

MEDICINES CONTROL COUNCIL



COMPLEMENTARY MEDICINES - HEALTH SUPPLEMENTS SAFETY AND EFFICACY

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of Health Supplements. It represents the Medicines Control Council's current thinking on the quality, safety, and efficacy of these medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants also adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines and the website www.mccza.com.

This guideline is published in anticipation of the publication of Regulations contemplating the inclusion of Health Supplements as a sub-category of Complementary Medicines. Further Annexures associated but not yet included with this guideline will be published for public comment.

First publication released for comment	November 2014
Version 2 – deletion of quality aspects for inclusion in separate guideline	June 2016
Version 3 - addition of Annexures G and I for comment	April 2017
Deadline for comment	31 May 2017
Version 3_1 - addition of Annexure J for comment	May 2017
Deadline for comment	30 June 2017

Use the Guideline Comments Form¹ available on the MCC website when submitting comments.

Submit comments in hard copy to the Registrar of Medicines, Civitas Building, Thabo Sehume Street, Pretoria. Comments may also be submitted by e-mail to Dr Jeanette Lotter at Jeanette.Lotter@health.gov.za

DR JC GOUWS
REGISTRAR OF MEDICINES

¹ 6.13 Guideline Comments Form Dec08 v1.doc

TABLE OF CONTENTS		Page
1	INTRODUCTION	3
1.1	Definition.....	4
1.2	Compliance with Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Agricultural and Collection Practices (GACP).....	5
1.3	Format of submission.....	5
2	ZA-CTD FORMAT	5
2.1	ZA Module 1: Administrative information.....	5
2.2	ZA Module 2: Common Technical Document summaries.....	6
2.3	ZA Module 4: Non-clinical study reports.....	8
2.4	ZA Module 5: Clinical study reports.....	8
3	SAFETY AND EFFICACY REQUIREMENTS	9
3.1	General.....	9
3.1.1	Single Substance Formulations.....	9
3.1.2	Multiple Substance Formulations.....	9
3.2	Labelling and Allowable Claims.....	9
3.2.1	Single Substance Formulations.....	10
3.2.2	Multiple Substance Formulation Claim Development.....	10
4	GLOSSARY OF TERMS	12
5	UPDATE HISTORY	16
ANNEXURE A		17
	Category D Decision Tree.....	17
ANNEXURE B		18
	Motivation for inclusion of Substance as Health Supplement.....	18
ANNEXURE C		19
	Allowable Levels and Claims: Probiotics.....	19
ANNEXURE D		20
	Allowable Levels and Claims: Prebiotics.....	20
ANNEXURE E		21
	Allowable Levels and Claims: Vitamins.....	21
ANNEXURE F		36
	Allowable Levels and Claims: Minerals.....	36

5	UPDATE HISTORY	3
ANNEXURE J		4
	Allowable levels and claims: Carotenoids.....	4

As indicated on the front page, further Annexures to this guideline will be published for public comment.

In the interest of focus, only the proposed additional Annexure is included to amend version 2 of the guideline published in June 2016 (*7.04_SE_Health_Supplements_Jun16_v2.doc*)

Sections 1 - 4 are unchanged as in version 2 published June 2016

Annexures A - F are unchanged as in version 2 published June 2016

Annexures G and I are as published in version 3 for comment in April 2017.

Annexure J is now published for comment:

ANNEXURE J - Allowable Levels and Claims: Carotenoids

In assessing the safety, efficacy and quality of health supplement and preparations the attached Annexure J has been developed to guide the use of carotenoids in Complementary Medicines as Health Supplements.

Annexures H and K - O are still to follow.

5 UPDATE HISTORY

Date	Reason for update	Version & publication
Nov 2014	First publication released for comment	v1 Nov 2013
26 Feb 2015	Deadline for comment	
June 2016	Deletion of section 2 "Quality Requirements" for inclusion in separate guideline Inclusion of new section 2 ZA-CTD format Amendments to 1 i), 1.1, 1.2, 3.1, 3.2, 3.2.1, 4, Annexure E	v2 June 2016
Feb 2017	Inclusion of Annexures G and I	v3 April 2017
31 May 2017	Deadline for comment	
April 2017	Inclusion of Annexure J	v3_1 May 2017
30 June 2017	Deadline for comment	

ANNEXURE J

Allowable levels and claims: Carotenoids

Any claims provided may be used with any of the stipulated dosage ranges.

Unless otherwise indicated, "Dosage" refers to the Maximum Daily Levels permitted as Health Supplement.

Carotenoids are divided into the following categories:

1. **Carotenoids currently regarded as Health Supplements** – *Comment invited on any aspect*
 - A. Carotenoids with **Pro-Vitamin A activity**.
 - B. Carotenoids mainly used as **Anti-oxidants**.
2. **Comment is invited to justify the use of the following Carotenoids as Health Supplements, including proposed claim and maximum levels**
 - C. Carotenoids used as **food colorants** but with **possible physiological effects**.
 - D. Carotenoids mainly used as **food colorants**.
 - E. **Other** carotenoids with possible physiological effects.

The maximum daily dose for these Carotenoids in combination with other vitamin A source materials must not exceed the maximum daily dose for vitamin A indicated in Annexure E.

Pharmacological Action: Source of Pro-vitamin A OR antioxidants.

General Statements:

Requirement for labelling:

If you are pregnant or breast feeding your baby please consult your doctor, pharmacist or other health care professional for advice before taking this medicine.

Store in airtight container, protected from light.

Do not exceed daily dosage level without consulting a registered healthcare provider.

Carotenoid	Health Supplement Claim	Specified Warning(s)	Dosage <i>RE: Retinol Equivalents</i>
A. Carotenoids with Pro-Vitamin A activity			
<p>β-Carotene <i>(all-E)-1,1'-(3,7,12,16-Tetramethyl-1,3,5,7,9,11,13,15,17-octadecanonaene-1,18-diyl)bis[2,6,6-trimethylcyclohexen. All-trans beta carotene Beta carotene Betatene CI 40800 CI 75130 CI Food Orange 5</i></p> <p>Sources: <i>All-trans-beta-carotene Beta-carotene</i></p>	<p>Provitamin A for the maintenance of good health. Provitamin A to help maintain eyesight, skin, membranes and immune function. Provitamin A to help in the development and maintenance of night vision. Provitamin A to help in the development and maintenance of bones and teeth. Helps to prevent vitamin A deficiency</p>	<p>Consult a health care practitioner prior to use if you are a tobacco smoker. β-carotene might decrease effectiveness of statins used to lower cholesterol.</p>	<p>Calculated to yield Retinal Activity Equivalents not exceeding dosages as stipulated in Annexure E, Vitamin A.</p>
<p>α-Carotene <i>(all-E)-1,3,3-Trimethyl-2-(3,7,12,1-tetramethyl-18-(2,6,6-trimethyl-2-cyclohexen-1-yl)-1,3,5,7,9,11,13,15,17-octadecanonaenyl)cyclohexene</i></p> <p>Sources: <i>Citrus sinensis (Fruit); Dunaliella salina (Whole); Elaeis guineensis (Branch); Elaeis guineensis (Fruit); Persea americana (Fruit); Rubus idaeus (Fruit); Solanum lycopersicum (Fruit); Zea mays (Seed)</i></p>	<p>As per Annexure E, Vitamin A. Source of antioxidant(s)/Provides antioxidant(s).</p>		<p>Calculated to yield Retinal Activity Equivalents (RAE) not exceeding dosages as stipulated in Annexure E, Vitamin A.</p>
<p>Cryptoxanthin <i>(3R)-beta,beta-Caroten-3-ol beta-Caroten-3-ol Cryptoxanthine E161c Kryptoxanthin</i></p> <p>Sources: <i>Capsicum annuum (Fruit); Capsicum annuum (Petal); Carica papaya (Fruit); Citrus aurantium (Fruit peel); Citrus limon (Fruit peel); Citrus paradisi (Fruit); Citrus paradisi (Fruit peel); Citrus sinensis (Fruit peel); Dunaliella salina (Whole); Persea americana (Fruit); Prunus persica (Whole plant); Tagetes erecta (Flower); Zea mays (Seed)</i></p>	<p>As per Annexure E, Vitamin A. Source of antioxidant(s)/Provides antioxidant(s).</p>		<p>Calculated to yield Retinal Activity Equivalents not exceeding dosages as stipulated in Annexure E, Vitamin A.</p>

Carotenoid	Health Supplement Claim	Specified Warning(s)	Dosage
B. Carotenoids mainly used as Anti-oxidants			
<p>Astaxanthin 3,3'-dihydroxy-4,4'-diketo-beta-carotene. 3,3'-Dihydroxy-beta,beta-carotene-4,4'-dione</p> <p>Sources: <i>Haematococcus pluvialis (Whole);</i> <i>Pandalus borealis (Internal shell)</i></p>	<p>Source of antioxidant(s)/Provides antioxidant(s).</p>	<p>Not suitable for children.</p> <p>Use should be avoided when taking immunosuppressants, patients with bleeding disorders, and patients on 5-α-reductase inhibitors (Testosterone-DHT).</p>	<p>6-8 mg</p>
<p>Lycopene All-trans-lycopene Lycopene psi,psi-Carotene CI 75125 E160(d) Natural yellow 27</p>	<p>Source of antioxidant(s)/Provides antioxidant(s).</p> <p>Antioxidant that helps fight/protect (cell) against/reduce (the oxidative effect of/the oxidative damage caused by/cell damage caused by) free radicals.</p> <p><i>For products providing at least 6,5 mg per day:</i> Helps to support prostate health. Products must contain more than 95 % lycopene.</p>	<p>Not suitable for children.</p> <p>Not suitable for patients diagnosed or suspected to suffer with prostate cancer.</p>	<p>20 mg</p>
<p>Sources: <i>Tomato extract; Blakeslea trispora (Whole); Citrullus lanatus var. lanatus (Fruit); Citrus aurantium (Fruit); Citrus limon (Fruit); Citrus paradisi (Fruit); Citrus sinensis (Fruit); Elaeis guineensis (Fruit); Rosa canina (Fruit); Solanum lycopersicum (Fruit); Solanum lycopersicum (Fruit flesh)</i></p>			
<p>Lutein (3R,3'R,6'R)-beta,epsilon-Carotene-3,3'-diol (3R,3'R,6'R)-beta,epsilon-Carotene-3,3'-diol CI 75125 E161(b) Mixed carotenoids (comprising xanthophylls and zeaxanthin) Vegetable lutein Vegetable luteol Xanthophylls</p>	<p>Antioxidant for the maintenance of good health/eye health.</p> <p>Antioxidant that helps fight/protect (cell) against/reduce (the oxidative effect of/the oxidative damage caused by/cell damage caused by) free radicals.</p> <p><i>For products providing at least 6 mg per day:</i> Helps to maintain/support eyesight in certain conditions (associated with sunlight damage), such as cataracts and age-related macular degeneration.</p>		<p>6 mg</p> <p><i>When combined with Zeaxanthin as "Marigold Extract", maximum acceptable daily intake 2,0 mg/kg of body weight.</i></p>

Carotenoid	Health Supplement Claim	Specified Warning(s)	Dosage
B. Carotenoids mainly used as Anti-oxidants			
	<p>Helps to reduce the risk of developing cataracts.</p> <p>Helps to improve macular pigment optical density.</p>		
<p>Sources: <i>Oleoresin from the flower of marigold (Tagetes erecta L.(Asteraceae)); Arnica montana (Flower); Capsicum annum (Fruit); Cucurbita pepo (Flower); Fucus vesiculosus (Whole); Oryza sativa (Whole plant); Pisum sativum (Whole plant); Solanum lycopersicum (Fruit); Tagetes erecta (Flower); Tagetes erecta (Herb flowering oleoresin); Tagetes erecta (Petal); Taraxacum officinale (Flower); Tussilago farfara (Flower); Viscum album (Leaf)</i></p>			
<p>Lutein Esters</p> <p>Sources: <i>Oleoresin from the flower of marigold (Tagetes erecta L.(Asteraceae))</i></p>	As for Lutein	As for Lutein	As for Lutein
<p>Zeaxanthin <i>(3R,3'R)-beta,beta-Carotene-3,3'-diol</i> <i>All-trans-beta-Carotene-3,3'-diol</i> <i>Anchovyxanthin</i> <i>beta-Carotene-3,3'-diol</i> <i>meso-zeaxanthin</i> <i>Zeaxanthol</i></p>	<p>Antioxidant for the maintenance of eye health.</p> <p>Helps to maintain eyesight / eye health in conditions (associated with sunlight damage), such as cataracts and age-related macular degeneration.</p> <p>Helps to reduce the risk of developing cataracts.</p> <p>Helps to improve macular pigment optical density.</p>		<p>6 mg</p> <p><i>When combined with Zeaxanthin as "Marigold Extract", maximum acceptable daily intake 2,0 mg/kg of body weight.</i></p>
<p>Sources: <i>Oleoresin from the flower of marigold (Tagetes erectaL.(Asteraceae)); Arnica montana (Flower); Asparagus officinalis (Whole plant); Berberis vulgaris (Whole plant); Camellia sinensis (Leaf); Capsicum annum (Fruit); Capsicum frutescens (Fruit); Carica papaya (Fruit); Citrus aurantiifolia (Fruit); Citrus aurantium (Fruit); Citrus bergamia (Fruit); Citrus limon (Leaf); Citrus medica var. sarcodactylis (Fruit); Citrus paradisi (Fruit); Citrus reticulata (Fruit); Citrus sinensis (Fruit); Crocus sativus (Peta); Crocus sativus (Stigma and style); Cucurbita pepo (Flower); Dunaliella salina (Whole); Eschscholzia californica (Whole plant)</i> <i>Fucus vesiculosus (Whole); Hippophae rhamnoides (Fruit); Lycium chinense (Fruit); Medicago sativa (Whole plant); Momordica charantia (Fruit); Nannochloropsis gaditana (Broken cell); Palmaria palmata (Whole plant); Prunus persica (Fruit); Rosa canina (Fruit); Solanum lycopersicum (Fruit); Tagetes erecta (Flower); Tagetes erecta (Herb flowering oleoresin); Zea mays (Seed); Zea mays (Whole plant)</i></p>			
<p>Zeaxanthin Esters</p> <p>Sources: <i>Oleoresin from the flower of marigold (Tagetes erecta L.(Asteraceae))</i></p>	As for Zeaxanthin		2 mg

Carotenoid	Health Supplement Claim	Specified Warning(s)	Dosage
C. Carotenoids used as food colorants but with possible physiological effects:			
<p>Bixin (2Z,4Z,6Z,8E,10Z,12E,14E,16E,18E)-20-methoxy-4,8,12,16-tetramethyl-20-oxo-icosa-2,4,6,8,10,12,14,16,18-nonaenoic acid. 6,6prime-Diapo-psi,psi-carotenedioic acid mono methyl ester. Methyl (9-cis)-hydrogen-6,6'-diapo-psi,psi-carotenedioate. Annatto Annatto extracts (bixin, norbixin) Bixa orellana extract CI 75120 CI Natural Orange 4 E160(b)</p>	<p>Allowed as colouring agent only. Role as a Health Supplement: COMMENT INVITED.</p>		<p>12 mg/kg body weight</p>
<p>Sources: Annatto, a natural food colouring obtained from the seeds of the achiote tree (<i>Bixa orellana</i>).</p>			
<p>Rhodoxanthin 4,5'-retro-beta,beta-Carotene-3,3'-dione, 4',5'-didehydro-. E161f.</p>	<p>Allowed as colouring agent only. Role as a Health Supplement: COMMENT INVITED.</p>		<p><u>ADDITIONAL COMMENT INVITED.</u></p>
<p>Sources: Seeds of the poisonous yew tree (<i>Taxus baccata</i>), and <i>Aloe arborescens</i> It is extracted via hexane solvent and normally contains other source plant material.</p>			

Carotenoid	Health Supplement Claim	Specified Warning(s)	Dosage
D. Carotenoids mainly used as colourants:			
<p>Capsanthin (2E,4E,6E,8E,10E,12Z,14Z,16E,18E)- 19-(4-hydroxy-2,6,6-trimethyl-1- cyclohexenyl)-1-(4-hydroxy-1,2,2- trimethyl-cyclopentyl)-4,8,13,17- tetramethyl-nonadeca- 2,4,6,8,10,12,14,16,18-nonaen-1-one. (3R,3'S,5'R)-3,3'-Dihydroxy-beta,kappa- caroten-6'-one 3,3'-Dihydroxy-beta,kappa-caroten- 6'one beta,kappa-Caroten-6'one, 3,3'dihydroxy- Capsanthin/capsorubin, Capsicum fruit oleoresin, Paprika oleoresin.</p> <p>Sources: Capsicum annuum (Fruit)</p>	<p>Allowed as colouring agent only.</p>		<p>4 mg</p>
<p>Capsorubin (2E,4Z,6Z,8E,10E,12E,14Z,16Z,18E)- 1,20-bis[(1R,4S)-4-hydroxy-1,2,2- trimethyl-cyclopentyl]-4,8,13,17- tetramethyl-icosa- 2,4,6,8,10,12,14,16,18-nonaene-1,20- dione (3S,3'S,5R,5'R)-3,3'-Dihydroxy- kappa,kappa-carotene-6,6'-dione</p> <p>Sources: Capsicum annuum (Fruit)</p>	<p>Allowed as colouring agent only.</p>		

Carotenoid	Health Supplement Claim	Specified Warning(s)	Dosage
D. Carotenoids mainly used as colourants:			
<p>Flavoxanthin <i>(2R,6S,7aR)-2-[17-[(1R,4R)-4-hydroxy-2,6,6-trimethyl-1-cyclohex-2-enyl]-6,11,15-trimethyl-heptadeca-2,4,6,8,10,12,14,16-octaen-2-yl]-4,4,7a-trimethyl-2,5,6,7-tetrahydrobenzofuran-6-ol</i> <i>beta,epsilon-Carotene-3,3'-diol, 5,8-epoxy-5,8-dihydro-, (3S,3'R,5R,6'R,8R)-</i> CI 75135 E161(a)</p> <p>Source Material: <i>Prunus armeniaca</i> (Fruit) <i>Prunus domestica</i> (Fruit) <i>Sambucus nigra subsp. nigra</i> (Fruit) <i>Taraxacum officinale</i> (Flower)</p>	<p>Allowed as colouring agent only.</p>		<p>5 mg/kg body weight</p>
<p>Rubixanthin <i>beta-4-Caroten-3-ol, (3R)-</i> CI 75135 E161(d) Natural yellow 27</p> <p>Sources: Isolated from rose hips, (<i>Rosa rubiginosa</i>)</p>	<p>Allowed as colouring agent only.</p>		

Carotenoid	Health Supplement Claim	Specified Warning(s)	Dosage
E. Other carotenoids with possible physiological effects:			
<p>Fucoxanthin (3S,3'S,5R,5'R,6S,6'R)-6',7'-Didehydro-5,6-epoxy-4',5',6,7-tetrahydro-3,3',5'-trihydroxy-beta,beta-caroten-8(5H)-one</p> <p>Source Material: Laminaria japonica (Whole) Undaria pinnatifida (Whole)</p>	<p><u>COMMENT INVITED.</u></p>		<p>Min: 2,4 mg – Max: 8 mg</p>
<p>Neoxanthin (1R,3S)-6-[(3E,5E,7E,9E,11E,13E,15Z,17E)-18-[(1R,3S,6S)-3-hydroxy-1,5,5-trimethyl-7-oxabicyclo[4.1.0]hept-6-yl]-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaenylidene]-1,5,5-trimethylcyclohexane-1,3-diol. beta,beta-Carotene, 6,7-didehydro-5',6'-epoxy-5,5',6,6'-tetrahydro-3,3',5'-trihydroxy-, (3S,3'S,5R,5'R,6R,6'S,9'-cis)-. Foliaxanthin</p> <p>Source Material: Capsicum annuum (Fruit) Prunus domestica (Fruit) Prunus persica (Fruit)</p>	<p><u>COMMENT INVITED.</u></p>		
<p>Xanthophyll Marigold (<i>Tagetes erecta</i>) extract Marigold extract</p> <p>Sources: Oleo-resin from the flower of marigold (<i>Tagetes erecta</i> L. (Asteraceae))</p>	<p>NOTE: Xanthophylls may include the carotenoids lutein, zeaxanthin, neoxanthin, flavoxanthin, and cryptoxanthin. Applicants must stipulate the source of the Xanthophyll and individual carotenoids included.</p>		