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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to glucosamine and maintenance of joints pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Béres Pharmaceuticals Ltd., submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Hungary, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim based on newly developed scientific evidence related to glucosamine and maintenance of joints. The food constituent that is the subject of the health claim is glucosamine, which is sufficiently characterised. The claimed effect is "contributes to the protection of joint cartilage exposed to excessive motion or loading and helps to improve the range of motion in joints". The target population proposed by the applicant is healthy individuals exposed to excessive load on the joints. Maintenance of joints is a beneficial physiological effect. The applicant provided two human studies as pertinent to the claim. One study was carried out in patients with acute injury of the knee. The evidence provided does not establish that patients with acute knee injury are representative of the target population with regard to the status of joint tissues, or that results obtained in studies on subjects with acute knee injury can be extrapolated to the proposed target population. The second study was an intervention with endpoints on putative biomarkers of collagen type II metabolism. The study was not adequately controlled and the evidence provided does not establish that changes in the proposed biomarkers over periods of three months can predict net changes in collagen type II in joint cartilage. The Panel concludes that a cause and effect relationship has not been established between the consumption of glucosamine and maintenance of joints.

KEY WORDS

Glucosamine, joints, health claims.

[1] On request from the Competent Authority of Hungary following an application by Béres Pharmaceuticals Ltd., Question No EFSA-Q-2011-00907, adopted on 25 November 2011.

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[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen for the preparatory work on this scientific opinion.

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SUMMARY

Following an application from Béres Pharmaceuticals Ltd., submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Hungary, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to glucosamine and maintenance of joints.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.

The food constituent that is the subject of the health claim is glucosamine, formulated as glucosamine sodium sulphate. Complete specifications, manufacturing process, bioavailability and stability information have been provided. The Panel considers that the food constituent, glucosamine, which is the subject of the health claim, is sufficiently characterised.

The claimed effect is "contributes to the protection of joint cartilage exposed to excessive motion or loading and helps to improve the range of motion in joints". The target population proposed by the applicant is healthy individuals exposed to excessive load on the joints. The Panel considers that maintenance of joints is a beneficial physiological effect.

The applicant provided two human studies as pertinent to the claim.

In a randomised, double-blind, placebo-controlled trial, 121 male patients who had a recent history of acute sports injury of the knee, and had clinical findings consistent with trauma, were divided into two groups which received 1.5 g glucosamine per day or a placebo for 28 days. Pain and functional ability were evaluated at the beginning of the study and at several time points after starting the intervention. The Panel considers that the evidence provided does not establish that patients with acute knee injury are representative of the target population with regard to the status of joint tissues, or that results obtained in studies on subjects with acute knee injury can be extrapolated to the proposed target population (i.e. healthy individuals exposed to excessive load on the joints). The Panel considers that no scientific conclusions can be drawn from this study for the substantiation of a claim on maintenance of joints in healthy individuals exposed to excessive load on the joints.

The second study was an open label intervention with glucosamine hydrochloride. Nineteen soccer players were divided into two groups which received 1.5 g or 3 g glucosamine per day for three months. No information was provided on the method of allocating the subjects to the two groups. There was no placebo control group. The endpoints of the study were the urinary levels of putative biomarkers of collagen type II metabolism in cartilage (CTX-II, C2C, CPII and ratio of CTX-II/CPII). Comparisons with baseline within groups were made for urinary markers after the glucosamine administration (at three months) and three months after the withdrawal of glucosamine administration (at six months). No comparisons were made between groups. The Panel notes that the study was not adequately controlled for factors which might have influenced the urinary analytes over the duration of the study. The Panel also considers that the evidence provided does not establish that changes in urinary CTX-II, C2C, CPII and ratio of CTX-II/CPII over periods of three months can predict net changes in collagen type II in joint cartilage. The Panel considers that no scientific conclusions can be drawn from this study for the substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of glucosamine and maintenance of joints.

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BACKGROUND

Regulation (EC) No 1924/2006[4] harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Art 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 05/08/2011.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
- On 17/08/2011, during the validation process of the application, EFSA sent a request to the applicant to provide additional information.
- The applicant provided the additional information on 24/08/2011.
- The scientific evaluation procedure started on 30/08/2011.
- On 16/09/2011, the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application and the clock was stopped on 21/09/2011, in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 30/09/2011, EFSA received the requested information as submitted by the applicant and the clock was restarted.
- During the meeting on 25/11/2011, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to glucosamine and maintenance of joints.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: glucosamine and maintenance of joints.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of glucosamine, a positive assessment of its safety, nor a decision on whether glucosamine is, or is

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Béres Pharmaceuticals Ltd., Mikoviny u. 2-4, H-1037 Budapest, Hungary.

The application includes a request for the protection of confidential data pertaining to the manufacturing process of the food constituent that is the subject of the health claim.

Food/constituent as stated by the applicant

According to the applicant, glucosamine, formulated as glucosamine sodium sulphate.

Health relationship as claimed by the applicant

According to the applicant, glucosamine, which is a constituent of the polysaccharide chains of cartilage matrix and synovial fluid glycosaminoglycans, stimulates the synthesis of physiological glycosaminoglycans and proteoglycans by chondrocytes, and of hyaluronic acid by synoviocytes, thus exerting a chondroprotective action in physically active people.

Wording of the health claim as proposed by the applicant

The applicant proposed the following wording for the health claim: "Glucosamine contributes to the protection of joint cartilage exposed to excessive motion or loading and helps to improve the range of motion in joints".

Specific conditions of use as proposed by the applicant

The applicant proposed an intake of 1500 mg glucosamine sodium sulphate per day. The target population is healthy individuals exposed to excessive load on the joints.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is glucosamine, formulated as glucosamine sodium sulphate.

The raw material for the production process is crustacean shells. Complete specifications, manufacturing process, bioavailability and stability information have been provided.

Glucosamine is a well characterised amino monosaccharide where a hydroxyl group (-OH) is replaced with an amino group (-NH2) (2-amino-2-deoxy-D-glucose). Glucosamine is usually formulated as the hydrochloride or as glucosamine sulphate, and can be quantified in foods by established methods.

The Panel considers that the food constituent, glucosamine, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect is "contributes to the protection of joint cartilage exposed to excessive motion or loading and helps to improve the range of motion in joints". The target population, as proposed by the applicant, is healthy individuals exposed to excessive load on the joints.

From the information provided, the Panel notes that the claimed effect relates to the maintenance of joints.

For claims on the maintenance of joints, possible outcomes related to joint structure and function include, for example, joint space width, mobility, stiffness and (dis)comfort (e.g. pain).

The Panel considers that the maintenance of joints is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in Medline and Embase, using the search term "glucosamine". The search was limited to human trials which were published in English. Trials were included if the study population was exposed to repetitive high physical impact and loading on the joints (people performing heavy physical work). Trials were excluded if the study population was diagnosed with or suspected to be affected by, osteoarthritis or osteoarthrosis.

The applicant provided one randomised controlled trial (RCT) and one open label human trial as pertinent to the claim.

The Panel has already issued an opinion on glucosamine and reduced rate of cartilage degeneration and reduced risk of development of osteoarthritis pursuant to Article 14 of Regulation (EC) No 1924/2006 with an unfavourable outcome (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009a). The Panel has also issued an opinion on glucosamine alone or in combination with chondroitin sulphate and maintenance of joints pursuant to Article 13(1) of Regulation (EC) No 1924/2006 with an unfavourable outcome (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009b).

In a randomised, double-blind, placebo-controlled trial (Ostojic et al., 2007), 121 male patients who had a recent history of acute sports injury of the knee, and had clinical findings consistent with trauma (acute minor knee injuries, less than grade II based on clinical findings according to the Outerbridge classification), received 1.5 g glucosamine (n=62) per day or placebo (cellulose; n=59) for 28 days. Pain and functional ability were evaluated at the beginning of the study and at 7, 14, 21 and 28 days after starting the intervention. The Panel notes that the study was carried out in patients with acute knee injury. The applicant was invited to justify extrapolation of the findings in the study group (patients with acute knee injury) to the proposed target population. In reply, the applicant mainly focused on the importance of a well defined study population, and stated that an acute knee injury is a well-defined clinical endpoint.

The Panel considers that the evidence provided does not establish that patients with acute knee injury are representative of the target population with regard to the status of joint tissues, or that results obtained in studies on subjects with acute knee injury can be extrapolated to the proposed target population (healthy individuals exposed to excessive load on the joints). No scientific conclusions can be drawn from this study for the substantiation of a claim on maintenance of joints in healthy individuals exposed to excessive load on the joints.

In another human study (Yoshimura et al., 2009), 21 male soccer players (19-22 years of age, mean 20.3) and, as a control group, 10 male college students (20-27 years of age, mean 23.5) were recruited. The soccer players were training five times a week for about 2 h/day, whereas the control subjects did not participate in any college athletics, nor had experienced moderate or hard exercise for over one year. The first part of the study was a comparison of putative urinary markers of collagen type II metabolism in cartilage in soccer players and controls. Urinary concentrations of the following biomarkers were assessed in both groups: as markers for collagen type II degradation, C-terminal crosslinking peptide (CTX-II) and neoepitope C2C; as a marker for collagen type II synthesis, C-terminal type II procollagen peptide (CPII). The authors stated that fragments of type II collagen

were targeted as biomarkers for cartilage breakdown because type II collagen is one of the major constituents of cartilage, and represents 90-95 % of the total cartilage collagen. In the soccer players the urinary concentrations of CTX-II, but not C2C, were significantly higher than in the control subjects ($p<0.01$). The concentrations of CPII were not different between groups. In addition, the ratio of CTX-II/CPII in soccer players was significantly higher than that in controls ($p<0.05$).

Subsequently, Yoshimura et al. (2009) carried out an open label intervention with glucosamine hydrochloride. To this end the soccer players were divided into two groups which received 1.5 g (n=9) and 3 g (n=10) glucosamine per day for three months respectively. No information was provided on the method of allocating the subjects to the two groups. There was no placebo control group. Urinary samples were taken at baseline, after the glucosamine administration (at three months) and three months after the withdrawal of glucosamine administration (at six months). The endpoints of the study were the urinary concentrations of CTX-II, C2C, CPII and ratio of CTX-II/CPII (concentration of analyte in second void morning urine, standardised for creatinine). Comparisons with baseline within groups were made for urinary markers after the glucosamine administration (at three months) and three months after the withdrawal of glucosamine administration (at six months). No comparisons were made between groups.

The applicant was invited to provide justification for the validity of the biomarkers used in the study, i.e. evidence that changes in urinary CTX-II, C2C and CPII over periods of three months can predict net changes in collagen type II content in joint cartilage in the proposed target population. In reply, the applicant provided three further studies: one study (Catterall et al., 2010) did not report any data on urinary CTX-II, C2C or CPII; two cross-sectional studies measured urinary CTX-II in athletes in training for different sports (O'Kane et al., 2006) and urinary CTX-II in early, occupational musculoskeletal disorders of the lower limbs (Mason, 2010). The Panel notes that none of these four studies (including Yoshimura et al., 2009) measured net changes in collagen type II content in joint cartilage in relation to changes in urinary CTX-II, C2C, CPII or ratio of CTX-II/CPII.

The Panel notes that the intervention study (Yoshimura et al., 2009) was not adequately controlled for factors which might have influenced the urinary analytes over the duration of the study, and that the evidence provided does not establish that changes in urinary CTX-II, C2C, CPII or ratio of CTX-II/CPII over periods of three months can predict net changes in collagen type II in joint cartilage. The Panel considers that no scientific conclusions can be drawn from this study for the substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of glucosamine and maintenance of joints.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent, glucosamine, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is "contributes to the protection of joint cartilage exposed to excessive motion or loading and helps to improve the range of motion in joints". The target population proposed by the applicant is healthy individuals exposed to excessive load on the joints. Maintenance of joints is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of glucosamine and maintenance of joints.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on glucosamine, formulated as glucosamine sodium sulphate, and "contributes to the protection of joint cartilage exposed to excessive motion or loading and helps to improve the range of motion in joints" pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0309_HU). August 2011. Submitted by Béres Pharmaceuticals Ltd.

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EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009b. Scientific Opinion on the substantiation of health claims related to glucosamine alone or in combination with chondroitin sulphate and maintenance of joints (ID 1561, 1562, 1563, 1564, 1565) and reduction of inflammation (ID 1869) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal, 7(9):1264, 17 pp.

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GLOSSARY / ABBREVIATIONS

CPII	C-terminal type II procollagen peptide
CTX-II	C-terminal crosslinking peptide
RCT	randomised controlled trial