) Chlorides	Yields reaction A characteristic of chloride salts.	Appendix VI
e) Citrates (if present)	Yields reactions A and B characteristic of citrates.	Appendix VI
f) Sodium bicarbonate (if present)	Vigorous effervescence is produced.	As per BP monograph of ORS
Assay		
a) Potassium	90–110%	Appendix II D
b) Sodium	90–110%	Appendix II D
c) Chlorides	90–110%	Titration, as per BP monograph of ORS
d) Citrate (if present)	90–110%	Appendix VIII A
e) Bicarbonate (if present)	90–110%	Titration, as per BP monograph of ORS
f) Glucose	90–110%	Appendix V F
Uniformity of mass	Meet the requirements	Appendix XII C

## Oral Rehydration

Additional tests for the ORS products as recommended by WHO are listed below:

### **Seal (only if packed in aluminum laminate)**

As in process control test during packaging, check 10 packets every 10–20 minutes.

Bundle up the packets and submerge them underwater in a vacuum desiccator or equivalent device. Draw a vacuum of about 18kPa (15 cm of mercury or -0.8 bar) and hold for one minute. Examine for air leakage indicated by a fine stream of bubbles. Reestablish normal pressure and open packets to examine for water penetration.

If water penetration (leakage) is observed, search for the reason (e.g., dirty sealing jaws, wrinkles, pinholes in laminate, product sealed with laminate), and reject the batch if necessary.

### **Appearance of product:**

A white, crystalline powder, odorless.

### **Appearance of solution**

Dissolve the entire contents of one packet of ORS or about 20.5 g of the mixture in 1,000 mL of water.

The solution should be clear and odorless, or should have only a faint yellow stain.



# PART I: CLINICAL PARTICULARS

## Therapeutic indications

ORS is indicated for the treatment of diarrhea and fluid loss due to diarrhea in infants, children, and adults.

## Posology, method, and duration of administration

The amount of ORS solution needed for rehydration is calculated based on the child's weight. The amount of solution required also depends on the child's dehydration status. Children with more marked signs of dehydration or who continue to pass frequent watery stools will require more solution than those with less marked signs or who are not passing frequent stools. If a child wants more than the estimated amount of ORS solution, and there are no signs of overhydration, give more.

The approximate amount of ORS solution to give in the first 4 hours:

- Below 4 months / less than 5 kg: 200–400 mL
- 4–11 months / 5–7.9 kg: 400–600 mL
- 12–23 months / 8–10.9 kg: 600–800 mL
- To 4 years / 11–15.9 kg: 800–1,200 mL
- To 14 years / 16–29.9 kg: 1,200–2,200 mL
- 15 years or older / 30 kg or more: 2,200–4,000 mL

### Notes

Use the patient's age only when the weight is not known. The amount may also be estimated by multiplying the child's weight in kg times 75 mL.

During the initial stages of therapy, while still dehydrated, adults can consume up to 750 mL per hour, if necessary, and children up to 20 mL/kg body weight per hour.

Normal feeding can continue after the initial fluid deficit has been corrected. Breastfeeding should continue between administrations of ORS.

Edematous (puffy) eyelids are a sign of overhydration. If this occurs, stop giving ORS solution, but give breast milk or plain water, and food. Do not give a diuretic. When the edema has gone, resume giving ORS solution or home fluids according to Treatment Plan A from WHO (<http://apps.who.int/iris/bitstream/10665/43209/1/9241593180.pdf>).

After 4 hours, reassess the child fully. Then decide what treatment to give next:

- If signs of severe dehydration have appeared, IV therapy should be started following WHO Treatment Plan C (<http://apps.who.int/iris/bitstream/10665/43209/1/9241593180.pdf>). This is very

unusual, however, occurring only in children who drink ORS solution poorly and pass large watery stools frequently during the rehydration period.

- If the child still has signs indicating some dehydration, continue oral rehydration therapy by repeating the treatment described above. At the same time, start to offer food, milk and other fluids, as described in WHO Treatment Plan A (<http://apps.who.int/iris/bitstream/10665/43209/1/9241593180.pdf>), and continue to reassess the child frequently.
- If there are no signs of dehydration, the child should be considered fully rehydrated.

## Contraindications

ORS is contraindicated in patients exhibiting the following conditions: cirrhosis of the liver, congestive cardiac failure, nephrotic syndrome, acute and chronic renal failure, ischemic heart disease, adrenocortical insufficiency, hyperkalemic periodic paralysis, hyperkalemia, hypoventilatory states, chloride depletion due to continuous gastric fluid loss, metabolic or respiratory alkalosis, hypocalcemia, hyperosmolar states in anuria or oliguria, edematous sodium retaining conditions, hypertension, peripheral or pulmonary edema or toxemia of pregnancy, severe vomiting, diarrhea and dehydration requiring fluid therapy, dextrose malabsorption, diabetes mellitus, thiamine deficiency, severe undernutrition, hemodilution, hypophosphatemia, sepsis, and trauma.

ORS is also contraindicated for use in patients undergoing treatment with the following: sodium-retaining drugs (e.g., corticosteroids, NSAIDs, carbenoxolone), or diuretics known to produce hypochloremic alkalosis.

## Special warnings and precautions for use

Administer with care in cases of acute dehydration, heat cramps, extensive tissue destruction, or if patients are receiving potassium-sparing diuretics. Concurrent use with other potassium-containing drugs may precipitate hyperkalemia.

It is very important to dissolve ORS in water of the correct volume. A weak solution will not contain optimum glucose and electrolyte concentration and a strong solution may give rise to electrolyte imbalance. Diarrhea can have very serious consequences in children under 3 years old. Immediate medical advice should be sought. In other age groups, if symptoms persist for more than 24–48 hours, consult a doctor.

If nausea and vomiting are present with the diarrhea, small and frequent amounts of ORS should be drunk first. In infants, immediate medical assistance should be obtained. Use within 1 hour of reconstitution, or within 24 hours if stored in a refrigerator.

See also “[Overdose](#)” section below.

## Interaction with other medicinal products and other forms of interaction

### Sodium bicarbonate

Increases excretion of lithium, resulting in a reduced plasma-lithium concentration.

### Potassium chloride

ACE inhibitors (hyperkalemia); cyclosporin (increased risk of hyperkalemia); potassium-sparing diuretics where hyperkalemia may result. No known interactions to other actives.

For more details, see also under “[Contraindications](#)” section.

### Pregnancy and lactation

Use in patients with pre-eclampsia is contraindicated. The product should only be administered if the expected benefit to the mother is thought to outweigh any possible risk to the fetus or neonate.

### Effects on ability to drive and use machines

ORS has no influence on the ability to drive or use machines.

### Undesirable effects

The following adverse effects have been reported although more commonly following excessive amounts: hypernatremia, edema, nausea, vomiting, diarrhea, abdominal cramps, thirst, reduced salivation, lachrymation, sweating, fever, tachycardia, renal failure, respiratory arrest, headache, dizziness, restlessness, irritability, weakness, muscular twitching, coma, convulsions, hyperkalemia, gastrointestinal ulceration, metabolic alkalosis, muscle hypertonicity, flatulence, dehydration, and raised blood pressure.

### Overdose

Iso-osmotic overload is managed by restricting sodium, potassium, and water intake plus measures to increase renal sodium, potassium and water output by using “loop diuretics” (e.g., frusemide).

## PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT<sup>1</sup>

Information contained in this annex is intended to assist procurement agencies who plan to perform a full prequalification of ORS products. When assessing the complete quality/CMC documentation, assessors should consider the following particular information on ORS.

### Raw materials (key ingredients)

#### **Glucose**

The use of glucose for the preparation of ORS does not require a pyrogen-free, pharmaceutical grade such as that used for parenteral preparations. An “oral grade” quality is therefore fully acceptable, provided that the quality is within the limits set in the pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP).

If such a quality is not available, or the limits set in the specifications prove to be a serious constraint for the establishment of local production and the provision of ORS in general, the food standard may be adopted.

Only anhydrous glucose is recommended. Contact of glucose monohydrate with trisodium citrate and prolonged exposure to tropical (hot and humid) conditions can lead to liquefaction of the whole mixture.

Whenever appropriate facilities for microbiological control are available, it is recommended that the microbiological purity of the glucose be checked.

#### **Sodium chloride**

The pharmaceutical grade is recommended and the specifications should be in line with a pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP).

If sodium chloride is produced locally, but is not of the mentioned pharmaceutical grade, a standard for a food grade quality may be applied.

#### **Potassium chloride**

The pharmaceutical grade is recommended and the specifications should be in line with a pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP).

If sodium chloride is produced locally, but is not of the mentioned pharmaceutical grade, a standard for a food grade quality may be applied.

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<sup>1</sup> World Health Organization. 2006. *Oral Rehydration Salts: Production of the New ORS*. WHO: Geneva. Available at [http://apps.who.int/iris/bitstream/10665/69227/1/WHO\\_FCH\\_CAH\\_06.1.pdf](http://apps.who.int/iris/bitstream/10665/69227/1/WHO_FCH_CAH_06.1.pdf).

## Sodium citrate

To achieve the required pH limits in the ORS solution, only trisodium citrate is indicated.

The recommended ORS-citrate composition contains trisodium citrate dihydrate in view of the fact that this quality is more widely available on the market and produced in large quantities. Anhydrous trisodium citrate can, however, be used without hesitation where such a quality is available and preferred, but a higher price (by about 40%) must be expected.

Stability tests have shown that a combination of glucose monohydrate and trisodium citrate dihydrate is far less stable, and the high total content of water of crystallization in both ingredients eventually leads to a liquefaction if packed in polyethylene and exposed to tropical conditions (23–40°C and 82–92%RH). Therefore, such combination should be avoided.

The pharmaceutical grade is recommended and the specifications should be in line with a pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP).

If sodium citrate is produced locally, but is not of the mentioned pharmaceutical grade, the standard for food grade may be applied.

Manufacturers of these key ingredients should provide evidence for GMP compliance. However, the key ingredients are atypical APIs, meaning that the manufacturing process and controls are not typically designed to meet API GMPs. As an alternative, there should be a clear specification; the site should have been audited; changes should be controlled, and appropriate checks should be made on incoming goods.

## Other ingredients

With the aim of making an essential medicines available at an affordable price in the public health system, the recommended composition should contain only the four basic ingredients (glucose, sodium chloride, potassium chloride, and trisodium citrate) in the concentrations described in this document for preparing an effective (clinically tested) ORS.

Excipient such as colloidal silicon dioxide (Aerosil®) improve the flow characteristics but do not dissolve in the solution and render it turbid. Their use is normally only indicated when automatic packaging equipment is used, and only recommended if the flow properties of the available raw materials hamper accurate dosing and proper functioning of the equipment.

ORS may contain flavoring or coloring agents, if this is seen as vital by a manufacturer for promoting the product or to compete with other brands. In practice, two or more types of flavoring are often needed, and saccharine is added to increase their effect. The ingredients used for flavoring ORS must be among those listed as “generally recognized as safe” for their intended use by the US FDA or by the US Flavor Extract Manufacturer’s Association. The responsibility for demonstrating the clinical efficacy, safety, and chemical stability of such products remains with the manufacturer.

## Manufacturing process

ORS is a straightforward product to manufacture, but some specific procedures should be observed to ensure the quality of the product. Recommendations and technical procedures that should be considered during the manufacture of ORS include the following:

- After prolonged storage in hot and humid climates, the raw materials may have absorbed a substantial amount of moisture, and have a water content higher than the indicated limit of 1%. The use of such ingredients for the manufacture of ORS may result in accelerated decomposition. Therefore, if a raw material containing water in excess of the indicated limit is to be used, it is preferable to dry it at the recommended temperature as follows: glucose, anhydrous at max. 105°C; sodium chloride, potassium chloride, and trisodium citrate at max. 130°C.

The time required for drying to the specified limit depends on the amount of water absorbed, but should not exceed 16 hours (overnight). In tropical countries, special attention must be given to the temperature and relative humidity of the air to be used for drying. It is therefore important to compare the moisture content in the raw material before and after the drying process in order to ascertain the extent of water loss during drying (efficacy of drying). The condition of the intake of air is less critical in countries with a cold and dry climate.

Dried material should not be exposed to high humidity and heat after it has been taken out of the dryer. It is therefore advisable to install the drying equipment in a controlled, air-conditioned room where the dried material can be filled into airtight drums and safely stored until required for use.

- However, whenever possible, drying should be avoided. This can be done by ordering raw materials with a specified low water content, or by placing orders at intervals so that the goods are fresh when used, and storing them in such a way that they are protected from humidity and other possible negative influences.
- All four ingredients should be of the same medium or fine crystalline grade (below 1,000 microns). This requirement can be specified when the ingredients are ordered, however, it is often difficult to obtain. Therefore, occasionally milling, grinding, or sifting to the required uniform particle size may be required to obtain a uniform particle size. This is important for uniform mixing of the product.
- Weighing of ingredients should be done only when they are ready for mixing—that is, after drying, grating, and sieving.
- During ORS blending, particularly in tropical countries, the following points should be noted:
  - Glucose, with its abrasive characteristics and especially when it is in fine powder form, may enter into the mechanical parts and damage shaft seals and gaskets; it may even cause the product to become contaminated with fine particles from the seals. In such case, the ordinary shaft seals should be replaced by air-purged seals, using compressed air (oil-free and dry).
  - ORS, with its tendency to caramelize rapidly in humidity and heat, requires almost daily cleaning of the mixing machine.
- Depending on the quality of the raw materials, particularly glucose, the handling of ORS on automatic filling/dosing equipment is normally accompanied by the development of dust, which can negatively influence the sealing operation. The intensity of dust formation is directly linked to the speed of the machine. A higher output can be achieved only if all the ingredients in the ORS mixer are of a dust-free, uniform medium crystalline or granular in size, which guarantees an easy flow.
- Intentional excess filling/dosing to compensate for any product that might remain in the packet at the time of use should be strictly avoided as it may result

in a higher sodium concentration in the solution and ultimately lead to hypernatremia, particularly in infants.

## Packaging

The kind of packaging material to be used for ORS depends mainly on the required standard of stability, the climatic conditions, and the available resources.

### Multi-ply laminations with aluminum foil

This type of packaging is usually recommended for ORS. This type of packaging material is available in numerous different combinations of compounds. A compound of polyethylene, aluminum, and polyester (or any other suitable coating compound) has proved to be a satisfactory combination for packing ORS. The polyethylene on the inner side is essential for heat-sealing the compound together; the aluminum in the middle reduces the permeability to gas and steam (so that it is no longer effectively measurable); and the polyester on the outside protects the aluminum, the ink on the aluminum, and improves the mechanical qualities in general.

For recommended ORS compositions, the thickness should, whenever possible, be selected within the following limits:

- Inside: polyethylene (PE) 0.040–0.050 mm or 36.9–46.1 g/m<sup>2</sup>
- Middle: aluminum (ALU) 0.009–0.015 mm or 24.3–40.5 g/m<sup>2</sup>
- Outside: polyester (P) 0.012–0.015 mm or 12.9–20.9 g/m<sup>2</sup>

Choice of the recommended compound does not guarantee a stable and satisfactory product if the raw material is not dry, the sealing is imperfect, and the final product is not stored appropriately.

### Polyethylene foil

ORS can in certain cases be perfectly well packed in transparent or printed polyethylene (low density), which in fact offers a particular advantage in dry and hot climates. In such conditions, the evaporating water of crystallization in the raw material can escape through the pores of the foil and thus the moisture content of the product is reduced. In hot and humid climates, however, the reaction may be the reverse, and the moisture may penetrate through the pores into the packet, where it is absorbed by the mixture, causing lumping or even deterioration.

ORS-citrate does not absolutely require an impermeable packaging material. If packed in polyethylene it may, however, absorb moisture and some lumping, which is usually acceptable.

The possibilities for the use of polyethylene packets are basically as follows:

- Use of a single polyethylene bag for the whole ORS mixture, with the composition, instructions, brand, and other information printed on the polyethylene
- Use of two unprinted polyethylene bags, one for the whole ORS mixture and a second to hold together the first bag containing ORS and a printed insert (with composition, instructions for use, illustrations, etc.)

Suitable sizes for these packets and the minimal gauges of polyethylene recommended for each are as follows:

- Inner bag containing glucose, sodium chloride, potassium chloride, and trisodium citrate with min. 0.04-mm gauge of PE and size 65 mm x 100 mm.
- Outer bag holding ORS and label with min. 0.05-mm gauge of PE and size 70 mm x 120 mm.

### Bioequivalence requirements

Not applicable.