1.0 General Information

1.1 Product Description

The United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) of a Multiple Micronutrient Supplement (MMS) for pregnant women is an evidence-based nutrition intervention and is listed on the World Health Organization (WHO) Model List of Essential Medicines.

The UNIMMAP MMS formulation contains 15 micronutrients at dosages that approximate the recommended dietary allowances for pregnancy.

The finished product described by this specification conforms to the UNIMMAP formulation of MMS for pregnant women, that is delivered in the form of a film coated tablet in a bottle containing 180 tablets.

1.2 Intended Use

To support the increased nutritional needs of pregnant women. The product may also be used during breastfeeding.

1.3 Target Population

Pregnant women

1.4 Product Classification

Vitamins and Minerals

2.0 Product Composition

2.1 Active Ingredients

Each tablet must contain the vitamin and mineral (active) ingredients listed in Table 1, in the indicated quantitative label claimed amount, as per the UNIMMAP formulation.

Table 1: UNIMMAP MMS formulation with active ingredients, indicative chemical forms and claimed label quantity

Nutrient	Active Ingredient	Chemical Form (indicative)	Nutrient Amount
Vitamin A	Retinol	Retinyl Acetate Retinyl Palmitate	800 mcg RAE
Vitamin C	Ascorbic acid	Ascorbic Acid Sodium Ascorbate Calcium Ascorbate	70 mg

Nutrient	Active Ingredient	Chemical Form (indicative)	Nutrient Amount
Vitamin D	D3: Cholecalciferol	Cholecalciferol	5 mcg (200 IU)
Vitamin E	alpha-Tocopherol	RRR- or all-rac-alpha-Tocopherol RRR- or all-rac-alpha-Tocopheryl acetate RRR- or all-rac-alpha-Tocopheryl acid succinate	10 mg alpha-TE
Vitamin B1	Thiamine	Thiamin Hydrochloride Thiamin Mononitrate	1.4 mg
Vitamin B2	Riboflavin	Riboflavin Riboflavin 5'-phosphate	1.4 mg
Vitamin B3	Niacin	Niacinamide	18 mg NE
Vitamin B6	Pyridoxine	Pyridoxine Hydrochloride	1.9 mg
Vitamin B9	Folic acid	Folic acid	400 mcg
Vitamin B12	Cyanocobalamin	Cyanocobalamin	2.6 mcg
Iron	Iron	Ionizable Form	30 mg
Iodine	Iodide	Ionizable Form	150 mcg
Zinc	Zinc	Ionizable Form	15 mg
Selenium	Selenium	Ionizable Form	65 mcg
Copper	Copper	Ionizable Form	2 mg

Abbreviations: RAE, retinol activity equivalents; IU, international units; α-TE, alpha tocopherol equivalent; NE, niacin equivalents.

The chemical forms indicated in Table 1 are only suggestions and not the mandatory forms. Selection of the specific chemical form of each active ingredient should be based on evidence of stability, bioavailability and suitability in the formulation.

The active ingredients must be compliant with the following internationally recognized pharmacopeia compendial standards: *United States Pharmacopeia* (*USP*), the *European Pharmacopoeia* (*Ph. Eur.), British Pharmacopoeia (BP),* or *International Pharmacopoeia* (*Ph. Int.).*

2.2 Excipients

Excipients must be pharmacologically inactive (i.e., inactive ingredients). Excipients used in the finished product should comply with applicable regulatory requirements.

Excipients must meet acceptable quality criteria recommended by international organizations or agencies, including but not limited to *USP*, *Ph. Eur., Ph. Int., National Formulary* (*NF*), *Food Chemical Codex* (*FCC*), the Joint FAO/WHO Expert Committee on Food Additives (JEFCA), or other globally recognized pharmacopeial or compendial standards. Where such standards do not exist, inactive ingredients must be of acceptable pharmaceutical or food grade quality.

Film coating with natural colorants such as mineral derived colorants is preferred.

2.3 Processing Aids and Other Substances

Processing aids or other materials used in the manufacture of the finished product must be of acceptable pharmaceutical or food grade quality. Potable water must meet, at minimum, all the requirements for drinking water promulgated by the appropriate regulatory authorities. Water not meeting such requirements should not be permitted for use in the water purification system for *Purified Water, USP or Water, Purified, Ph. Eur*.

3.0 Manufacturing Requirements and Quality Standards

3.1 Finished Product Manufacturing Requirements

The finished product must be manufactured according to the requirements specified in *WHO good manufacturing practices: main principles for pharmaceutical products*, Annex 2, WHO Technical Report Series (TRS) 986, (latest version), and all other applicable guidelines available in the following two WHO compendia:

- Quality assurance of pharmaceuticals: a compendium of guidelines and related materials: volume 1: Good practices and related regulatory guidance, 10th Edition
- Quality assurance of pharmaceuticals: a compendium of guidelines and related materials: volume 2: Good manufacturing practices and inspection 10th Edition

4.0 Finished Product Test Specification

The finished product specification must comply with the following USP-NF monograph *Oil- and Water-Soluble Vitamins with Minerals Tablets (latest version).*

The test methods listed for identification and strength assay (Table 2.a) have been found to be applicable for most formulations of UNIMMAP MMS, but other test methods in the USP-NF monograph may be used. The acceptance criteria provided is based on the USP-NF monograph, suppliers may apply higher limits if justified by manufacturing processes or allowed under applicable regulations.

Alternative test methods or procedures may be used in line with requirements described in section 4.1.

Table 2.a: Identification and Strength assay test methods for UNIMMAP MMS finished product testing

Nutrient (active moiety)	Test Method	Label Claim	Acceptance Criteria
Identification and Strength Assay			
Vitamin A (retinol)	Vitamin A, Method 2, Vitamin A Assay <571>, Assay, Chromatographic Methods, Procedure 2	800 mcg RAE	NLT 90.0% NMT 165.0%
Vitamin C (ascorbic acid)	Vitamin C, Method 2, Vitamin C Assay <580>, Method II, Chromatographic Methods, Procedure 1	70 mg	NLT 90.0% NMT 150.0%
Vitamin D (cholecalciferol)	Vitamin D, Method 1, Vitamin D Assay <581>, Assay, Chromatographic Methods, Procedure 1	5 mcg (200 IU)	NLT 90.0% NMT 165.0%
Vitamin E (alpha tocopherol)	Vitamin E, Method 2, Vitamin E Assay <551>, Assay, Procedure 2	10 mg alpha-TE	NLT 90.0% NMT 165.0%
Vitamin B_1 (thiamine)	Niacin or Niacinamide, Pyridoxine Hydrochloride, Riboflavin and Thiamine, Method 1	1.4 mg	NLT 90.0% NMT 150.0%
Vitamin B_2 (riboflavin)		1.4 mg	NLT 90.0% NMT 150.0%
Vitamin B_3 (niacin)		18 mg NE	NLT 90.0% NMT 150.0%
Vitamin B_6 (pyridoxine)		1.9 mg	NLT 90.0% NMT 150.0%
Vitamin B_9 (folic acid)	Folic Acid, Method 1, Folic Acid Assay <411>, Assay, Procedure 1	400 mcg folic acid	NLT 90.0% NMT 150.0%
Vitamin B_{12} (cyanocobalamin)	Cyanocobalamin, Method 1	2.6 mcg	NLT 90.0% NMT 150.0%
Iodine (iodide)	Iodide	150 mcg	NLT 90.0% NMT 160.0%

Nutrient (active moiety)	Test Method	Label Claim	Acceptance Criteria
Identification and Strength Assay			
Iron	Copper, Iron, and Zinc, Method 2; Selenium, Method 3 Plasma Spectrochemistry <730>	30 mg	NLT 90.0% NMT 125.0%
Zinc		15 mg	NLT 90.0% NMT 125.0%
Selenium		65 mcg	NLT 90.0% NMT 160.0%
Copper		2 mg	NLT 90.0% NMT 125.0%

Table 2.b: Physical, Performance, Elemental Impurities and Contaminants test methods for UNIMMAP MMS formulation

Test	Test Method	Acceptance Criteria
Physical Characteristics		
Appearance	Visual	TBD by Manufacturer
Shape	Visual	TBD by Manufacturer
Tablet Thickness	Micrometer	TBD by Manufacturer
Tablet Length	Micrometer	TBD by Manufacturer
Tablet Friability	USP <1216>	TBD by Manufacturer
Tablet Breaking Force	USP <1217>	TBD by Manufacturer
Performance		
Average Tablet Weight	USP <2091>	TBD by Manufacturer Preferably, as small as technically and functionally feasible
Weight Variation		Weights of NMT 2 of the tablets differ from the average weight by 5% no tablet differs in weight by more than 10%

Test	Test Method	Acceptance Criteria
Dissolution for Vitamin A (index for oil-soluble Vitamins)	USP <2040> Apparatus 2, at 75 rpm, in 0.05 M phosphate buffer pH 6.8, w/ 1% (w/v) sodium ascorbate and 1% (w/v) octoxynol 9, 900 mL	NLT 75% of the labeled amount of Vitamin A dissolved in 45 minutes
Dissolution for Folic Acid	USP <2040> Apparatus 2, at 75 rpm, in water or 0.05M pH 6.0 citrate buffer, 900 mL	NLT 75% of the labeled amount of Folic Acid dissolved in 1 hour
Dissolution for Riboflavin (Index for water-soluble vitamin)	USP <2040> Apparatus 2, at 75 rpm, in 0.1 N hydrochloric acid, 900 mL	NLT 75% of the labeled amount of riboflavin dissolved in 1 hour
Dissolution for Iron (Index element)		NLT 75% of the labeled amount of iron dissolved in 1 hour
Elemental Impurities		
Arsenic (inorganic)	USP <233> and USP <2232>	NMT 15 mcg/day
Cadmium		NMT 5 mcg/day
Lead		NMT 5 mcg/day
Mercury (total)		NMT 15 mcg/day
Methylmercury (as Hg)		NMT 2 mcg/day
Microbial Contaminants		
Total Aerobic Microbial Count (TAMC)	USP <2021>	NMT 3 x 10^3 CFU/g
Total Combined Yeast & Mold (TCYM)	USP <2021>	NMT 3 x 10^2 CFU/g
Absence of Escherichia coli	USP <2022>	Absent in 10 g
Absence of Salmonella spp.	USP <2022>	Absent in 10 g
Absence of Staphylococcus aureus	USP <2022>	Absent in 10 g

Test	Test Method	Acceptance Criteria
Enterobacterial Count (Bile-Tolerant Gram-Negative Bacteria)	USP <2021>	NMT 10 MPN/g

4.1 Analytical Test Methods

Tests and examinations used to determine whether the finished product meets its defined specification must be appropriate for their intended use. Tests methods or procedures must meet proper standards of accuracy and precision.

Test methods used should be in accordance with official test methods in USP, BP, Ph. Eur., or Ph. Int. and must be verified for its suitability under actual conditions of use.

In-house test methods that are not in the above pharmacopeia must be validated according to ICH Q2(R1) *Validation of Analytical Procedures: Text and Methodology*.

5.0 Packaging

Packaging materials used should comply with internationally recognized pharmacopeial standards.

5.1 Primary Packaging - Container Closure System

The container closure system must be tamper-evident, with child-resistant-cap. Preferably, the bottle should be white, opaque and made of high-density polyethylene HDPE with a polypropylene (PP) or low-density polypropylene (LDPE) cap.

The container closure system must have minimal headspace and the need for desiccant or oxygen absorbers must be determined by the manufacturer based on experience and supporting stability data.

5.2 Secondary Packaging

The finished product should be packaged in robust cardboard boxes in a suitable manner considering long shipments and humanitarian logistics. For further guidance please refer to UNICEF's specification on packing, packaging and labelling (secondary packaging) linked under References.

6.0 Labeling and Artwork

6.1 Product Labeling Requirements

Product labels must be in English and French. Other languages such as Spanish, Arabic or other local languages may be requested. The product label must contain the minimum information listed in section 6.1.1.

Labelling should comply with regulatory requirements of the recipient country. Additional information, as requested by donors, partners or local authorities, may be requested in Purchase Orders, in discussion with the supplier.

The label should follow the format of the mock label provided in Annex I and must be reviewed by UNICEF.

6.1.1 Minimum Information

The product label should include, at minimum, the following information:

- Name/description of the product prominently displayed on the front panel as “Multiple Micronutrient Supplement for Pregnant & Breastfeeding Women”
- Pink lady figure, along with the wording UNIMMAP, to indicate the specific MMS formulation
- List of active ingredients and their quantitative amount per tablet (dosage unit)
- List of excipients in descending order of predominance by weight
- Net content, i.e. number of tablets
- Directions for use (e.g., DIRECTIONS: Take one tablet daily with food , or upon retiring. Not to be chewed. Do not exceed recommended dose.)
- Warnings and precautions that may be necessary (e.g., WARNING: Keep out of reach of children. Iron overdose can be fatal for children under 6. In case of overdose, seek medical help or contact poison control immediately.)
- Batch number assigned by the manufacturer[1]
- Manufacturing date
- Expiration date
- Storage conditions and handling precautions (e.g., STORAGE: Store in original container, below 30°C, protect from light and moisture. Do not repack.)
- Name and address of the manufacturer

6.1.2 Additional Labelling Information

Additionally, in line with applicable local regulations, the following information may be required on the product label:

- Percent amount (%) per dosage unit of the Recommended Dietary Allowance (RDA) or Recommended Nutrient Intake (RNI), if established

[1] Note that UNICEF requires the batch number to consist of not more than 10 digits due to limitations of its enterprise resource planning SAP system

- Company responsible for placing the product on the market
- Product registration number

6.1.3 Primary Labeling Artwork

The supplier must ensure the “pink lady” figure is prominently displaced, and the minimum product label information is accurate, truthful and legible. An example of a mock-up is provided in Annex I.

6.2 Patient Information

Each finished product should include a Patient Information Leaflet (PIL), either as part of a peel-back label consisting of front-of-pack label and the PIL, or the PIL attached to the bottle, or in a box with each pack.

A QR code containing PIL information in relevant languages can be included on the front-of-pack label, developed and maintained by the supplier.

Additionally, under certain circumstances, the recipient country may request a Summary of Product Characteristics (SmPC).

The PIL and SmPC should be in the format of WHO standard templates for an SmPC and PIL.

Exceptionally, based on donor or partner requirements, a simplified label with PIL presented in QR code may be accepted. In this case, a physical PIL should be provided with at least each carton.

6.3 Secondary Container Labeling

Secondary container labelling should follow standard GS labelling requirements and further guidance can be found in UNICEF’s specification on packing, packaging and labelling (secondary packaging) linked under References.

7.0 Stability

The finished product labeling must state a shelf life (expiration) date that is indicative of the date before which the product is ensured to meet applicable specifications of identity, strength, quality, and purity when stored under labeled conditions. The shelf life (expiration) date must be supported by suitable stability data, following the guidelines in the International Council for Harmonizations of Technical Requirements for Pharmaceuticals for Human Use (ICH), *Stability Testing of New Drug Substances and Products* Q1A(R2).

7.1 Shelf Life

The shelf life should be, at minimum, 30 months, while 36 months is preferred for product intended for export.

The shelf life should be, at minimum, 24 months, for the product to be used domestically in the country of manufacture.

7.2 Storage and Transport Conditions

The finished product should not be stored above 30 °C, and transported within 15 - 25 °C.

8.0 Additional Requirements

8.1 Dietary or Religious requirements

The finished product must be manufactured to meet halal requirements, if requested in line with the recipient countries' regulatory requirements. The exact requirements for halal certification should be obtained from a recognized and accredited source.

8.1.1 Certificate of Analysis (CoA)

A certificate of analysis (CoA) must be issued for each manufacturing lot of the finished product.

8.1.2 Change Control

The supplier must notify, in writing, of any significant change(s) to the finished product specification (i.e., the finished product specification as agreed in the signed LTA) that might affect product quality, for approval prior to supplying batches with the proposed changes. The supplier must also notify of any change to its manufacturing site, including any changes to the certification status held by the manufacturer from a GMP certificate issuing authority.

8.2 Additional Regulatory Requirements

The manufacturing site and operations must have adequate documentation for manufacturing and export of the product to the country of destination. To facilitate importation, the following technical documents will be requested in the Purchase Order: Certificate of Analysis (CoA); GMP certificate; Certificate of Pharmaceutical Product (CoPP) or Free Sales Certificate (FSC) as issued by the National Drug Regulatory Authority.

9.0 References

9.1 Applicable References

- Technical Requirements for Micronutrient Products
- Inter-Agency Finished Pharmaceutical Product Questionnaire
- Technical Questionnaire for Pharmaceutical Manufacturers
- UNICEF Specification on (secondary) packing, packaging and labelling
- USP Oil- and Water- Soluble Vitamins with Minerals Tablets

9.2 Useful References

- Expert consensus on an open-access United Nations International Multiple Micronutrient Antenatal Preparation–multiple micronutrient supplement product specification
- Vitamin and mineral requirements in human nutrition, 2nd edition (who.int)
- UNICEF/WHO/UNU (1999) "United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP)"
- WHO Recommendations on antenatal care for a positive pregnancy experience. World Health Organization, 2016
- WHO Nutritional interventions update multiple micronutrient supplements during pregnancy

10.0 Acknowledgment

With special acknowledgement to Kirk Humanitarian for their support and collaboration on the UNIMMAP MMS initiative.

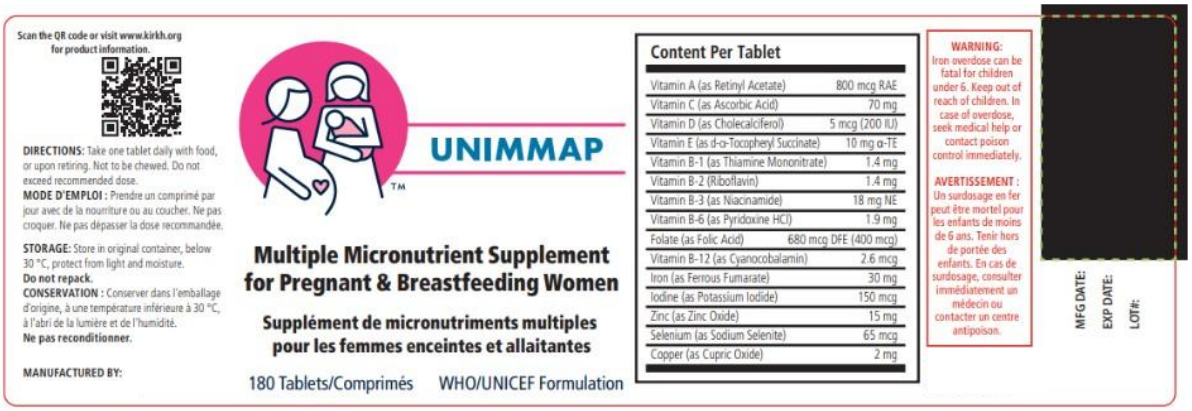
FOR MORE INFORMATION

Contact CPHHQ-SD-Nutrition Supplies: sd.nutritionsupplies@unicef.org
UNIMMAP MMS Resource Hub: https://unimmap-mms.org/
Browse Technical resources for nutrition products | UNICEF Supply Division

Annex I: Mock peel-back label with PIL

The example below is for reference only. Additional information may be requested based on recipient country's requirements or partner requirements.

1) The following example shows product label for UNIMMAP MMS product when procured for UNICEF or partners



2) The following example shows product label for UNIMMAP MMS product donated by Kirk Humanitarian.