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Risk assessment of chondroitin sulfate in food supplements

Updated BfR Opinion No. 40/2018 of 7 December 2018¹

Chondroitin sulfate is a natural component of joint cartilage. The substance is contained in numerous products offered as food supplements which have market significance. Food supplements are foodstuffs. They serve the purpose of supplementing the normal diet. Chondroitin sulfate is not authorised as a medicinal product for oral use in the treatment of joint disease in Germany. Unlike medicinal products, food supplements are not generally subject to authorisation or official assessment before they are put onto the market. They must be safe and must not be harmful to health. The responsibility here lies with the manufacturers/distributors of the products. Their ingredients should not have substantial pharmacological effects.

The German Federal Institute for Risk Assessment (BfR) conducted a risk assessment of the use of chondroitin sulfate as an ingredient of food supplements in 2007. As a number of new scientific publications on the use of the substance by humans have appeared in the meantime, the BfR has updated its assessment.

Conducting the risk assessment of chondroitin sulfate as a constituent of food supplements, the BfR based its assessment on intake quantities of 800 – 1,200 mg/day, on the one hand because these daily intakes were used in most of the available human studies and on the other because the presented data is not sufficient to derive a dose-response relationship with regard to the occurrence of adverse health effects. The BfR explicitly points out that no statement on any possible pharmacological effect is connected with the present Opinion and that this does not constitute a recommendation to fully utilise daily intake quantities at this level in food supplements.

Most of the available human studies were conducted on patients suffering from arthritis. In the intake range of 800 – 1,200 milligrams per day (mg/day), the frequency (incidence) of adverse events observed in these studies was in most cases comparable to that of the placebo groups, who were not given the substance. Adverse gastrointestinal events, which were the most frequently observed adverse events, occurred to a lesser degree in the chondroitin sulfate groups than in the placebo groups. This raises the question regarding the extent to which adverse gastrointestinal events, as well as other observed adverse events of the chondroitin sulfate groups, reflect the customary “background noise” of adverse events of everyday life in the sometimes lengthier studies, or whether they should be ascribed to the administration of chondroitin sulfate.

It has to be considered, however, that most of these studies were carried out with arthritis patients so that the additional intake of medicines such as paracetamol (acetaminophen) and sometimes anti-inflammatory drugs (non-steroidal anti-inflammatory drugs) were permitted for ethical reasons. These drugs themselves can produce adverse health effects or alleviate certain adverse effects. There are therefore scientific uncertainties as to whether and to what extent the frequency of observed adverse events was influenced by the intake of additional medicines, and whether and to what extent the study results regarding the occurrence of adverse events can be extrapolated to the general population (i.e. persons who do not use the additional medicines or only to a much lesser extent than the investigated patient groups), or

¹ This updated opinion supersedes BfR Opinion No. 031/2007 of 15 June 2007

whether this is due to the sole intake of chondroitin sulfate. The general population constitutes the reference group for the risk assessment of food supplements.

It has not yet been clarified either to what extent chondroitin preparations show different effects on health depending on the production method, raw material, composition, molecular weight distribution or degree of sulfation and whether results achieved with individual products can be simply transferred to other chondroitin preparations.

In the case of oral-use medicinal products containing chondroitin sulfate marketed in other European countries with daily intake doses of 730 – 1,000 mg/day (and sometimes with initial doses of 1,200 mg/day for 4-6 weeks with particularly affected patients), gastrointestinal complaints (indigestion, abdominal pain, diarrhoea, nausea) and headache or dizziness are listed as common adverse effects of two of these products in recent summaries of product characteristics.

In addition, the BfR provides the following information to the following population groups: Food supplements containing chondroitin sulfate in isolated form cannot be recommended to pregnant or lactating women, children and adolescents. Persons who take antiplatelet drugs should seek medical advice before taking products in the intake range of 800 – 1,200 mg chondroitin sulfate/day. There is a possible risk of allergy for people who are allergic to fish protein if they ingest products containing isolated chondroitin sulfate made from shark tissue or from the tissue of other fish.

Food supplements are not intended to cure or alleviate diseases. The BfR recommends that people who suffer from arthritic/joint complaints seek medical advice in order to identify the actual disorder and ascertain the form of treatment. According to an assessment published by the European Food Safety Authority (EFSA, 2009), there is currently no scientific evidence of the efficacy of chondroitin/chondroitin sulfate in maintaining normal joint function in the general population (i.e. persons who do not suffer from arthritic/joint disorders).

		BfR Risk Profile: Chondroitin sulfate in food supplements [1] (Opinion No. 40/2018)				
A	Affected groups	General population 				
B	Probability of a health impairment through the intake of 800-1200 mg/day chondroitin sulfate in food supplements	Practically excluded	Unlikely	Possible	Probable	Certain
C	Severity of the health impairment through the intake of 800-1200 mg/day chondroitin sulfate in food supplements	No impairment	Slight impairment (reversible)	Moderate impairment [reversible/irreversible]		Severe impairment [reversible/irreversible]
D	Reliability of available data	High: The most important data are available and are free of contradiction		Moderate: Some important data are missing or contradictory	Low: Numerous important data are missing	
E	Controllability by the consumer [2]	Control not necessary	Controllable through precautionary measures	Controllable through avoidance	Not controllable	

Squares highlighted in dark blue indicate the properties of the risk assessed in this Opinion (more detailed information on this is contained in BfR Opinion No. 40/2018 of 7 December 2018).

Explanations

The risk profile is intended to visualise the risk outlined in the BfR Opinion. It is not intended for the purpose of comparing risks. The risk profile should only be read in conjunction with the opinion.

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[1] – The BfR based its evaluation of chondroitin sulfate as an ingredient of food supplements on intake quantities of 800 – 1,200 mg/day. The BfR explicitly points out that no statement on any possible pharmacological effect is connected with this Opinion and that it does not constitute a recommendation to fully utilise daily intake quantities of food supplements at these levels.

Line E – Controllability by the consumer

[2] – The information in the line “Controllability by the consumer” should not be seen as a recommendation by the BfR; it has a purely descriptive character. The BfR recommends courses of action in its opinion: pregnant and lactating women, children and adolescents should avoid products of this kind; persons who take antiplatelet drugs should seek medical advice, there is a possibility of allergenic potential regarding chondroitin sulfate made from fish for persons who show an allergic reaction to fish protein.

1 Subject of the assessment

Chondroitin sulfate is used as an ingredient in food supplements. The German Federal Institute for Risk Assessment (BfR) published a risk assessment of the use of chondroitin sulfate as a constituent of food supplements in 2007. As a number of new scientific publications on the use of the substance by humans have appeared in the meantime, the BfR has updated its assessment.

This assessment applies only to products containing chondroitin that are designated as foods due to their intended purpose, advertising and form of presentation.

2 Result

The BfR based its assessment of chondroitin sulfate as an ingredient of food supplements on intake quantities of 800-1,200 mg/day – firstly, because these are the doses that were used in most of the human studies and, secondly, as the available data are not sufficient to derive a dose-response relationship with regard to the occurrence of adverse health effects. The BfR explicitly notes that this does not constitute a recommendation to fully utilise this level of daily intake via food supplements.

In the available human studies using intakes in the range from 800-1,200 mg/day, most of which were carried out on patients suffering from arthritis, the incidence of observed adverse events was mostly comparable to that in the placebo group. Undesirable gastrointestinal effects were the most frequently observed adverse events and occurred less often in the chondroitin sulfate groups than in the placebo groups. This raises the question regarding the extent to which adverse gastrointestinal events, as well as other observed adverse events, reflect the customary “background noise” of adverse events which occur in everyday living in this patient group in the sometimes lengthier studies, or whether they should be ascribed to the chondroitin intake. It has to be considered, however, that most of these studies were carried out with arthritis patients so that the additional intake of medicines such as paracetamol (acetaminophen) and sometimes also non-steroidal anti-inflammatory drugs was permitted in the verum and placebo groups and that these medications themselves can produce adverse health effects and also alleviate certain undesirable effects.

There are therefore scientific uncertainties as to what extent the results of these studies regarding the occurrence of adverse events can be transferred to the sole intake of chondroitin sulfate or to the general population, respectively (i.e. persons who do not use the above mentioned drugs or only to a much lesser extent than the patient groups examined). The general population constitutes the reference group for the risk assessment of food supplements.

It has not yet been clarified either to what extent chondroitin sulfate preparations show different effects on health depending on the production method, raw material, composition, molecular weight distribution or degree of sulfation and whether results achieved with individual products can be simply transferred to other chondroitin products.

With respect to oral-use medications containing chondroitin sulfate that are being marketed in other European countries with daily intake doses of 730 – 1,000 mg/day (and sometimes with initial doses of 1,200 mg/day for 4-6 weeks among particularly affected patients), gastrointestinal complaints (indigestion, abdominal pain, diarrhoea, nausea) and headache or dizziness are listed as common adverse events in the recent summaries of product

characteristics for two of these products (type and frequency of mentioned possible undesirable effects differ slightly depending on the product in question) (Arzneimittel-Kompendium der Schweiz²/Pierre Fabre Pharma AG, 2018; Arzneimittel-Kompendium der Schweiz/IBSA Institut Biochimique SA, 2018). The BfR does not have any information as to whether these data are based on a comparison of observed incidences in the verum and placebo groups in performed clinical studies or on some other procedure.

The BfR provides the following information to the following population groups:

Food supplements containing chondroitin sulfate in isolated form cannot be recommended to pregnant or lactating women, children and adolescents.

Persons who take antiplatelet drugs should seek medical advice before taking products in the intake range of 800 – 1,200 mg chondroitin sulfate/day.

There is a possible risk of allergy for people who are allergic to fish protein if they ingest products containing isolated chondroitin sulfate made from shark tissue or from the tissue of other fish.

Due to a lack of scientific data, it is currently not possible to make broader, differentiated statements on the assessment of daily intake quantities of isolated chondroitin sulfate as a food supplement that are above or below the range of 800-1,200 mg chondroitin sulfate/day.

3 Reasons

3.1 Agent

Chondroitin sulfates are polysaccharides that belong to the group of glycosaminoglycans. Among other things, they are building blocks of proteoglycans and as such are natural components of cartilage tissue. Chondroitin sulfate chains are possibly also involved in the development of the central nervous system or in wound healing. Chondroitin sulfates are macromolecules comprising different numbers of repeating heterodimers consisting of β -d-glucuronic acid and N-acetyl- β -d-galactosamine that are sulfated at different positions – in the case of chondroitin-4-sulfate (mainly) at position 4 of the N-acetyl- β -d-galactosamine, and in the case of chondroitin-6-sulfate (mainly) at position 6 (sulfation can also occur at position 2 of the glucuronic acid and, very rarely, at position 3). The sulfation position in the polysaccharide chain is not always consistent, however, which means that the other sulfation position can also occur in different proportions, as can unsulfated heterodimers or also heterodimers with multiple sulfate residues. Depending on their origin, chondroitin sulfates can have different chain lengths (M_r: 5,000-50,000) or sulfation degrees, and this has a major influence on their biological properties. Dermatan sulfate is an isomer of the chondroitin sulfates. Alongside β -d-glucuronic acid, it also contains α -L-iduronic acid which is formed by epimerisation and N-acetyl- β -d-galactosamine, which is primarily sulfated at position 4 (Römpp online, 2012; Volpi, 2009; 2014).

Chondroitin sulfate is obtained from the cartilage of cattle, pigs, poultry or marine animals such as sharks (as well as, in some countries, via bacterial synthesis with chemical modification, but this is not the subject of this assessment). The sulfation degree, the percentage of distribution of the sulfation positions³, the molecular mass distribution of chondroitin sulfate chains, or the product purity may vary depending on the raw material and the production method (Volpi,

² Swiss Compendium of Medicines

³ In chondroitin sulfate obtained from shark cartilage, the proportion of sulfation at position 6 is greater than at position 4, whereas in chondroitin from the trachea of cattle, pigs and poultry the proportion of sulfation at position 4 is greater, with the extent depending on the animal species in question (Conte, 2009).

2009; 2014). There are no binding specifications for chondroitin sulfate which is used in food supplements in Germany. In the US market, there are specifications⁴ for the sodium salt of chondroitin sulfate (sodium chondroitin sulfate) obtained from cattle, pig or poultry cartilage (US Pharmacopeial Convention, 2015). In Europe, sodium chondroitin sulfate used for pharmaceutical purposes and made from the cartilage of animals of terrestrial or maritime origin (which are suitable for human nutrition) is subject to purity requirements⁵ (European Directorate for Quality of Medicines and Healthcare, 2017).

In the case of chondroitin sulfate made from fish, it must be taken into account that it may possess an allergenic potential. Annex II of Regulation (EU) 1169/2011 lists fish and products obtained from fish among the substances or products that can trigger allergies or intolerances.

Oral intakes of the substance have been used in scientific studies primarily in the investigation of degenerative joint disease (arthritis). In Germany, there is currently no authorisation of Chondroitin sulfate as a drug for oral treatment of joint diseases.

3.2 Metabolism and exposure

Chondroitin sulfates in small quantities are normal constituents of blood plasma. Following the oral intake of chondroitin sulfate, the macromolecules are partly hydrolysed and – to a lesser extent – desulfated, and this results in metabolites with a broad range of molecular weight distribution (Conte et al., 1991; 1995; Volpi, 2002; Verbruggen et al., 2002).

No information exists on whether or to what extent chondroitin sulfate is ingested as part of the normal diet (as a constituent of processed cartilage tissue, for example). Based on the available information, food supplements are on the market in Germany containing daily doses of up to 1,200 mg chondroitin sulfate. Chondroitin sulfate is often used in combination with glucosamine (MinaerBa-Mikronährstoff-Produktdatenbank (micronutrient product database, 2017).

3.3 Hazard identification and characterisation

3.3.1 Assessments by scientific bodies or state authorities

Chondroitin sulfate and sodium chondroitin sulfate are used in individual European countries as oral medication for the treatment of arthritis/polyarthritis or to combat the symptoms of osteoarthritis. The available summaries of product characteristics for three medicinal products list doses of 730-1,000 mg chondroitin sulfate/day; in one case, the summary specifies that patients with severe inflammatory symptoms can be given 1,200 mg/day for a period of 4-6 weeks at the start of the treatment process, with the dose being subsequently reduced to 800 mg/day. With regard to the occurrence of adverse effects, one of the summaries states that rare side-effects include nausea and gastrointestinal upset as well as – very rarely – oedemas. In the case of two further medicinal products with more recent summaries, one lists indigestion, abdominal pain and headache as common adverse effects (frequency: $\geq 1/100$, $< 1/10$), nausea, constipation, dizziness and skin rash as uncommon adverse effects (frequency: $\geq 1/1,000$, $< 1/100$) and oedemas and/or water retention in patients with renal and/or cardiac insufficiency as rare adverse effects (frequency: $\geq 1/10,000$,

⁴ Among other things: chondroitin sulfate content; 90.0-105.0% based on the dry mass, protein content: $\leq 6\%$; chloride: $\leq 0.05\%$; (free) sulfate: $\leq 0.24\%$.

⁵ Among other things: chondroitin sulfate content: 95-105% based on the dry mass, protein content: $\leq 3\%$; chloride $\leq 0.05\%$

<1/1,000). In the second case, abdominal pain, diarrhoea, nausea and dizziness are listed as common, hives, pruritus and facial oedemas as uncommon, and vomiting, angioedema and erythema as rare adverse effects. The data on these two medicinal products are based on clinical studies using the product in question; in the case of one of the medicinal products, the information on uncommon and rare adverse events is based on pharmacovigilance data.

With regard to children and adolescents, it is noted that there is no experience or data on the efficacy and tolerance of use in these population groups. It is indicated that there are no clinical data or insufficient data on the use of chondroitin sulfate during pregnancy. In regard to lactation it is noted that it is not known whether chondroitin sulfate or its metabolites are carried over into breast milk and that information regarding safety in the case of newborn children is lacking (Arzneimittel-Kompendium der Schweiz/Pierre Fabre Pharma AG, 2018; Arzneimittel-Kompendium der Schweiz/IBSA Institut Biochimique SA, 2018; Bioiberica, 2009).

Canadian authorities have named daily doses of 800 - 1,200 mg/day for the use of chondroitin sulfate as an ingredient in so-called “natural health products” intended for various purposes⁶. In order to achieve positive effects, the substance should be taken for at least 3 months, and no contraindications or known adverse reactions are listed for this use. The products have to carry an advisory note to the effect that pregnant and lactating women should consult a physician before taking chondroitin sulfate. People should also consult a physician if the (osteoarthritic) symptoms worsen (Health Canada, 2008).

With regard to the use of chondroitin sulfate in food supplements, there is information that the addition of up to 500 mg chondroitin sulfate per daily consumption quantity is permitted in Italy (Ministero della Salute, 2017).

In a written response to a GRAS⁷-notification, the US-Food and Drug Administration (FDA) had no questions regarding a GRAS-notification for the use of chondroitin sulfate made from *Escherichia coli* in various foods. The mean intake resulting from intended use was estimated at approx. 590 mg chondroitin sulfate per day and person, and at 1,190 mg per day and person for the 90th intake percentile (FDA, 2017).

With regard to the admissible “health claims” for foods for which approval was requested pursuant to Article 13 (1) of Regulation (EC) No. 1924/2006, EFSA stated that, with reference to the general population, there is no scientific evidence to support a cause-effect relationship between the consumption of chondroitin/chondroitin sulfate and the maintenance of normal joints (in terms of joint health or joint health and mobility). The general population (in other words, people who do not suffer from arthritis/joint complaints) was considered to be the target population for these kinds of health claims. The authority pointed out that all submitted human studies on the effect of chondroitin/sulfate on joint health were conducted with patients suffering from osteoarthritis and that no evidence was submitted to support the assumption that this group of people was representative of the general population in terms of the condition of their joint tissue – or that the study results achieved with these patients in terms of their disease symptoms (erosion of articular cartilage, reduced mobility of joints) can be extrapolated to the maintenance of normal joints in the general population (EFSA, 2009).

⁶ A) Helps to relieve joint pain associated with osteoarthritis

B) Helps to relieve pain associated with osteoarthritis of the knee

⁷ GRAS = Generally Recognized As Safe.

3.3.2 Information from published human studies

From human intervention studies on the medicinal use of chondroitin sulfate (CS), the majority of which were conducted with intakes of 800 or 1,200 mg/day, there are, apart from studies with shorter study durations, several scientific publications with substance administrations over periods from 24 weeks or six months up to three years (*1,200 mg/day and three years duration*: Verbruggen et al., 2002; *1,200 mg/day and two years duration*: Sawitzke et al., 2010, Pelletier et al., 2016; *1,200 mg/day and six months duration*: Clegg et al., 2006⁸, Yue et al., 2012, Pavelka et al., 2010, Fardellone et al., 2013⁹; *1,000 mg/day and 24 weeks or 48 weeks duration*: Mazieres et al., 2007, Railhac et al., 2012; *800 mg/day and two years duration*: Fransen et al., 2015, Kahan et al., 2009, Michel et al., 2005; *800 mg/day and one year duration*: Uebelhart et al., 1998; *800 mg/day and six months duration*: Reginster et al., 2017, Gabay et al., 2011, Wildi et al., 2011, Bucsi et al., 1998). Most of these studies were conducted in patients suffering from osteoarthritis. Some of the studies included an additional group of patients who received the substance in combination with glucosamine. However, a part of the cited publications only include incomplete or no information on the occurrence of adverse effects, and clinical laboratory parameters are frequently not reported systematically.

With the administration of 2,000 mg chondroitin sulfate/day (duration: 3 months; $n_{(CS)}$: 58), a comparable number of patients in the chondroitin (CS) and placebo (PI) group were affected by adverse events during the treatment period (CS: 7; PI: 9), with two cases of constipation and one case of eyelid oedema occurring in the chondroitin group (Mazières et al., 1992). Observed cases of stomach pain (CS: 3, PI: 5) could be at least partially caused by the permitted use of non-steroidal anti-inflammatory drugs as "emergency medicine".

A study of high scientific quality financed by the American National Institutes of Health which examined the therapeutic effectiveness of chondroitin sulfate (1,200 mg/day), glucosamine hydrochloride (1,500 mg/day), and the combination of chondroitin sulfate and glucosamine (1,200 mg and 1,500 mg/day) as compared to Celecoxib (200 mg/day) or to placebo for knee osteoarthritis over a two-year period (approx. 120-140 patients per treatment group) provides the information across all intervention groups that observed adverse events showing a statistically significant difference compared to the placebo group were of a mild nature and were distributed evenly over the treatment groups. A total of 84 serious adverse events (SAE) were observed in 64 patients. Five SAEs were classified as possibly caused by the study drugs, but none of these occurred with the administration of chondroitin only (one myocardial infarction with combined administration of chondroitin sulfate and glucosamine, one case of coronary angioplasty with administration of placebo, three different cases with administration of Celecoxib) (Sawitzke et al., 2010)¹⁰.

In a further study with the administration of 1,200 mg chondroitin sulfate/day over two years as compared to the administration of 200 mg Celecoxib (Cel)/day to patients with knee osteoarthritis (n : 97 per group), 80.4% of the patients in the chondroitin group and 81.4% of the patients in the Celecoxib group reported the occurrence of at least one adverse event. The most frequent adverse events related to musculoskeletal and connective tissue disorders (CS: 72; Cel: 59) such as arthralgias (CS: 19; Cel: 14), back pain (CS: 17; Cel: 5),

⁸ The study duration here was 24 weeks.

⁹ Two preparations with a dosage of 1,200 and 1,000 mg/day were used.

¹⁰ An earlier evaluation of this study after 24-week administration of the substances which included approximately 300 people per treatment group provides the information that the observed adverse events were generally mild and distributed evenly over the treatment groups, with the chondroitin group seeing the highest incidence of musculoskeletal and connective tissue adverse events and the lowest incidence of vomiting (Clegg et al., 2006).

pain in the extremities (CS: 6; Cel: 8) and infections (not to be classified as undesirable effects of the tested substances), followed by gastrointestinal disorders (CS: 37; Cel: 44) such as dyspepsia (12 adverse events in each group) and gastrointestinal reflux (5 adverse events in each group), and nervous system disorders (CS: 21; Cel: 22) such as headaches (CS: 15; Cel: 10). Vascular disorders (CS: 7; Cel: 5) related mainly to hypertension, varicose veins and ulcers (Pelletier et al., 2016). It must be taken into account here that this study did not include a placebo group, i.e. an adequate comparison group for the issue being examined.

In the examination of different dosing patterns with the administration of 1x1,200 or 3x400 mg chondroitin sulfate/day (from fish) as compared to a placebo (3 months, approx. 40 subjects per group), gastrointestinal disorders were the most frequently reported adverse events. However, with both dosing patterns, these occurred to a lesser extent than in the placebo group (CS₁₂₀₀: 4; CS_{3x400}: 7; PI: 10). The same applied to undesirable skin manifestations (itchiness, itchy skin eruptions) (CS₁₂₀₀: 1; CS_{3x400}: 1; PI: 2). With administration of chondroitin, one case of an ankle oedema was observed (Bourgeois et al., 1998).

With the administration of 1,000 mg/day over a period of 48 weeks to patients with knee osteoarthritis, 18 of 25 verum patients (72%) and 13 of 23 placebo patients (56%) reported adverse events. As can be expected in this type of population group, musculoskeletal and connective tissue disorders were the most frequent adverse events, reported by 40% of verum patients and 17% of placebo patients, followed by infections, reported by 24% and 39% of patients, respectively, and gastrointestinal disorders, reported by 20% of verum patients and 22% of placebo patients. In two patients in the verum group and one patient in the placebo group, the adverse events were classified by the study authors as possibly or probably caused by the study drug (Railhac et al., 2012). In a further study involving administration of 1,000 mg/day over 24 weeks ($n_{(CS)}=153$ people), 49% of patients in the verum group and 49% in the placebo group reported adverse events. 18 adverse events in 14 patients of the verum group and 20 adverse events in 16 placebo patients were classified as possibly or probably caused by the treatment, and 50% of these undesirable effects were gastrointestinal in each group (dyspepsia, nausea, vomiting, abdominal pain, diarrhoea). 13 patients in the verum group and 8 patients in the placebo group terminated the study prematurely due to adverse events (Mazieres et al., 2007).

With the administration of 800 mg chondroitin sulfate (from fish) over a period of two years to patients with knee osteoarthritis ($n: 150$ per treatment group), the most frequently observed adverse events were infections of the upper respiratory tract (CS: 44 cases; PI: 46), headaches (CS:11; PI: 14), abdominal pain (CS: 6; PI: 17), allergies (CS: 9; PI: 9), heart problems (CS: 9; PI: 8) and urinary tract infections (CS: 8; PI: 7), but there was no statistically significant difference as compared to the placebo group. Adverse events led 9 people in each group to terminate the study prematurely. Two adverse events (one case of abdominal pain and one case of nausea) were ascribed to the administration of chondroitin. The other adverse events were not considered to have been caused by the study medication. The study authors considered that these effects could most likely be ascribed to the concomitant disorders (Michel et al., 2005). A further placebo-controlled study with the administration of 800 mg/day (bovine origin) over a period of two years ($n_{(CS)}= 309$) provides the information relating to the occurrence of adverse events that most of these were temporary and mild in nature and that there was no significant difference between the chondroitin group and the placebo group. Adverse gastrointestinal effects were the most common adverse events (6% in the CS group, 5.9% in the placebo group). For 16 patients in the chondroitin group and 17 patients in the placebo group, the occurrence of adverse events was the reason for

prematurely ending the study. During routine laboratory tests, no significant abnormalities were detected in either group. More detailed information on this result is not available (Kahan et al., 2009). With the administration of 800 mg chondroitin sulfate/day (bovine origin) over a six-month period ($n_{(CS)}=35$ people), the most common adverse events observed were musculoskeletal effects (CS: 13, PI: 12), infections (CS:12, PI: 6), gastrointestinal disorders (CS: 7; PI: 7) and skin disorders (CS: 8; PI: 0) (Wildi et al., 2011).

In the examination of different chondroitin dosages of 200, 800 and 1,200 mg chondroitin sulfate/day compared to the placebo (90 days; $n=35$ per group), no differences with respect to the occurrence of adverse events were observed between the chondroitin and the placebo group. In addition, no dosage dependency of adverse events was observed. One patient in the 200 mg chondroitin group reported mild epigastralgia and three patients in the placebo group reported mild nausea, stomach pain or digestion problems (Pavelka et al., 1999).

In a more recent meta-analysis which dealt with the effectiveness of chondroitin sulfate in the treatment of osteoarthritis, no statistically significant difference was observed in the evaluated studies with administration of chondroitin alone (dose ≥ 800 mg/day) as compared to placebo administration regarding the (total) number of adverse events (RR: 0.96; 95% CI: 0.78-1.18; $P=0.69$). This also applies to the differentiated consideration of adverse gastrointestinal events (RR: 0.68; 95% CI: 0.45-1.04; $P=0.07$) and so-called "other" adverse events¹¹ (RR: 0.95; 95% CI: 0.79-1.15; $P=0.66$). In a combined consideration of short-term (< 6 months) and long-term (≥ 6 months) studies, the number of subjects who terminated the study prematurely due to adverse events was somewhat higher in the chondroitin group than in the placebo group (RR 1.08; 95% CI: 0.74-1.57), although the difference was not statistically significant. With combined consideration of long-term and short-term studies, the administration of chondroitin was associated with a significantly lower risk of the occurrence of serious adverse events (RR: 0.40; 95% CI: 0.19-0.82). In these evaluations, the question of the extent to which the occurrence of adverse events was dose-dependent was not addressed (Singh et al., 2015).

In addition to the specified studies with osteoarthritis patients, there is an older long-term study with patients ($n=60$) with coronary heart disease who had already experienced a myocardial infarction and/or suffered from chronic angina pectoris. The duration of the study was six years. The patients received 10 g/day of specially produced chondroitin sulfate (chondroitin sulfate A) for three months, after which the majority ($n=51$) received 1.5 g/day for 4.5 years and then 0.75 g/day. Usual medication including anticoagulants was continued. A lower number of deaths (4 versus 14 cases) was observed in the treatment group as compared to the placebo group. Only rudimentary information is given on the occurrence of adverse events. It is stated that the study medication was tolerated well and no haemorrhagic complications were observed. Likewise, no deviations in the studied laboratory parameters that could be ascribed to the study medication were observed. However, it is also reported that administration of 10 g chondroitin sulfate/day to angina pectoris patients was associated with a lengthening of the (possibly disease-related) shorter thrombus formation time, as observed in vitro tests¹². However, this study did not include a placebo control group (Morrison and Enrick, 1973).

Overall, in the existing intervention studies with chondroitin sulfate, most of which involved the administration of 800-1,200 mg/day, primarily adverse gastrointestinal events were observed, as well as musculoskeletal/connective tissue disorders, headaches and adverse

¹¹ = Adverse effects apart from adverse gastrointestinal, haematological or cardiac effects

¹² Time until formation of a blood clot in a test procedure

skin effects, and the incidence of these adverse events was comparable to the incidence in the placebo group and in some cases lower than in the placebo group (e.g. adverse gastrointestinal effects, headaches). It has to be considered, however, that most of these studies were carried out with arthritis patients so that the additional intake of paracetamol and sometimes also of non-steroidal anti-inflammatory drugs was permitted as "emergency medication" for ethical reasons. On the one hand, these medicines could themselves cause adverse events. On the other hand, they could also reduce the incidence of observed adverse effects (e.g. due to their analgesic effects). It is therefore possible that they may influence the incidence of observed adverse events in such studies, both in the verum group and in the placebo group. Scientific uncertainties therefore exist regarding the extent to which the results of these studies with respect to the occurrence of adverse events can be attributed to the administration of chondroitin alone, or the extent to which the incidences observed in the placebo groups which were used as comparison for the adverse events observed with the administration of chondroitin actually reflect the incidences without administration of chondroitin or other medicines. In this respect, there are scientific uncertainties as to the extent to which these study results can be extrapolated to the general population. It is not clear either to what extent chondroitin preparations show different effects on health depending on the production method, raw material, composition, molecular weight distribution or degree of sulfation and whether results achieved with individual products can be simply transferred to other chondroitin products.

3.3.3 Information from other sources and individual case reports

- In the case of one chondroitin-containing drug, it is specified that neither human studies nor systematic monitoring of the safety of the drug (pharmacovigilance monitoring) observed any effects at the thrombocyte level at the recommended dose¹³ but that slight possible platelet antiaggregant activity was observed in animal experiments with considerably higher doses (50 mg/kg body weight, corresponding to 4 g/day in humans) and that this needs to be taken into consideration in the event of simultaneous administration with platelet antiaggregants (acetylsalicylic acid, dipyridamole, clopidogrel, ditazole, triflusal, ticlopidine). Additional information on this is not available (Bioiberica S.A., 2009).
- For products containing combinations of chondroitin sulfate with glucosamine and, in some cases, other substances, there are individual reports on suspected cases of liver damage (von Felden et al., 2013; ANSES, 2015). The extent to which a causal relationship exists with the intake of the products or specific constituents thereof cannot be definitively determined at the present time.

3.3.4 Children and adolescents

Adequate published scientific data for the risk assessment of chondroitin sulfate intakes in children and adolescents are not available. From the medical application of the substance, there is information that no scientific data or experience on application in children or adolescents is available (Bioiberica, 2009; Arzneimittel-Kompendium der Schweiz/Pierre Fabre Pharma AG, 2018; Arzneimittel-Kompendium der Schweiz/IBSA Institut Biochimique SA, 2018).

¹³ Drug dose: 800 mg/day; also 1200 mg/day during the first 4-6 weeks in patients with significant inflammation symptoms

3.3.5 Pregnant and lactating women

Aside from an intervention study in which an iron-chondroitin-sulphuric acid complex (chondroitin sulfate dose not specified) was given as a source of iron to a small group of pregnant women (Fochi et al., 1985), no other intervention study involving isolated chondroitin administration to pregnant or lactating women has been identified. From the medical application of the substance, there is information that no clinical data or insufficient data is available on the oral administration of chondroitin to pregnant women (Bioiberica, 2009; Arzneimittel-Kompendium der Schweiz/Pierre Fabre Pharma AG, 2018; Arzneimittel-Kompendium der Schweiz/IBSA Institut Biochimique SA, 2018); the same applies to lactating women with respect to the transfer of chondroitin sulfate and its metabolites into breastmilk and its safety for newborns (Bioiberica, 2009; Arzneimittel-Kompendium der Schweiz/Pierre Fabre Pharma AG, 2018). Overall, there is insufficient data for a risk assessment of chondroitin administration to pregnant or lactating women.

3.3.6 Additional aspects

Chondroitin sulfate is partly derived from shark cartilage or the tissues of other fish. To date, there are no binding specifications for chondroitin sulfate used in food supplements. It is possible that the chondroitin sulfate produced from these source materials could still contain corresponding allergens and could trigger allergic reactions in people who are allergic to fish protein.

4. Risk characterisation

There are a number of scientific studies on the oral administration of chondroitin sulfate to humans, particularly to patients suffering from osteoarthritis. The administered doses in these studies were usually in the range of 800-1,200 mg chondroitin sulfate/day. For this reason and because the available scientific data are not sufficient for a dose-response relationship to be determined with respect to the occurrence of adverse events, this assessment of chondroitin sulfate is based on daily intakes of 800-1,200 mg/day. However, this does not constitute a recommendation to fully utilise such daily intake levels in food supplements.

In existing human studies with intakes in the range of 800-1,200 mg chondroitin sulfate/day and study durations of up to 2-3 years, adverse gastrointestinal events were the most commonly observed adverse events, followed by musculoskeletal/connective tissue disorders, headaches and adverse skin effects. The incidences of observed adverse events in the studied patient groups, i.e. usually arthritis patients, were mostly comparable to those in the placebo group, and the adverse gastrointestinal events, which were the most frequently observed adverse events, occurred to a lower extent in the chondroitin group than in the placebo group (this also applies to headaches). This raises the question regarding the extent to which this reflects the usual occurrence of adverse events in these patients in the sometimes lengthier studies ("background noise" of adverse events in everyday living) or whether they should be ascribed to the administration of chondroitin sulfate. However, it must be taken into consideration that the intake of paracetamol and, in some cases, other non-steroidal anti-inflammatory drugs ("emergency medication") was permitted in the cited studies, that these medicines themselves can cause adverse events (or alleviate certain adverse events) and that this can influence the incidences of observed adverse events in both the placebo group and the verum group (e.g. due to differences in the use of the "emergency medication" or different individual sensitivities). For this reason, there are scientific uncertainties with respect to the transferability of these study findings to the general

population (i.e. people who do not take the above-mentioned medicines or take them to a considerably lower extent than the studied patient groups) or to the administration of chondroitin alone. It is not clear either to what extent chondroitin preparations show different effects on health depending on the production method, raw material, composition, molecular weight distribution or degree of sulfation and whether results achieved with individual products can be simply transferred to other chondroitin preparations.

With oral-use medicinal products containing chondroitin sulfate that are being marketed in other European countries with daily intake doses of 730 – 1,000 mg/day (and sometimes with initial doses of 1,200 mg/day for 4-6 weeks among particularly affected patients), gastrointestinal complaints (indigestion, abdominal pain, diarrhoea, nausea) and headache or dizziness are listed as common adverse events in recent summaries of product specifications for two of these products (type and frequency of the mentioned possible undesirable effects differ slightly depending on the medicinal product in question) (Arzneimittel-Kompendium der Schweiz/Pierre Fabre Pharma AG, 2018; Arzneimittel-Kompendium der Schweiz/IBSA Institut Biochimique SA, 2018). The BfR does not have any information on the extent to which this information relates to a comparison of observed incidences in the verum and placebo groups of conducted clinical trials or to a different procedure.

Due to a lack of data, a risk assessment of isolated chondroitin sulfate intakes in pregnant or lactating women and in children or adolescents is not possible.

The BfR provides the following information for following population groups:

Food supplements containing chondroitin sulfate in isolated form cannot be recommended to pregnant and lactating women, children and adolescents.

Persons who take antiplatelet drugs should seek medical advice before taking products in the intake range of 800 – 1,200 mg/day.

There is a possible risk of allergy for people who are allergic to fish protein if they ingest products containing isolated chondroitin sulfate made from shark tissue or from the tissue of other fish.

Due to a lack of data, it is not possible at this time to make broader, differentiated statements relating to the safety of daily intake levels above or below the range of 800-1,200 mg/day from food supplements.

5. References

ANSES (2015). AVIS de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à un cas d'hépatite survenu après la prise d'un complément alimentaire à visée articulaire. Saisine no. 2014-SA-0192. 27 mars 2015.

Arzneimittel-Kompendium der Schweiz/Pierre Fabre Pharma AG (2014). Pierre Fabre Pharma AG. Fachinformation Structum[®] 500 (update: April, 2018), in: Arzneimittel-Kompendium der Schweiz. compendium.ch[®] (<https://compendium.ch/mpro/mnr/4429/html/de>).

Arzneimittel-Kompendium der Schweiz/IBSA Institute Biochimique SA (2018). Fachinformation Condrosulf[®] (update: May, 2018), in: Arzneimittel-Kompendium der Schweiz. compendium.ch[®] (<https://compendium.ch/mpro/mnr/1892/html/de>).

BfR (2007). Verwendung von Chondroitinsulfat in Nahrungsergänzungsmitteln. Stellungnahme Nr. 031/2007 des BfR vom 15. Juni 2007.

Bioiberica (2009). Datasheet Condrosan (Stand: 03/2009) (<https://www.bioiberica.com/human-health/joint-health-1/b2b-joint-health/drugs/condrosan-1/#sthash.w9QWA7kC.dpbs>; meanwhile no longer available). (currently available: <https://www.bioiberica.com/en/products/human-health/prescription-medicines/condrosan>).

Bourgeois P, Chales G, Dehais J, Delcambre B, Kuntz JL, Rozenberg S (1998). Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 x 400 mg/day vs placebo. *Osteoarthritis Cartilage*. 6 Suppl A: 25-30.

Bucsi L, Poor G (1998). Efficacy and tolerability of oral chondroitin sulfate as a symptomatic slow-acting drug for osteoarthritis (SYSADOA) in the treatment of knee osteoarthritis. *Osteoarthritis Cartilage*. 6 Suppl A: 31-36.

Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, Bradley JD, Bingham CO, 3rd, Weisman MH, Jackson CG, Lane NE, Cush JJ, Moreland LW, Schumacher HR, Jr., Oddis CV, Wolfe F, Molitor JA, Yocum DE, Schnitzer TJ, Furst DE, Sawitzke AD, Shi H, Brandt KD, Moskowitz RW, Williams HJ (2006). Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med*. 354: 795-808.

Conte A, de Bernardi M, Palmieri L, Lualdi P, Mautone G, Ronca G (1991). Metabolic fate of exogenous chondroitin sulfate in man. *Arzneimittelforschung*. 41: 768-772.

Conte A, Volpi N, Palmieri L, Bahous I, Ronca G (1995). Biochemical and pharmacokinetic aspects of oral treatment with chondroitin sulfate. *Arzneimittelforschung*. 45: 918-925.

EFSA (2009). EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific Opinion on the substantiation of health claims related to chondroitin and chondroitin sulphate and maintenance of joints (ID 1504, 1505) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. *EFSA Journal* 7(9):1262. [14 pp.]. doi:10.2903/j.efsa.2009.1262. Available online: www.efsa.europa.eu

European Directorate for Quality of Medicines and Healthcare (2017). European Pharmacopoeia Online 9.1. Chondroitin sulfate sodium.

FDA (2017). Food and Drug Administration. Agency response letter GRAS-Notice No. GRN 000666 (<https://www.fda.gov/downloads/food/ingredientpackaginglabeling/gras/noticeinventory/ucm549591.pdf>).

Fardellone P, Zaim M, Saurel AS, Maheu E (2013). Comparative efficacy and safety study of two chondroitin sulfate preparations from different origin (avian and bovine) in symptomatic osteoarthritis of the knee. *Open Rheumatol J*. 7: 1-12.

Foch F (1985). Efficacy of iron therapie: A comparative evaluation of four iron preparations administered to anemic pregnant women. *J Int Med Res* 13: 1-11

Fransen M, Agaliotis M, Nairn L, Votrubec M, Bridgett L, Su S, Jan S, March L, Edmonds J, Norton R, Woodward M, Day R (2015). Glucosamine and chondroitin for knee osteoarthritis:

a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. *Ann Rheum Dis.* 74: 851-858.

Gabay C, Medinger-Sadowski C, Gascon D, Kolo F, Finckh A (2011). Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial at a single center. *Arthritis Rheum.* 63: 3383-3391.

Health Canada (2008). Chondroitin sulfate (July 17, 2008).

Kahan A, Uebelhart D, De Vathaire F, Delmas PD, Reginster JY (2009). Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 60: 524-533.

Mazieres B, Hucher M, Zaim M, Garnero P (2007). Effect of chondroitin sulphate in symptomatic knee osteoarthritis: a multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis.* 66: 639-645.

Mazieres B, Loyau G, Menkes CJ, Valat JP, Dreiser RL, Charlot J, Masounabe-Puyanne A (1992). [Chondroitin sulfate in the treatment of gonarthrosis and coxarthrosis. 5-months result of a multicenter double-blind controlled prospective study using placebo]. *Rev Rhum Mal Osteoartic.* 59: 466-472.

Michel BA, Stucki G, Frey D, De Vathaire F, Vignon E, Bruehlmann P, Uebelhart D (2005). Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. *Arthritis Rheum.* 52: 779-786.

MinaerBa-Mikronährstoff-Produktdatenbank (2017). Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart (Zugang: Juli 2017).

Ministero della salute, 2017. ALTRI NUTRIENTI E ALTRE SOSTANZE AD EFFETTO NUTRITIVO O FISILOGICO (*), Revisione maggio 2017 (http://www.salute.gov.it/imgs/C_17_pagineAree_1268_listaFile_itemName_4_file.pdf).

Morrison LM, Enrick N (1973). Coronary heart disease: reduction of death rate by chondroitin sulfate A. *Angiology.* 24: 269-287.

Pavelka K, Coste P, Geher P, Krejci G (2010). Efficacy and safety of piascalidene 300 versus chondroitin sulfate in a 6 months treatment plus 2 months observation in patients with osteoarthritis of the knee. *Clin Rheumatol.* 29: 659-670.

Pavelka K, Manopulo R, Bucsi L (1999). Double-blind, dose-effect study of oral chondroitin 4&6 sulfate 1200 mg, 800 mg, 200 mg and placebo in the treatment of knee osteoarthritis. In *Litera Rheumatologica*, pp. 21-30.

Pelletier JP, Raynauld JP, Beaulieu AD, Bessette L, Morin F, de Brum-Fernandes AJ, Delorme P, Dorais M, Paiement P, Abram F, Martel-Pelletier J (2016). Chondroitin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: a 2-year multicentre exploratory study. *Arthritis Res Ther.* 18: 256.

Railhac JJ, Zaim M, Saurel AS, Vial J, Fournie B (2012). Effect of 12 months treatment with chondroitin sulfate on cartilage volume in knee osteoarthritis patients: a randomized, double-blind, placebo-controlled pilot study using MRI. *Clin Rheumatol.* 31: 1347-1357.

Reginster JY, Dudler J, Blicharski T, Pavelka K (2017). Pharmaceutical-grade Chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the ChONDroitin versus CElecoxib versus Placebo Trial (CONCEPT). *Ann Rheum Dis.* 76:1537-1543. doi: 10.1136/annrheumdis-2016-210860. Epub 2017 May 22.

Römpf Online (2012). Chondroitinsulfate. Georg Thieme Verlag KG, Stuttgart.

Sawitzke AD, Shi H, Finco MF, Dunlop DD, Harris CL, Singer NG, Bradley JD, Silver D, Jackson CG, Lane NE, Oddis CV, Wolfe F, Lisse J, Furst DE, Bingham CO, Reda DJ, Moskowitz RW, Williams HJ, Clegg DO (2010). Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. *Ann Rheum Dis.* 69: 1459-1464.

Singh JA, Noorbaloochi S, MacDonald R, Maxwell LJ (2015). Chondroitin for osteoarthritis. *Cochrane Database Syst Rev.* 1: Cd005614.

Uebelhart D, Thonar EJ, Delmas PD, Chantraine A, Vignon E (1998). Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. *Osteoarthritis Cartilage.* 6 Suppl A: 39-46.

U.S. Pharmacopeial Convention (USP) (2015). Dietary Supplements Compendium 2015, Volume 1. Chondroitin sulfate sodium.

Verbruggen G, Goemaere S, Veys EM (2002). Systems to assess the progression of finger joint osteoarthritis and the effects of disease modifying osteoarthritis drugs. *Clin. Rheumatol* 21: 231-243.

Volpi N (2002). Oral bioavailability of chondroitin sulfate (Condrosulf) and its constituents in healthy male volunteers. *Osteoarthritis Cartilage.* 10: 768-777.

Volpi N (2009). Quality of different chondroitin sulfate preparations in relation to their therapeutic activity. *J Pharm Pharmacol.* 61: 1271-1280.

Volpi N (2014). Condrosulf(R): structural characterization, pharmacological activities and mechanism of action. *Curr Med Chem.* 21: 3949-3961.

von Felden J, Montani M, Kessebohm K, Stickel F (2013). Drug-induced acute liver injury mimicking autoimmune hepatitis after intake of dietary supplements containing glucosamine and chondroitin sulfate. *Int J Clin Pharmacol Ther.* 51: 219-223.

Wildi LM, Raynauld JP, Martel-Pelletier J, Beaulieu A, Bessette L, Morin F, Abram F, Dorais M, Pelletier JP (2011). Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. *Ann Rheum Dis.* 70: 982-989.

Yue J, Yang M, Yi S, Dong B, Li W, Yang Z, Lu J, Zhang R, Yong J (2012). Chondroitin sulfate and/or glucosamine hydrochloride for Kashin-Beck disease: a cluster-randomized, placebo-controlled study. *Osteoarthritis Cartilage*. 20: 622-629.

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