

Food supplements that contain glucosamine can constitute a health risk for patients who take coumarin anticoagulants as blood coagulation inhibitor

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Glucosamine is an amino sugar that occurs naturally in human connective tissue, in cartilage and synovial fluid. It is used as medicinal product to treat arthrosis of the knee joints. Yet glucosamine is also provided in numerous food supplements that are also considered foodstuffs in intake amounts that are below medicinal dosages. The *German* authorities for the official control of foodstuffs are responsible for controlling the marketability of these substances.

BfR has already assessed the health risks associated with glucosamine in food supplements in a past Opinion¹ and identified three risk groups: a) diabetics and/or individuals with impaired glucose tolerance, b) patients with a known risk for cardiovascular diseases and c) persons who take certain blood coagulation inhibitors known as coumarin anticoagulants. In the present Opinion, BfR has once again assessed the health risk for risk groups b) and c). This was carried out because these risk groups were not identified as such in a recent Opinion of the European Food Safety Authority (EFSA) on the use of glucosamine as food ingredient.

In regard to the group of individuals with a known risk for cardiovascular diseases, BfR concurs with EFSA after a review of the latest research findings. Thus, packages of food supplements that contain glucosamine do not require a notice on the health risks for these consumer groups.

However a repeated assessment has led BfR to continue to classify individuals who take coumarin anticoagulants as belonging to a risk group. The Institute has assessed the health risks using case studies and concluded that the combined intake of glucosamine with coumarin anticoagulants that contain the active substance warfarin or acenocoumarol bears the risk of an adverse increase of the anticoagulation effect of coumarin anticoagulants. BfR currently has no case studies available on the active substance phenprocoumon, which also belongs to the group of coumarin anticoagulants. For daily intake amounts of 390-790 milligrams of isolated glucosamine in food supplements, BfR deems measures that protect individuals who take coumarin anticoagulants necessary. The Institute advises consumers who take such medication (coumarin anticoagulants) to abstain from consuming food supplements that contain said amounts of isolated glucosamine as daily rations.

¹ "Verwendung von Glucosamin und dessen Verbindungen in Nahrungsergänzungsmitteln" – "Use of glucosamine and its derivatives in food supplements" (currently only available in German) (BfR, 2007). This BfR Opinion contains a comprehensive assessment of glucosamine by BfR.

1 Subject of the assessment

The Federal Institute for Risk Assessment (BfR) already evaluated the risks of food supplements that contain glucosamine in an Opinion in 2007 and referred to risk groups including: risks for diabetics, for patients with a known risk for cardiovascular diseases and for individuals who take anticoagulants (substances that inhibit blood coagulation). In regard to healthy, non-pregnant adults, BfR determined that there are no indications that suggest that the intake of glucosamine (as glucosamine sulphate or hydrochloride) below levels of 1250 mg/day constitutes a substantial risk (BfR, 2007).

In 2009, the European Food Safety Authority (EFSA) published a Scientific Opinion on the safety of glucosamine hydrochloride from *Aspergillus niger* and reached the conclusion that the intake of up to 750 mg glucosamine/day is safe for adults. Diabetics and individuals with impaired glucose tolerance should be advised to consult a physician prior to intake (EFSA, 2009). Risks for individuals who take coumarin anticoagulants and those with a known risk for cardiovascular diseases are not mentioned.

BfR has therefore re-evaluated the health risks of individuals who take coumarin anticoagulants and those with a known risk for cardiovascular diseases in regard to food supplements with daily intake amounts of 390-790 mg isolated glucosamine/day.

2 Results

In light of possibly severe health related effects of a potential interaction between glucosamine and coumarin anticoagulants, BfR concludes that the use of isolated glucosamine in food supplements at intake amounts of 390-790 mg glucosamine/day or more requires measures to protect individuals who take coumarin anticoagulants. Potential interactions pertain to altered blood coagulation ability possibly resulting in haemorrhage, even subdural haematoma (a specific type of cerebral haemorrhage) resulting in a vegetative state. BfR recommends that these groups of individuals are excluded from the use of such food supplements. One possible measure to counteract this risk is the use of warning labels on packaging. BfR also deems it legitimate to assess these products as unsafe in terms of Art 14 Reg. (EC) 178/2002.

Furthermore, the risk for diabetics should be noted (EFSA, 2009; BfR, 2007).

After a review of the present state of research knowledge, BfR has reached the conclusion that such warnings for individuals with a known risk for cardiovascular diseases are not necessary for food supplements containing glucosamine if their daily intake amounts are below medicinal dosage (below 1250 mg/day).

3 Reasons

3.1 Individuals who take coumarin anticoagulants

3.1.1 Hazard potential

Several reports are available concerning possible interactions when coumarin anticoagulants are taken together with glucosamine by itself or of warfarin (an active substance from the group of coumarins) and a combination of glucosamine and chondroitin sulphate (Yue et al., 2006; ADRAC/ADRU, 2008; Knudsen & Sokol, 2008; Garcia et al., 2004; Rozenfeld et al., 2004). Case reports state that when coumarin anticoagulants were taken with glucosamine or glucosamine/chondroitin sulphate, changes in the INR value (INR = International Normalised Ratio) were observed. Most often the value increased, while in a few cases it decreased. Elevated INR values express decreased blood coagulation ability or an increase of the anticoagulant (coagulation inhibiting) effect of coumarin anticoagulants. In this case, blood coagulation time is increased in a test procedure. When warfarin was taken together with glucosamine (without the simultaneous intake of chondroitin sulphate), elevated INR values in some cases occurred in conjunction with haemorrhage, in one case with life-threatening haemorrhage.

The scientific panel *Australian Adverse Drug Reactions Advisory Committee (ADRAC)* and the *Adverse Drug Reaction Unit (ADRU) of the TGA*² reported 12 cases that indicate an interaction between warfarin and glucosamine. In most cases, the increase in INR values was asymptomatic. However, in one case, haemorrhage occurred in the anterior chamber of the eye and in another case haemoptysis (coughing up or spitting of blood or blood-streaked mucus or small amounts of blood from the lungs or respiratory tract) and petechiae (small spots of haemorrhaging) occurred (ADRAC/ADRU, 2008). Researchers of the *WHO Collaborating Centre for International Drug Monitoring* described 22 suspected cases, which included nine of the above mentioned Australian cases. In two cases, the intake of glucosamine was combined with that of chondroitin sulphate. Of those cases in which the continuing course was known, the INR changes required a doctor's visit in nine cases and/or hospitalisation and/or closer INR value monitoring. In four cases, the adverse interaction required hospitalisation or an extension of the hospitalisation and/or treatment with vitamin K. In 17 out of the 21 cases with elevated INR values, the discontinuation of glucosamine intake was connected with a normalisation of INR values (Yue et al., 2006).

Knudsen and Sokol (2008) described a clinical case and identified 20 additional cases of potential interactions in the FDA³ MedWatch database, which collected spontaneous cases of adverse effects reported by consumers. The publication covers four cases, in which warfarin was taken together with glucosamine. However it could not be clarified in any of the cases whether chondroitin sulphate was also taken. In one of these cases, a person suffered from a subdural haematoma resulting in a vegetative state. Furthermore, 16 cases are reported with simultaneous intake of warfarin and a combination of glucosamine and chondroitin sulphate, and one case of simultaneous intake of warfarin with chondroitin sulphate. Additional cases were reported where the simultaneous intake of warfarin and a combination of glucosamine with chondroitin sulphate was associated with decreased blood coagulation ability or increased warfarin effects, which sometimes occurred in conjunction with haemorrhage or haematoma. Four cases required hospitalisation as a result of blood complications,

² TGA = Therapeutic Goods Administration

³ FDA = Food and Drug Administration of the United States

e.g. one case of gastrointestinal haemorrhage that required blood transfusion and treatment with vitamin K or one case of intraventricular haemorrhage (bleeding in cerebral ventricles).

According to researchers at the WHO Collaborating Centre, the close temporal relationship between glucosamine intake and increased warfarin effects indicates a possible causality (additionally, most of the patients experienced a normalisation/improvement after glucosamine intake was discontinued) (Yue et al., 2006). The researchers concluded that glucosamine could increase the effect of warfarin. Knudson and Sokol (2008) reached a similar conclusion. The *Australian Adverse Drug Reactions Advisory Committee and the Adverse Drug Reaction Unit of the TGA* (2008) as well as the *British Commission on Human Medicines/Medicines and Healthcare products Regulatory Agency* (2006) correspondingly state that the isolated cases which they have reported are “reports suggesting an interaction between warfarin and glucosamine”. The European Medicines Agency (EMA) also assessed the known case reports similarly. In its assessment of a glucosamine-containing medicinal product (dosage 1250 mg glucosamine/day), the Agency reached the conclusion that “[n]o formal drug interaction studies have been performed with glucosamine-containing medicinal products. Therefore, a general caution was proposed to be included in the SPC. Pharmacovigilance surveillance has resulted in some reports indicating a potential interaction with warfarin, and hence a warning has been added in the SPC text” (EMA, 2006; Annex II).

At present, the mechanism of an interaction between glucosamine and warfarin is still unclear (ADRAC/ADRU, 2008; Yue et al, 2006). In tests concerning the interaction of glucosamine with coagulation mechanisms, it was observed that when glucosamine was administered in *in-vitro* reaction batches, the aggregation of thrombocytes caused by ADP was inhibited (Bertram et al., 1980; Hua et al., 2004; Lu-Suguro et al., 2005). The inhibition of ADP-induced aggregation was also reported *ex-vivo* for thrombocytes of individuals who were given 1.5 g glucosamine/day over a period of seven days or for thrombocytes of guinea pigs when given high dosages of glucosamine (400 mg per animal and day) (Hua et al., 2004; Lu-Suguro et al., 2005). However, the changes were not sufficient to influence the clinically relevant parameters (bleeding time) that were examined in the study on guinea pigs mentioned above. The clinical relevance of these studies is still uncertain at present.

BfR is not aware that the SPC (summary of product characteristics) or package leaflets on coumarin anticoagulants includes any special warnings stating that food supplements or foods and medicinal products containing additives of isolated glucosamine can amplify the effects.

3.1.2 Dose-effect relationship

Sufficient data necessary to deduce a dose-effect relationship in regard to possible interactions of glucosamine and warfarin are not available. This is true for elevated INR levels expressing an interaction as well as for the severity of adverse effects which may be dose-dependent and have ranged from changes in INR levels without symptoms all the way to life-threatening haemorrhage. Only three case reports contained information on doses. In one case with elevated INR levels, the *British Medicines and Healthcare products Regulatory Agency* refers to a “suspected drug dose” of 1500 mg glucosamine, which corresponds to the daily dose (MHRA, 2007). In their case report, Rozenfeld et al. (2004) (elevated INR levels) cite a daily dose of 3 g glucosamine hydrochloride, 2.4 g chondroitin sulphate as well as an unspecified amount of manganese ascorbate. Kundsens und Sokol (2008) report an isolated case in which the dose increase from 1 g glucosamine hydrochloride and 800 mg chondroitin sulphate to 3 g glucosamine and 2.4 g chondroitin was related to increased INR levels (yet it cannot be ruled out that interactions already resulted from a low dose of glucosamine, which

was compensated through low doses of warfarin). In both of the cases named, the affected individuals also took various medicinal products/food supplements. The Australian AD-RAC/ADRU report states that in one case, elevated INR levels were related to an increased, yet unspecified, dose of glucosamine (ADRAC/ADRU, 2008). The daily doses of glucosamine are unspecified in other published case reports. Even when it is alleged that in the isolated cases that have been published, doses of glucosamine which are common in medicinal products (about 1250-1500 mg glucosamine/day) or in some cases also higher doses were administered, these doses should be considered to be amounts that were able to cause effects, i.e. adverse interactions or amplify the effects of coumarin anticoagulants. The question of the (highest) doses at which such effects are no longer observable would remain unanswered. Coumarin anticoagulant therapy and the degree of intended inhibition of coagulation depend on the ailment/condition that is to be treated. INR levels in the range of 2.0 – 4.0 are aspired depending on the type of ailment, whereas recommendations in this regard are not standardised (Martindale, 2009). It is therefore possible that potential interactions not only depend on the dose of glucosamine, but also on the degree of individual anticoagulants therapy of each patient.

It can be assumed that lower doses of glucosamine are connected with a lower probability and/or lower frequency and/or lower severity of the effect of an adverse interaction of glucosamine with coumarin anticoagulants. However, at the current state of knowledge it is not possible to deduce a dose that would be unlikely to increase the risk of occurrence of the above mentioned adverse interactions when taken on a regular basis, similar to a “tolerable upper intake level”.

The fact that lower dosages of glucosamine than are common in medicinal products are not known to have caused reports of suspected health problems can also be related to the fact that there is no reporting systems for foods, which include food supplements, comparable to the pharmacovigilance that exist for medicinal products. Furthermore, a connection between possible health problems and an interaction with food supplements is probably not assumed due to the lack of awareness of the risk.

3.1.3 Assessments by other committees

In the pharmaceutical sector, EMEA has taken precautionary measures for a glucosamine-containing medicinal product (as glucosamine hydrochloride) that is administered at a dose of 1250 mg glucosamine/day. The “Summary of Product Characteristics” contains the information that “[d]ata on possible drug interactions with glucosamine is limited, but increased INR with coumarin anticoagulants (warfarin and acenocoumarol) has been reported. Patients treated with coumarin anticoagulants should therefore be monitored closely when initiating or ending glucosamine therapy” (EMEA, 2006, Annex III). In its report on possible interactions, the *Australian Adverse Drug Reactions Advisory Committee and the Adverse Drug Reaction Unit of the TGA* (2008) states that product information on warfarin-containing drugs includes the information that “*there is some evidence that glucosamine might increase the activity of warfarin*” and recommends that patients who take warfarin should check the coagulation time when they begin taking products of the “complementary medicine” category or when changing the dose (ADRAC/ADRU, 2008). In connection with the suspected cases described by the *British Commission on Human Medicines/Medicines and Healthcare Products Regulatory Agency* (2006), the Agency recommended that patients who are undergoing warfarin therapy should abstain from glucosamine. The French Food Safety Agency (AFSSA) and the European Food Safety Agency (EFSA) have assessed the use of glucosamine in food supplements and for food fortification. These agencies did not note a relevant consumer risk of interactions with coumarin anticoagulants for a dose of 500 or 750 mg glucosamine/day, i.e.

these assessments do not address possible interactions with coumarin anticoagulants (Afssa, 2008; EFSA, 2009). The Canadian agency *Health Canada*'s publication on glucosamine as "Natural Health Product" (dosing ca. 1180-1662 mg) also provides no measures to protect individuals who take coumarin anticoagulants. Neither the publication text itself nor the referred scientific publications go into possible interactions with coumarin anticoagulants (Health Canada, 2008).

3.1.4 Exposure

The present risk assessment pertains to food supplements at daily intake amounts of 390-790 mg isolated glucosamine.

3.1.5 Risk characterisation

Several reports have been published on possible interactions of glucosamine in isolated form and coumarin anticoagulants. The case reports should be taken as a clear indication of potential interactions of glucosamine with coumarin anticoagulants. In this regard, BfR also refers to conclusions of EMEA, whereby some reports that are part of pharmacovigilance surveillance suggest a potential interaction with warfarin (EMEA, 2006; Annex II). The severity of observed effects ranged from INR changes without symptoms all the way to life-threatening haemorrhage. Haemorrhage due to potential interactions can occur in nearly all organs, and it is safe to assume that the clinical indications, bodily symptoms and the degree of severity of the problem vary depending on the point of occurrence (e.g. gastrointestinal tract, brain) as well as on the extent of haemorrhage. In isolated cases severe adverse effects are possible. The number of people treated with coumarin anticoagulants in Germany alone comprises hundreds of thousands of people. In the United States, the number of prescriptions for the anticoagulant warfarin for outpatient treatment rose from 21 million prescriptions in 1998 to 30.6 million prescriptions in 2004 (Wysowski et al., 2007).

For the majority of existing case reports of potential interactions, no information on the dosages of glucosamine used is available. In those cases where such information is available, the dosages are clearly higher than the doses in question here, whereas one suspected case reports a dose of 1.5 g glucosamine/day (MHRA, 2007). However, the data available does not constitute a reliable basis for the identification of an "effect level". Furthermore, the health assessment of potential interactions must consider additional factors such as interindividual variability, questions concerning the extrapolation of "effect level" on "no-effect level", the quality of the data pool or adequate regard for sufficient safety margins. While it can be assumed that lower doses of glucosamine are accompanied by a lower probability of the occurrence and/or lower frequency and/or lower severity of possible adverse interactions of glucosamine with coumarin anticoagulants, a dosage taken on a regular basis that bears an improbable risk of the occurrence of potential interactions of glucosamine with coumarin anticoagulants cannot be deduced based on the present state of knowledge.

In light of the severity of possible health effects of potential interactions of glucosamine with coumarin anticoagulants and the frequency of prescription of warfarin, BfR deems measures that protect individuals who take coumarin anticoagulants necessary when isolated glucosamine is used in food supplements in the amounts in question (393-786 mg glucosamine/day). Otherwise, individuals in this group are in danger of experiencing adverse interactions with coumarin anticoagulants.

3.2 Individuals with a known risk of cardiovascular disease

In 2004, the Danish Medicines Agency (DKMA) reported that elevated cholesterol levels were observed in six patients who were given glucosamine. According to the Agency's accounts, the reports show that the cholesterol levels fell when glucosamine was discontinued and rose when glucosamine therapy was resumed. The Agency also reported that in clinical studies carried out before glucosamine was approved, increased cholesterol levels were not observed, that (however) no blood tests to determine the cholesterol levels or other lipids were carried out in any of the studies, and that these studies did not record increased cholesterol levels as adverse effects (Danish Medicines Agency, 2004). In a follow-up report in 2005, the Agency published provisional data of a study with 212 patients. Overall, no changes in blood cholesterol or lipid levels were observed in the comparison of glucosamine treatment (1.5 g glucosamine/day) with a placebo treatment. However, the Agency pointed out that only an analysis of the entire group of patients was available. It could thus not be ruled out that additional analyses might identify a subpopulation with elevated cholesterol levels. The Agency concluded that the latest information would not support the assumption that glucosamine treatment in general leads to elevated cholesterol levels, that available reports show only few patients who are affected by elevated cholesterol levels, and that further analyses of the above mentioned data could determine the actual existence of a sensitive subpopulation. The Danish Medicines Agency recommended that the cholesterol levels of patients with known risk factors for cardiovascular diseases should continue to be checked before glucosamine treatment commences (Danish Medicines Agency, 2005).

In the "Summary of Product Characteristics, Labelling and Package Leaflet" of the above mentioned glucosamine-containing medicinal product, EMEA stated that "[s]poradic, spontaneous cases of hypercholesterolaemia have been reported, but causality has not been established". However, in the subchapter "special warnings and precautions for use", the Agency deemed it necessary to note that "[i]n patients with a known risk factor for cardiovascular disease, monitoring of the blood lipid levels is recommended, since hypercholesterolemia has been observed in a few cases in patients treated with glucosamine" (EMA, 2006, Annex III).

In more recent studies, Pham et al. (2007) observed an increase in triglycerides or LDL cholesterol levels in some patients when they received 1500 mg glucosamine/day, yet no data is provided for this. In two additional clinical studies no significant changes in cholesterol levels were observed (Albert et al., 2007; Muniyappa et al., 2006).

4 References

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- Annex I: List of the Names, Pharmaceuticals, Form, Strength of the Medicinal Products, Route of Administration, Applicant, Marketing, Authorisation Holder in the member states
- Annex II: Scientific Conclusions and Grounds for Amendment of the Summary of Product Characteristics, Labelling and Package Leaflet Presented by the EMA
- Annex III: Summary of Product Characteristics, Labelling and Package Leaflet (<http://www.emea.europa.eu/pdfs/human/referral/glucomed/Glucomed-AnnexesI-II-III-en.pdf>).

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