Health Canada Santé Canada

NATURAL HEALTH PRODUCT

MULTIPLE INGREDIENT JOINT HEALTH PRODUCTS

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredients.

Notes

- Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant's discretion.
- The solidus (/) indicates that the terms and/or statements are synonymous. Either term or statement may be selected by the applicant.

Date February 25, 2019

Proper name(s), Common name(s), Source material(s)

Table 1. Proper name(s), Common name(s), Source material(s)[1]

Proper name(s)	Common name(s)	Source material(s)				
		Common name(s)	Proper name(s)	Organism group(s)	Part(s)	Preparation
▸ All-trans-beta-carotene ▸ Beta-carotene	▸ All-trans-beta-carotene ▸ Beta-carotene	Beta-carotene	N/A	N/A	N/A	N/A
Boron	Boron	NNHPD Multi-Vitamin/Mineral Supplements monograph	N/A	N/A	N/A	N/A
Boswellia serrata	▸ Boswellia ▸ Indian frankincense ▸ Indian olibanum ▸ Indian olibanum-tree ▸ Shallaki	N/A	*Boswellia serrata*	N/A	▸ Stem bark oleogum resin ▸ Trunk bark oleogum resin	N/A
Fruit bromelain	▸ Fruit bromelain ▸ Juice bromelain ▸ Pineapple fruit bromelain	N/A	▸ *Ananas comosus* var. *bracteatus* ▸ *Ananas comosus* var. *comosus*	N/A	Fruit	N/A

Proper name(s)	Common name(s)	Source material(s)				
		Common name(s)	Proper name(s)	Organism group(s)	Part(s)	Preparation
Stem bromelain	▸ Stem bromelain ▸ Bromelain ▸ Pineapple stem bromelain	N/A	▸ *Ananas comosus* var. *bracteatus* ▸ *Ananas comosus* var. *comosus*	N/A	Stem	N/A
Calcium	Calcium	NNHPD Multi-Vitamin/Mineral Supplements monograph	N/A	N/A	N/A	N/A
Chondroitin sulfate[2]	Chondroitin sulfate	Sodium chondroitin sulfate	▸ *Anas platyrhynchos* ▸ *Anser anser* ▸ *Bos taurus* ▸ *Cygnus olor* ▸ *Dromaius novaehollandiae* ▸ *Gallus gallus* ▸ *Meleagris gallopavo* ▸ *Numida meleagris* ▸ *Rhea americana* ▸ *Struthio camelus* ▸ *Sus scrofa*	N/A	Cartilage	N/A
(1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione	Curcumin	N/A	*Curcuma longa*	N/A	Rhizome	N/A
Curcuma longa	▸ Common turmeric ▸ Curcuma ▸ Indian-saffron ▸ Jianghuang ▸ Turmeric ▸ Yellow ginger	N/A	*Curcuma longa*	N/A	Rhizome	Dried
Harpagophytum procumbens	▸ Devil's claw ▸ Grapple plant ▸ Wood spider	N/A	*Harpagophytum procumbens*	N/A	Secondary root tubers	Dried
Harpagophytum zeyheri	▸ Devil's claw ▸ Grapple plant	N/A	*Harpagophytum zeyheri*	N/A		

Proper name(s)	Common name(s)	Source material(s)				
		Common name(s)	Proper name(s)	Organism group(s)	Part(s)	Preparation
Fish oil	Fish oil	N/A	N/A	▸ Ammodytidae ▸ Carangidae ▸ Clupeidae ▸ Engraulidae ▸ Osmeridae ▸ Salmonidae ▸ Scrombridae	Whole	N/A
2-Amino-2-deoxy-beta-D-glucopyranose hydrochloride	▸ Glucosamine HCl ▸ Glucosamine hydrochloride	Glucosamine hydrochloride	N/A	▸ Crab[3] ▸ Krill[3] ▸ Lobster[3] ▸ Prawn[3] ▸ Shrimp[3]	Exoskeleton	N/A
			▸ *Aspergillus flavus var. oryzae* ▸ *Aspergillus melleus* ▸ *Aspergillus niger* ▸ *Aspergillus niger var. awamori* ▸ *Monascus pilosus* ▸ *Monascus purpureus* ▸ *Rhizopus orysae*	N/A	Whole	Fermented
2-Amino-2-deoxy-D-glucose sulfate	Glucosamine sulfate	▸ Glucosamine Sulfate Potassium Chloride ▸ Glucosamine Sulfate Sodium Chloride	N/A	▸ Crab[3] ▸ Lobster[3] ▸ Prawn[3] ▸ Shrimp[3]	Exoskeleton	N/A
			▸ *Aspergillus flavus var. oryzae* ▸ *Aspergillus melleus* ▸ *Aspergillus niger* ▸ *Aspergillus niger var. awamori* ▸ *Monascus pilosus* ▸ *Monascus purpureus* ▸ *Rhizopus oryzae*	N/A	Whole	Fermented

Proper name(s)	Common name(s)	Source material(s)				
		Common name(s)	Proper name(s)	Organism group(s)	Part(s)	Preparation
Hyaluronic acid[4]	Hyaluronic acid	Sodium Hyaluronate	*Gallus gallus*	N/A	Comb	N/A
		▸ Hyaluronic acid ▸ Sodium Hyaluronate	*Streptococcus equi*	N/A	Extracellular capsule	Fermented
Hydrolyzed collagen[5]	▸ Collagen hydrolysate ▸ Hydrolyzed collagen	N/A	N/A	Bovine	Skin/hide	N/A
				Porcine	▸ Bone ▸ Skin	
				Fish	▸ Bone ▸ Skin	
				Chicken	Cartilage	
Magnesium	Magnesium	NNHPD Multi-Vitamin/Mineral Supplements monograph	N/A	N/A	N/A	N/A
Manganese	Manganese					
▸ Dimethyl sulfone ▸ Methylsulfonylmethane ▸ Sulfonylbismethane	▸ Methylsulfo-nylmethane ▸ MSM	Dimethyl sulfone	N/A	N/A	N/A	Synthetic
Salix alba	White willow	N/A	*Salix alba*	N/A	Bark	Dried
Vitamin A	Vitamin A	NNHPD Multi-Vitamin/Mineral Supplements monograph	N/A	N/A	N/A	N/A
Vitamin C	▸ Vitamin C ▸ Ascorbic acid					
Vitamin D	▸ Vitamin D ▸ Vitamin D_2 ▸ Vitamin D_3					
Vitamin K_1	Vitamin K_1					
Vitamin K_2	Vitamin K_2					

[1] References: Proper names: ChemIDPlus 2018, USDA 2018, O'Neil 2013, Martindale 2012, Ph.Eur. 2012, USP 35 2012, ICIDH 2008, Kralovec and Barrow 2008, Towheed and Anastassiades 2007, O'Neil et al. 2006, IUBMB 1992;Common names: ChemIDPlus 2018, USDA 2018, O'Neil 2013, BP 2012, Martindale 2012, Ph.Eur. 2012, USP 35 2012, Goel et al. 2008, ICIDH 2008, Kralovec and Barrow 2008, Towheed and Anastassiades 2007, O'Neil et al. 2006, Boon and Smith 2004, McGuffin et al. 2000, Moskowitz 2000, IUBMB 1992, Deodhar et al. 1980; Source materials: Froese and Pauly. 2018, USDA 2018, O'Neil 2013, Martindale 2012, Ph.Eur. 2012,Schauss et al. 2012, Sitanggang et al. 2012, USP 35 2012, EP 2011, ITIS 2011, FCC 7 2010, Khan and Abourashed 2010, Evans 2009, Yoshida et al. 2009, Goel et al. 2008, Kalman et al. 2008, Kralovec and Barrow 2008, NIH 2008, Sato and Iwaso 2008, Chmielowski et al. 2007, Schrieber and Gareis 2007, Dahiya et al 2006, O'Neil et al. 2006, Chong et al. 2005, PPRC 2005, Boon and Smith 2004, Wichtl 2004, Baziwane and He 2003, ESCOP 2003, Barnes et al. 2002, Sato et al. 2002, Blumenthal et al. 2000, BHC 1992, Deodhar et al. 1980.

[2] Cartilage must be derived from healthy and domestic animals used for food by humans (USP 35 2012).

[3] The specific organisms used as source material(s) must be indicated in the Animal Tissue Form (ATF); simply indicating "crustaceans" is insufficient.

[4] The stabilizing salt (i.e. sodium) if present should be indicated.

[5] For the purpose of this monograph, hydrolyzed collagen has no jelling power and is soluble in cold water (Schrieber and Gareis 2007; Moskowitz 2000). The average molecular weight of hydrolyzed collagen is approximately 2-6 kDa (Moskowitz 2000; Oesser *et al*. 1999).

Route of administration

Oral

Dosage form(s)

This monograph excludes foods or food-like dosage forms as indicated in the Compendium of Monographs Guidance Document.

Acceptable dosage forms for the age category listed in this monograph and specified route of administration are indicated in the Compendium of Monographs Guidance Document.

Use(s) or Purpose(s)

Refer to Tables 2 and 3.

Notes

- It is mandatory for all products to cite at least one use or purpose statement from Table 2.
- A use or purpose statement is acceptable only if at least one medicinal ingredient associated with that statement is present at a dose at or above the minimum daily dose listed in Table 2.
- Medicinal ingredients which do not meet the minimum daily dose for a use or purpose statement will be considered as acceptable complementary medicinal ingredients in product formulations.
- The daily dose for glucosamine hydrochloride in combination with glucosamine sulfate is subject to the following limitations: the sum of the percentages of their individual maximum daily doses must not exceed 120%; [(e.g. a product providing a daily dose of 2000 mg glucosamine hydrochloride (100% of the 2000 mg maximum daily dose) + 300 mg glucosamine sulfate (20% of the 1500 mg maximum daily dose) would be acceptable (100%+20%=120%)].
- Claims for traditional use must include the term “Herbal Medicine”, “Traditional Chinese Medicine”, or “Ayurveda”.

Dose(s)

Subpopulation(s)

Adults 18 years and older

Quantity(ies)

Refer to Tables 2 and 3.

Table 2. Joint health uses or purposes and associated daily doses

Medicinal ingredients	Uses or purposes[1]	Methods of preparation	Dose/day		Single dose
			Minimum[2]	Maximum[3]	Maximum single dose[3]
Boswellia serrata	Helps to relieve joint pain and swelling associated with osteoarthritis of the knee.	Standardized extracts	1,000 mg extracts standardized to 40% boswellic acid	1,000 mg extracts standardized to 40% boswellic acid	333 mg extracts standardized to 40% boswellic acid
Chondroitin sulfate	Helps to relieve (joint) pain associated with osteoarthritis (of the knee).	Isolate	800 mg	1,200 mg	N/A
Curcumin	Used in Herbal Medicine to help relieve joint inflammation.	Isolate	1,200 mg	1,200 mg	400 mg
Turmeric	(Traditionally) used in Herbal Medicine as an anti-inflammatory to help relieve joint pain.	Dry, Powder, Non-Standardised Extracts (Dry extract, Tincture, Fluid extract, Decoction, Infusion)	1,000 mg dried rhizome; For dry extracts, maximum ratio is 25:1	9,000 mg dried rhizome; For dry extracts, maximum ratio is 25:1	N/A
		Standardized extracts	Extracts providing up to 35% curcuminoids and a Quantity crude equivalent of 1,000 mg dried rhizome	Extracts providing up to 35% curcuminoids and a Quantity crude equivalent of 9,000 mg dried rhizome	
Devil's claw	Used in Herbal Medicine to help relieve joint pain associated with osteoarthritis.	Dry, Powder, Non-Standardised Extracts (Dry extract, Tincture, Fluid extract, Decoction, Infusion)	600 mg dried secondary root tubers	7,500 mg dried secondary root tubers	N/A

Medicinal ingredients	Uses or purposes[1]	Methods of preparation	Dose/day		Single dose
			Minimum[2]	Maximum[3]	Maximum single dose[3]
Fish oil[4]	In conjunction with conventional therapy, helps to reduce the pain of rheumatoid arthritis.	Standardized fixed oil	2,800 mg eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) with a EPA:DHA ratio of 0.5:1-2:1	5,000 mg EPA + DHA with a EPA:DHA ratio of 0.5:1-2:1	N/A
Glucosamine hydrochloride	Helps to maintain healthy cartilage/ joint health.	Isolate	1,500 mg	2,000 mg	N/A
Glucosamine sulfate	▸ Helps to relieve joint pain associated with osteoarthritis (of the knee). ▸ Helps to protect against the deterioration of cartilage. ▸ A factor in maintaining healthy cartilage and/or joint health.	Isolate	1,500 mg	1,500 mg	N/A
Hyaluronic acid	Helps support joint health.	Isolate	48 mg (sourced from *Gallus gallus* comb)	120 mg (sourced from *Gallus gallus* comb)	N/A
			120 mg (sourced from microbial fermentation)	200 mg (sourced from microbial fermentation)	
Hydrolyzed collagen	Helps to reduce joint pain associated with osteoarthritis.	Isolate	1,200 mg	10,000 mg	N/A
Methysulfonylmethane (MSM)	Helps to relieve (joint) pain associated with osteoarthritis (of the knee).	N/A	1,500 mg	6,000 mg	2,000 mg
White willow	(Traditionally) used in Herbal Medicine for the relief of minor joint pain (due to osteoarthritis).	Dry, Powder, Non-Standardised Extracts (Dry extract, Tincture, Fluid extract, Decoction, Infusion)	3,000 mg dried bark	9,000 mg dried bark	3,000 mg dried bark
		Standardized extracts	45 mg total salicin	240 mg total salicin	120 mg total salicin

[1] At least two of the following references were consulted per use or purpose: Bruyère et al. 2012; Benito-Ruiz et al. 2009; EMEA 2009; Yoshida et al. 2009; Clark et al. 2008; Winston and Kuhn 2008; Herrero-Beaumont et al. 2007; Mazières et al. 2007; Sontakke et al. 2007; Towheed and Anastassiades 2007; Kim et al. 2006; Mills and Bone 2005; Uebelhart et al. 2004; Usha and Naidu 2004; Braham et al. 2003; ESCOP 2003; Hoffmann 2003; Kimmatkar et al. 2003; Pavelka et al. 2002; Sato et al. 2002; Mazières et al. 2001; Reginster et al. 2001; Thie et al. 2001; Blumenthal et al. 2000; Mills and Bone 2000; Volker et al. 2000; Houpt et al. 1999; Bourgeois et al. 1998; Bucsi and Poor 1998; Uebelhart et al. 1998; Sköldstam et al. 1992; Deodhar et al. 1980.

[2] At least one of the following references was consulted per minimum dose: Bruyère et al. 2012; Benito-Ruiz et al. 2009; EMEA 2009; WHO 2009; Yoshida et al. 2009; Clark et al. 2008; Kalman et al. 2008; Herrero-Beaumont et al. 2007; Mezieres et al. 2007; Sontakke et al. 2007; Fitzpatrick 2005; Mills and Bone 2005; Boon and Smith 2004; Uebelhart et al. 2004; Usha and Naidu 2004; Wichtl 2004; ESCOP 2003; Hoffmann 2003; Kimmatkar et al. 2003; Williamson 2003; Barnes et al. 2002; Pavelka et al. 2002; Mezieres et al. 2001; Reginster et al. 2001; Blumenthal et al. 2000; Volker et al. 2000; Houpt et al. 1999; Bucsi and Poor 1998; Uebelhart et al. 1998; Deodhar et al. 1980.

[3] At least one of the following references was consulted per maximum dose: Bruyère et al. 2012; Benito-Ruiz et al. 2009; EMEA 2009; WHO 2009; Clark et al. 2008; Sato et Iwaso 2008; Herrero-Beaumont et al. 2007; Sontakke et al. 2007; Hathcock and Shao 2006; Kim et al. 2006; Mills and Bone 2005; Boon and Smith 2004; Wichtl 2004; Braham et al. 2003; ESCOP 2003; Kimmatkar et al. 2003; Williamson 2003; Barnes et al. 2002; Pavelka et al. 2002; Sato et al. 2002; Reginster et al. 2001; Blumenthal et al. 2000; Bourgeois et al. 1998; US FDA 1997; BHC 1992; Deodhar et al. 1980.

[4] The EPA:DHA ratio for fish oil must be between 0.5:1 and 2:1 (Volker et al. 2000; Sköldstam et al. 1992) and potency must be expressed as the quantity (mg) and/or percent (%) of EPA and DHA (% w/w) relative to the total quantity of fish oil.

Table 3. Uses or purposes related to joint and bone health and associated daily doses

Medicinal ingredients	Uses or purposes[1]	Methods of preparation	Dose/day		Single dose
			Minimum[2]	Maximum[3]	Maximum/ single dose[3]
Beta-carotene	Provitamin A/Source of vitamin A to help/helps in the development and maintenance of bones.	N/A	390 µg	18,000 µg	N/A
Boron	Helps maintain healthy calcium metabolism.	N/A	0.7 mg	3.36 mg	N/A
Fruit Bromelain[4] Stem Bromelain[4]	Used in herbal medicine to help relieve minor pain, swelling and inflammation.	Isolate	480,000 FCC papain units (PU)[4]	20,000,000 FCC PU[4]	10,000,000 FCC PU
Calcium	▸ Adequate calcium (and vitamin D) (throughout life) as part of a healthy diet, (along with physical activity) may help prevent bone loss/ osteoporosis/may reduce the risk of developing osteoporosis (in peri- and postmenopausal women) (in later life). ▸ As part of a healthy diet (when taken with Vitamin D) may help prevent bone loss/osteoporosis. ▸ Helps in the development and maintenance of bones. ▸ Helps support bone health.	N/A	65 mg	1,500 mg	N/A

Medicinal ingredients	Uses or purposes[1]	Methods of preparation	Dose/day		Single dose
			Minimum[2]	Maximum[3]	Maximum/ single dose[3]
Magnesium	Helps in the development and maintenance of bones.	N/A	20 mg	500 mg	N/A
Manganese	Helps in the development and maintenance of bones.	N/A	0.13 mg	9 mg	N/A
Vitamin A	▸ Helps in the development and maintenance of bones. ▸ Helps to build strong bones	N/A	65 µg RAE	All-trans retinol: 3,003 µg RAE All-trans retinyl acetate: 3,000 µg RAE All-trans retinyl palmitate: 3,022 µg RAE	N/A
Vitamin C	▸ Helps in the development and maintenance of bones. ▸ Helps in collagen formation to maintain healthy bones.	N/A	6 mg	2,000 mg	N/A
Vitamin D	▸ Helps in the development and maintenance of bones. ▸ Calcium intake, when combined with sufficient Vitamin D, a healthy diet and regular exercise may reduce the risk of developing osteoporosis.	N/A	1 µg	25 µg	N/A
Vitamin K_1 Vitamin K_2 and total Vitamin K_1 + K_2	Helps in the maintenance of bones.	N/A	6 µg	120 µg	N/A

[1] At least two of the following references were consulted per use or purpose: HC 2018; Hunt 2012; FDA 2008; Tang et al. 2007; IOM 2006; NAMS 2006; Shils et al. 2006; Devirian and Volpe 2003; Brown and Josse 2002; Walker et al. 2002; Groff and Gropper 2000; NIH 2000; Blumenthal 1998; IOM 1997; Nielsen et al. 1987.

[2] At least one of the following references was consulted per minimum daily dose: HC 2018; Hunt 2012; IOM 2006; Walker et al. 2002; Blumenthal 1998.

[3] At least one of the following references was consulted per maximum daily dose: HC 2018; Hunt 2012; IOM 2006; Kerkhoffs et al. 2004; Singer et al. 2001.

[4] Dose information must include the quantities of both the enzyme preparation and its enzymatic activity, in FCC PU. The enzymatic activity quantity should be indicated in the Quantity/Unit field and its quantity of enzyme preparation in mg or ml in the Additional Quantity/Unit field. Note that:
One papain unit (PU) is defined as that quantity of enzyme that liberates the equivalent of 1 microgram of tyrosine per hour under the conditions of the assay (FCC 8 2012).
One gelatin digestion unit (GDU) is approximately equivalent to 15 000 FCC papain units (1 GDU ≈ 15 000 FCC PU).

Direction(s) for use

Table 4. Direction(s) for use

Medicinal ingredients	Daily dose	Directions for use[1]
Boron	All doses if product is not a source of Vitamin D and Calcium	Take with vitamin D and calcium.
► Fruit Bromelain ► Stem Bromelain	All doses (Optional)	Take with food/meal.
Calcium	All doses	Take with food, a few hours before or after taking other medications or natural health products.
Methysulfonylmethane (MSM)	1,500 mg or more MSM	► Take with food. ► Avoid taking at bedtime.

[1] The following references were consulted for the directions for use: Boron: Devirian and Volpe 2003; Zittermann 2003; Calcium: Sweetman 2015, IOM 2011, ASHP 2005; MSM: Kim et al. 2006.

Duration(s) of use

Notes

- A minimum duration of use statement is required for all products citing use or purpose statements associated with boswellia, chondroitin sulfate, devil's claw, glucosamine (hydrochloride and sulfate), hydrolyzed collagen or methysulfonylmethane (MSM).
- If more than one duration of use statement is indicated for a particular product formulation, only the shortest applicable duration of use statement is required on the PLA and product label. For example, a product citing use or purpose statements for chondroitin sulfate and glucosamine hydrochloride need only include the following duration of use statement on the product label: "Use for at least 1 month to see beneficial effects."
- A maximum duration of use statement is required for all products containing bromelain or white willow.

Minimum duration(s) of use

Table 5. Minimum duration(s) of use

Medicinal ingredients	Minimum durations of use[1]
Hydrolyzed collagen	Use for at least 5 months to see beneficial effects.
Chondroitin sulfate	Use for at least 3 months to see beneficial effects.
Devil's claw	Use for at least 2-3 months to see beneficial effects.
Boswellia	Use for at least 2 months to see beneficial effects.

Medicinal ingredients	Minimum durations of use[1]
Glucosamine hydrochloride	Use for at least1 month to see beneficial effects.
Glucosamine sulfate	
Methysulfonylmethane (MSM)	

[1] At least one of the following references was consulted per duration of use: Bruyère et al. 2012; Benito-Ruiz et al. 2009; Clark et al. 2008; Bjordal et al. 2007; Mehta et al. 2007; Sontakke et al. 2007; Kim et al. 2006; Usha and Naidu 2004; ESCOP 2003; Kimmatkar et al. 2003; Houpt et al. 1999; Qiu et al. 1998.

Maximum duration(s) of use

Products containing bromelain and/or white willow

Consult a health care practitioner/health care provider/health care professional/doctor/physician for prolonged use (EMEA 2009; Beer and Wegener 2008; Biegert et al. 2004; Chrubasik 2000).

Risk Information

Caution(s) and warning(s)

All products

- Consult a health care practitioner/health care provider/health care professional/doctor/ physician prior to use if you are pregnant or breastfeeding.
- Consult a health care practitioner/health care provider/health care professional/doctor/ physician if symptoms worsen.

Products containing following medicinal ingredients

Table 6. Caution(s) and warning(s)

Medicinal ingredients	Daily dose	Cautions and warnings[1]
Beta-carotene	More than 6,000 µg	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are a tobacco smoker.
Boron	All doses	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have been diagnosed with estrogen-dependant cancer or have a kidney disorder.

▸ Fruit Bromelain ▸ Stem Bromelain	All doses	▸ Consult a health care practitioner/health care provider/ health care professional/doctor/physician prior to use if you have gastrointestinal lesions/ulcers or are having a surgery. ▸ Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are taking an anticoagulant agents, anti-inflammatory agents or antibiotics.
Curcumin	All doses	▸ Consult a health care practitioner /health care provider/ health care professional/doctor/physician prior to use if you are taking antiplatelet medication or blood thinners. ▸ Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have gallstones, bile duct obstruction, stomach ulcers or excess stomach acid.
Fish oil AND White willow combined	All doses	▸ Consult a health care practitioner/health care provider/ health care professional/doctor/physician prior to use if you have a gastrointestinal lesion/ulcer or are having a surgery. ▸ Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are taking blood thinners.
Manganese	More than 5 mg	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have a liver disorder.
Turmeric	All doses	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have gallstones, bile duct obstruction, stomach ulcers or excess stomach acid.
Vitamin K_1 and/or K_2	All doses	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are taking blood thinners.
White willow	All doses	▸ Consult a health care practitioner/health care provider/ health care professional/doctor/physician prior to use if you have asthma or peptic ulcer disease. ▸ Consult a health care practitioner/health care provider/ health care professional/ doctor/physician prior to use if you are taking anticoagulants or products containing acetylsalicylic acid (ASA) or other salicylates.

[1]The following references were consulted for the caution and warning statements: Beta-carotene: Touvier et al. 2005; Omenn et al. 1996; ATBC 1994; Boron: Usuda et al. 1996; Nielsen et al. 1992; Fruit/Stem Bromelain: Martindale 2011; Brinker 2010; Blumenthal et al. 2000; Curcumin: Brinker 2010; ESCOP 2003; McGuffin et al. 1997; Curcumin : Brinker 2010; Mills and Bone 2005; ESCOP 2003; McGuffin et al. 1997; Fish oil AND White willow combined: Block et al. 2012, 2013; Larson et al. 2008; Manganese: IOM 2006; IOM 2001; Krieger et al. 1995; Turmeric: Brinker 2010; ESCOP 2003; McGuffin et al. 1997; Vitamin K1, K2: ASHP 2005; Franco et al 2004; IOM 2001; Hansten et al 1997; White willow: EMEA 2009.

Contraindication(s)

Products containing white willow

- Do not use this product if you are pregnant or breastfeeding (Brinker 2010; EMEA 2009; Wichtl 2004; ESCOP 2003; Barnes et al. 2002; Blumenthal et al. 2000).
- Do not use this product if you are allergic to acetylsalicylic acid (ASA) or other salicylates (Brinker 2010; EMEA 2009; Wichtl 2004, ESCOP 2003; Barnes et al. 2002; Blumenthal et al. 2000).

Known adverse reaction(s)

Products containing boswellia and/or bromelain

Stop use if hypersensitivity/allergy occurs (Martindale 2011; Brinker 2010; WHO 2009; Murray and Pizzorno 2006; Blumenthal et al. 2000; Baur and Fruhmann 1979).

Products containing boswellia, bromelain, hydrolyzed collagen, methysulfonylmethane and/or white willow

Stop use if diarrhoea, abdominal pain, heartburn, nausea or vomiting occur (Martindale 2011; Brinker 2010; EMEA 2009; Sontakke et al. 2007; Brien et al. 2006; Kim et al. 2006; Wichtl 2004; ESCOP 2003; Kimmatkar et al. 2003; Barnes et al. 2002; Blumenthal et al. 2000; McGuffin 2000; Moskowitz 2000).

Products providing more than 350 mg magnesium per day

Some people may experience diarrhoea (IOM 2006, IOM 1997).

Non-medicinal ingredients

Must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in that database.

Storage conditions

All products

Store in airtight container, protected from light (Ph.Eur. 2012; USP 35 2012).

Products containing fish oil, except those encapsulated

Refrigerate after opening (Wille and Gonus 1989).

Products containing hydrolyzed collagen

Protect from heat and moisture (Ph.Eur. 2012).

Specifications

- The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Products Directorate (NNHPD) Quality of Natural Health Products Guide.
- The medicinal ingredient must comply with the requirements outlined in the NHPID.

- *Ingredients sourced from bovine tissues*

  In order to minimize the risk of Transmissible Spongiform Encephalopathies (TSEs) from products sourced from bovine tissues, product licence applicants must have a veterinary certificate on file and must ensure that the following criteria have been met (Ph.Eur. 2012):

  i. Source animal is fit for human consumption;
  ii. Source material can be traced back to the herd or animal;
  iii. Avoidance of cross-contamination with high-infectivity tissues is ensured during sourcing;
  iv. Manufacturing procedures that are known to reduce infectivity are implemented (e.g. procedures that are in accordance with those outlined in Chapter 5.02.08 of the European Pharmacopoeia 2012 ‘Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products’).

- *Fish oil*

  i. Peroxide, anisidine, and totox values of fish oil and omega-3 fatty acids derived from fish oil must be in accordance with the methods set out by the Association of Analytical Community (AOAC) and/or Pharmacopoeial analytical methods. These specifications are necessary to ensure the oxidative stability of the fish oil and the omega-3 fatty acids derived from fish oil (HC 2015). The maximum peroxide value (PV) must be 5 mEq/kg, the maximum anisidine value (AV) must be 20 while the maximum Totox value must be 26 (calculated as 2 X PV + AV).
  ii. The dioxins, polychlorinated dibenzo-*para*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs); the dioxin-like polychlorinated biphenyls (dioxin-like PCBs; and the polychlorinated biphenyls (PCBs) are contaminants in oils from marine sources. Testing for these contaminants are required. Testing should be performed using appropriate analytical methods, such as method No. 1613 revision B of the Environmental Protection Agency for PCDDs and PCDFs and method No. 1668B of the Environmental Protection Agency for chlorinated biphenyl congeners (Ph. Eur: EPA 2008; EPA 1994). Licence holders are advised to consult the Commission of the European Communities documents on dioxins and dioxin-like PCB contaminants in marine oil for further information (EU 2006a.b; EU 2001). Refer to Section 3.3.8 of the Quality of Natural Health Products Guide for more information on the acceptable limits of dioxins and dioxin-like PCBs.

- *Bromelain*
    i. Details of the manufacturing of the enzyme at the raw material stage should include fermentation medium, and the isolation process of the medicinal ingredient.
    ii. The specifications must include testing for enzymatic activity of the medicinal ingredient at appropriate stages of formulation and manufacturing using the assay outlined in the current Food Chemicals Codex (FCC): PLANT PROTEOLYTIC ACTIVITY.
    iii. Where published methods are not suitable for use, manufacturers will use due diligence to ensure that the enzymes remain active to the end of the shelf life indicated on the product label.

- *Chondroitin sulfate*
    The medicinal ingredient must either: i. Comply with the specifications outlined in the Chondroitin Sulfate Sodium Monographs published in the British or European Pharmacopoeiae, or the United States Pharmacopoeia or, ii. Be cited in an approved NHP Master File, authorized by a letter of access issued to the applicant by the NHP Master File's registered owner

- *Hyaluronic acid*
    i. Information pertaining to the molecular weight of the hyaluronic acid must be available upon request for characterization (e.g. Certificate of Analysis, Technical Data Sheet, Product Information, etc). The molecular weight of hyaluronic acid obtained from *Gallus gallus* comb must be 800 kDa. The molecular weight of sodium hyaluronate from *Streptococcus equi* must be between 30-900 kDa
    ii. Information regarding Method of preparation must be provided upon request
    iii. For all products obtained through microbial fermentation, the species of Streptococcus used must be provided upon request and should be substantiated by the evidence. Information regarding manufacturing processes that reduce or eliminate pyrogenic or inflammatory components of the cell wall must be submitted upon request.
    iv. The content of sulfated glycosaminoglycans, nucleic acids, protein, and microbial contamination derived from this ingredient must be in accordance with the methods set out by the European Pharmacopoeia:
        - Sulfated glycosaminoglycans: maximum 1%, if the ingredient is extracted from *Gallus gallus* comb
        - Nucleic acids: the absorbance of solution at 260 nm is maximum 0.5
        - Protein: maximum 0.3%
        - Microbial contamination: Total Aerobic Microbial Count of 10^2 CFU/g

- *Hydrolyzed Collagen*
    i. For the purpose of this monograph, hydrolyzed collagen has no jelling power and is soluble in cold water (Schrieber and Gareis 2007; Moskowitz 2000).
    ii. The average molecular weight of hydrolyzed collagen is approximately 2-6 kDa (Moskowitz 2000; Oesser et al. 1999).

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