Svar på Lægemiddelstyrelsens høring over Medicintilskudsnævnets indstilling om tilskudsstatus for lægemidler med indhold af glucosamin

- Dansk Selskab for Klinisk Farmakologi
- Laboratoires Expanscience
- Orifarm Generics A/S
- Pharmazan Pharmaceuticals ApS

Lægemiddelstyrelsen den 19. september 2011

ULLA KIRKEGAARD MADSEN

Til: ULLA KIRKEGAARD MADSEN
Emne: VS: Høringssvar om glukosamin

-----Oprindelig meddelelse-----
Fra: Jens Peter Konnerup Kampmann [mailto:jkam0005@bbh.regionh.dk]
Sendt: 9. juni 2011 10:10
Til: ELISABETH THOMSEN - 9306
Emne: Høringssvar om glukosamin

Kære Elisabeth,

DSKF (Dansk Selskab for Klinisk Farmakologi) støtter beslutningen om tilskudsfritagelse, men vil gerne oplyse om to punkter:

Det er vigtigt, at lægerne bliver informeret om, hvad de så skal gøre? Selv om man kan sige, at når glukosamin nu ikke virekr, skal patienterne ikke have noget andet - men næppe alle ser sådan på det, og hvad så? Kan I ikke alliere jer med IRF og få dem til at skrive om problemet? Hvis lægerne i stedet for giver et NSAID-præparat, har vi IKKE gjort sundheden her i landet en tjenete. Så må de hellere tage placeo-glukosamin. Dette er realiternes verden!!

I bør også holde særligt øje med forbruget af specielt NSAID - det skulle også nødigt stige.

Med mange gode hilsner

Jens P. Kampmann/
Overlæge, dr.med., formand for DSKF.

GLUCOMED
(GLUCOSAMINE HYDROCHLORIDE)

AD HOC REASSESSMENT OF REIMBURSEMENT STATUS OF GLUCOSAMINE (M01AX05) BY THE DANISH MEDICINES AGENCY

DISCUSSION OF THE DANISH MEDICINES AGENCY STATEMENT BY THE MAH

SECOND PART OF THE DISCUSSION FOLLOWING THE REVIEW BY THE REIMBURSEMENT COMMITTEE

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LIST OF ABBREVIATIONS

CLBP	Chronic Low Back Pain
CRF	Case Report Form
DMA	Danish Medicine Agency
ES	Effect size
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GAIT	Glucosamine/Chondroitin Arthritis Intervention Trial
HAQ	Health Assessment Questionnaire
JSW	Joint Space Width
KL	Kellgren-Lawrence
MA	Meta-analysis
MAH	Marketing Authorization Holder
MRI	Magnetic Resonance Imaging
NIH	National Institute of Health
NSAID	Non steroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcomes measures in rheumatology
RMDQ	Roland Morris Disability Questionnaire
SPC	Summary of Product Characteristics
SYSADOA	Symptomatic Slow acting drugs in osteoarthritis
VAS	Visual analog scale
WOMAC	Western Ontario and McMaster Universities

1. Introduction

On March 3rd, 2011, the Danish Medicines Agency (DMA) started a procedure or reassessment of the reimbursement status of Glucosamine (M01AX05) on the grounds stated hereafter.

"Clinical studies have called into question the efficacy of glucosamine for the alleviation of painful osteoarthritis (1). This was recently highlighted in a Norwegian study of patients with chronic low back pain and lumbar arthritis (13). Against this background, the Reimbursement Committee, at its meeting on 21 September 2010, encouraged the Danish Medicines Agency to reassess the reimbursement status of glucosamine as soon as possible. In addition, a new meta-analysis has concluded that health authorities ought not to grant reimbursement for glucosamine (12).

Consequently, the Danish Medicines Agency has decided to initiate ad hoc reassessment of glucosamine-containing medicines, which today have general conditional reimbursement when prescribed for the alleviation of symptoms of mild to moderate osteoarthritis and when prescribed to old-age pensioners. Should the Reimbursement Committee recommend to change the reimbursement status of these medicines, we will submit the Committee's recommendation for consultation to the affected companies, the relevant scientific societies and relevant patient organisations. We have not yet scheduled the reassessment of reimbursement status of the remaining medicines in ATC group M (musculo-skeletal system).

The affected companies, the relevant scientific societies and relevant patient organisations have all been informed of the coming reassessment of glucosamine."

Considering the arguments developed by the Danish Medical Agency (DMA), the MAH, Expanscience, presented the scientific arguments likely to offer an alternate view of the publications on glucosamine. The dossier was then submitted to the Danish Medical Agency in April 2011.

Following the receipt of this dossier as well as those submitted by other glucosamine manufacturers in Denmark, the Danish reimbursement Committee has discussed the reimbursement status for glucosamine-containing medicines at its meetings held on 26 April 2011 and 24 May 2011.

During these meetings, the Committee maintained his recommendation to discontinue the reimbursement of glucosamine-containing medicines, based on the following arguments:

- The Committee mentions the results of the last update of the Cochrane meta-analysis on glucosamine published by Towheed (11) and considers: *"The results of the different studies vary considerably. The analysis shows overall a pain-relieving effect for glucosamine in comparison with a placebo. On the other hand, looking at only the high-quality studies with adequate blinding procedures, no pain-relieving effect for glucosamine can be seen. The function-improving effect depends on the measurement scale used".*
- The Committee takes into account the statement of the Danish National Board of Health, which does not recommend treatment with glucosamine as "*there is no positive effect on pain and functional level".*
- The Committee takes also into account the statement of the Institute for Rational Pharmacotherapy, which does not recommend glucosamine as the available evidence "*does not indicate that there are clinically-relevant pain-relieving or function-improving effects".*

2. Discussion of the arguments developed by the Danish Reimbursement Committee

2.1. Discussion of the results of the last update of Glucosamine Cochrane meta-analysis (Towheed, 2009)

Briefly, this new update (11), after the meta-analyses published in 2001 (9) and 2005 (10), concerned a total of 25 clinical trials meeting the minimal inclusion criteria defined by the authors.

The main results observed in the whole sample of trials are given in table 1 hereafter.

These results **confirms the significant efficacy of glucosamine in most standard pain outcomes, Lequesne index, JSW**, and to a lesser extent WOMAC total scores, but not subscores.

But, surprisingly, the authors emphasized straightaway the "negative" results observed in "*studies with adequate allocation concealment*" which "*failed to show any benefit of glucosamine for pain (…), function and stiffness*", despite a significant effect on the Lequesne index.

The MAH does not consider that the grouping in studies "*with adequate allocation concealment*" is adequately implemented and this is likely to result in an artificial separation between two groups of studies. Actually, the authors mentioned as the primary quality study criterion "a correct allocation concealment".

This should be acceptable provided it was possible for ALL studies included in the meta-analysis to take this criterion into account on the same basis.

But that is precisely not the case for "allocation concealment". It is to be emphasized that this quality criterion became rather recently a key criterion. A literature search of the term (Pubmed) "allocation concealment" returns 896 references, the first of which published in 1984, but the second one only in 1994, with a clear increase in the occurrence of the term from 2000 onwards (831 references, with a peak in year 2000 with 94 citations).

This observation is to explain that papers published before 2000 were not systematically checked for the presence / absence of allocation concealment (about one half of the studies taken in the meta-analysis were published in year 2000 and before).

It is likely to be explained by the fact that "allocation concealment" was generally confounded with double-blinding. Therefore, it is clear that the lack of mention of "allocation concealment" in studies published prior to 2000 cannot be considered as a lack of quality, but only as a lack of mention of a "future" quality criterion.

Therefore, the MAH considers that the focus of the conclusion of the meta-analysis on: "*analysis restricted to studies with adequate allocation concealment failed to show any benefit of glucosamine for pain (based on a pooled measure of different pain scales) and WOMAC pain, function and stiffness subscales"* is excessive and probably erroneous due to the hypertrophic role of allocation concealment, as a key quality criterion of clinical studies.

Of course, there is no discussion that it represents a "minimal" quality criterion, as regards to its mention in recent studies. In older studies, the lack of mention of this term does not necessarily mean that blinding procedures were not adequate.

Owing to the arguments developed hereabove, it is clear that the "allocation concealment" criterion is insufficient and/or inadequate in defining "quality studies":

- Inadequate while it excludes studies performed at a time when the term "allocation concealment was not currently in use,
- Inadequate while it accepts as "quality studies", clinical trials where, for instance, more than one study treatment was used in the active treatment group, or where GCP were not adequately documented (MacAlindon, 4), or where the patient OA diagnosis was not defined in accordance with guidelines in about one half of the study population [1] (Rozendaal, 8),
- Insufficient while it accepts studies with particular issues, such as the GAIT study (Clegg, 1) for which the authors themselves recognized the possible role of those issues in the misinterpretation of results.

Another subgroup analysis was also performed according to the origin of the tested preparation, labeled by the meta-analysis authors as "Rotta" and "non-Rotta" preparations.

[1] The last version of the EMEA guidance relating to osteoarthritis states that : "*For studies of structure-modifying drugs, it is recommended to include patients with Kellgren and Lawrence radiographic entry criteria of grades 2 or 3 (i.e., sufficient remaining interbone distance to permit detection of worsening/progression) or a certain pre-defined amount of joint space width (in mm)".*

This classification cannot be considered as relevant, because of the global identity of the two salts, sulfate and hydrochloride. The term used by Towheed: "Rotta-preparation" does not meet any standard pharmaceutical definition. For instance, the "Rotta-preparation" label in the studies of the Towheed meta-analysis generally corresponds to glucosamine sulfate salts, but there is exceptions in studies where, for instance, both sulfate and hydrochloride salts were used under the same "label" (see Mac Alindon, 4).

In addition, the MAH considers that the simple dichotomy between "Rotta-preparation" (that should be understood as " Glucosamine sulfate of pharmaceutical grade") and "Non Rotta-preparation", that includes all other forms of glucosamine (pooling pharmaceutical grade glucosamine hydrochloride with all other glucosamine food supplements) results in a pejorative view of the "pharmaceutical" glucosamine hydrochloride, that is not supported by any relevant scientific argument.

It is to be emphasized that, on the occasion of the European MA renewal, a thorough argumentation about the identities between the sodium salt and the hydrochloride salt has be submitted to the European health authorities. They fully agreed upon this equivalence that was one of the basis of the marketing authorization. Then, the therapeutic interest of Glucosamine, has been ascertained by the Commission who granted a renewal of the MA for glucosamine hydrochloride.

Moreover, it is to be stressed that the equivalence between the two salts has been documented in a recent paper (1), where it is concluded that the differences in clinical efficacy are likely to be mainly of pharmacokinetic nature.

In conclusion, the global analysis of the last update of the Cochrane meta-analyses confirmed the effectiveness of glucosamine in reducing OA symptoms, as assessed by VAS pain, Lequesne index, with global effect sizes of 0.47[1] and to a lesser extent by WOMAC global score (ES = 0.18).

The recent paper by Towheed does not present any relevant subgroup analysis that should restrict the global conclusions.

[1] Except otherwise specified in the text of the document, effect sizes given as positive values (without mention of the "+" sign means a better result of the intervention under study.

Table 1: Summary of results (effect sizes) reported in the latest version of the Towheed meta-analysis on glucosamine.

Comparison 1. Glucosamine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	18	2543	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.72, -0.23]
2 Lequesne Index	5	951	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.82, -0.12]
3 Lequesne Index	2	407	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.20, 1.91]
4 WOMAC Pain Subscale	10	2017	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.14, 0.03]
5 WOMAC Stiffness Subscale	7	1390	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.13, 0.08]
6 WOMAC Function Subscale	10	2017	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.17, 0.00]
7 WOMAC Total	6	882	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.31, -0.05]
8 Mean Joint Space Width	1	212	Std. Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.20, 0.34]
9 Minimum Joint Space Width	2	414	Mean Difference (IV, Fixed, 95% CI)	0.32 [0.05, 0.58]
10 Patient global assessment of disease status score (0-100mm scale)	1	630	Mean Difference (IV, Fixed, 95% CI)	1.10 [-2.77, 4.97]
11 Patient global assessment - number responding they are better than at start of trial	1	118	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.80, 1.82]
12 Physician global assessment of disease status score (0-100)	1	630	Mean Difference (IV, Fixed, 95% CI)	0.80 [-2.78, 4.38]
13 Physician global assessment of good or excellent response	2	100	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [1.49, 3.43]
14 Osteoarthritis Research Society International Responder Criteria (OARSI)	3	918	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.83, 1.83]
15 Toxicity (Number of Patients Reporting Adverse Events)	16	2117	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.07]
16 Toxicity (Number of Withdrawals due to Adverse Events)	20	2970	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.05]

2.2. Discussion of the statement by the Danish National Board of Health

Briefly, this board stated in September 2007, that there is no positive effect on pain and functional level" when using glucosamine in the treatment of osteoarthritis.

The statement of this board was based on the "negative" studies, and notably the GAIT study, which was shown to present with significant issues, as underlined by the authors themselves (see discussion developed in the dossier submitted to Danish Medicines Agency in April.

Furthermore, the board also discussed the potential role of the nature of the salts, sodium and hydrochloride, which was also shown to be irrelevant.

2.3. Discussion of the statement by the Institute for Rational Pharmacotherapy

The institute justified his negative advice by using approximately the same arguments, and notably, again, the lack of effect in the "quality" studies of the previous version of the Towheed meta-analysis.

We have shown in the present document that this allocation-concealment-based subgroup analysis is not adequate to fully characterize the assessment of glucosamine efficacy.

3. Conclusion

After reviewing the arguments submitted by the glucosamine hydrochloride MAH, the Danish Reimbursement Committee maintained his recommendation of discontinuation of the general conditional reimbursement of these medicinal substances on the grounds of the results of a new meta-analysis published by the Cochrane Collaboration and considering the recommendations of two Danish health scientific societies: the Danish National Board of Health and the Institute for Rational Pharmacotherapy.

Considering the arguments developed in each of these three instances, the MAH suggests the Reimbursement Committee not to take it into account for the following reasons :

1. The new Cochrane meta-analysis enlightens the lack of any glucosamine benefit for pain, function and stiffness in the analysis restricted to studies with "good allocation concealment" and in a subgroup of Non-Rotta preparation studies. The MAH considers that both subgroup analyses are not relevant.

First, because "allocation concealment" cannot be considered as an unique indicator of the quality of the studies, especially for those studies performed before year 2000, when this term was almost nonexistent. *A contrario*, this simple classification results in defining as "good quality studies", certain trials in which significant methodological issues were raised.

Second, because the classification between Rotta and Non Rotta preparations relies upon non standard criteria, each of the two categories encompassing quite different pharmaceutical entities, and also because it is now officially recognized (renewal of glucosamine-HCl MA in Europe), that there is strictly no intrinsic differences between the sulfate and the hydrochloride salt.

2. The recommendations of the two Societies that were taken into account by the Reimbursement Committee, were based upon the same "negative" studies, mainly the GAIT study, and the same subgroup analyses in meta-analysis, that lead to a negative view of the product. Therefore, the MAH suggests to review those recommendations in line with the arguments developed in the dossier supplied in April, as well as the present one.

Finally, the MAH propose to only take into account the global analysis provided in the last update of glucosamine meta-analysis, that evidences a significant efficacy on pain and function with consistent effect sizes of 0.47 for both criteria.

Therefore the MAH suggests to the Danish Medical Agency to maintain the present status of Glucomed, while the relative view of the proposed arguments is not likely to modify in any extent the previously defined therapeutic profile of the drug and therefore its reimbursement status.

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Lægemiddelstyrelsen
Medicintilskud
Axel Heides Gade 1
2300 København S
Att: Ulla Kirkegaard Madsen

Re: "Partshøring – Revurdering af tilskudsstatus for lægemidler med indhold af glucosamin (M01AX05)" – Orifarm comment to "Medicintilskudsnævnets indstilling"

Dear Ulla Kirkegaard Madsen,

Thank you for providing information about the opinion of "Medicintilskudsnævnet" dated 25. May 2011.

We would like to comment on the opinion by submitting a summary of the scientific evidence for the efficacy of glucosamine together with a conclusion to support our recommendation for reimbursement status for glucosamine which is:

- "Generelt klausuleret tilskud" for the indication symptom relief for mild to moderate osteoarthritis in the knee.

Summary of the scientific evidence for the efficacy of glucosamine

1. Introduction

The purpose of this report is to briefly provide a summary of the glucosamine efficacy data with a particular emphasis on studies published since the most recent update of the Cochrane Review in 2008 [1].

2. Current status as of the latest reviews of glucosamine efficacy

Three contemporaneous reviews of glucosamine therapy were published in 2008 and 2009 and provide information regarding the efficacy of glucosamine.

2.1 Cochrane Review:

The 2008 update of the Cochrane Review [1] is the second and most recent update of the Cochrane Review originally published in 2001. Only RCTs that evaluated the efficacy or toxicity, or both, of glucosamine in OA were considered. Twenty-five RCTs containing 4963 adults (of age 18 years and older) with a diagnosis of either primary or secondary OA at any site, including the axial and peripheral skeleton, which evaluated the effectiveness and toxicity of glucosamine were included in the final analyses.

The main results of the 2008 update of the Cochrane Review can be summarized as follows:

Analysis restricted to studies with adequate allocation concealment did not to show any benefit of glucosamine for pain (based on a pooled measure of different pain scales) and WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain, function and stiffness subscales. However, it was found to be better than placebo using the Lequesne index, standardized mean difference (SMD) -0.54.

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Collectively, the 25 RCTs favoured glucosamine with a 22% (change from baseline) improvement in pain, SMD -0.47; and an 11% (change from baseline) improvement in function using the Lequesne index, SMD -0.47.

The results were not uniformly positive, however, and the reasons for this remain unexplained. WOMAC pain, function and stiffness outcomes did not show statistical significance.

RCTs in which the Rotta preparation of glucosamine (a pharmaceutical grade of crystalline GS manufactured by Rottapharm Inc.) was compared to placebo found GS superior for pain (SMD -1.11) and function (Lequesne index SMD -0.47). Two RCTs using the Rotta preparation also showed that glucosamine was able to slow radiological progression of OA of the knee over a three-year period (mean difference (MD) 0.32). However, pooled results for pain (SMD -0.05) and function using the WOMAC index (SMD -0.01) in RCTs using a non-Rotta preparation of glucosamine did not show statistical significance. Glucosamine was as safe as placebo in terms of the number of participants reporting adverse reactions.

The authors conclude that pooled results from studies using a non-Rotta preparation or adequate allocation concealment did not show benefit in pain and WOMAC function while those studies evaluating the Rotta preparation showed that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic OA.

2.2 UK Health Technology Assessment:

A systematic review by the Health Technology Assessment Programme of the National Institute for Health Research (NIHR) in the UK [2] published in November 2009 had the objective of assessing the clinical and cost effectiveness of GS, glucosamine hydrochloride (GH) and chondroitin sulphate in modifying the progression of OA of the knee. The report consisted of an analysis of systematic reviews of RCTs of at least 12 months duration. Cost-effectiveness, sensitivity and value of information analysis were also performed in addition to a mechanism of action analysis.

The authors reported that, in primary trials with duration of at least 12 months, there was evidence of statistically significant improvements in joint space loss, pain and function for GS; however, the clinical importance of these differences was less clear. In the two RCTs using the Rotta preparation the need for knee arthroplasty was reduced from 14.5% to 6.3% at 8 years follow-up.

Their conclusion was that there was evidence that GS is clinically effective in the treatment of OA of the knee. In addition to evidence from human RTCs there was evidence from *in vitro* and biological studies conducted in animals to suggest a biological basis (e.g., increase in both serum and synovial levels of glucosamine, anabolic or catabolic effects) for the potential clinical impact of GS administration. For other preparations of glucosamine (i.e., GH), chondroitin and combination therapy, there was less evidence for a clinical effect. For chondroitin, the evidence base was less consistent while for GH the evidence was absent.

2.3 OARSI recommendations, Part III:

Part III of Osteoarthritis Research Society International (OARSI) recommendations for the management of hip and knee osteoarthritis [3] contained results of 19 placebo-controlled RCTs of glucosamine for OA[1]; 16 of these studies were of GS (13 oral, 2 intra-muscular (IM) and 1 intra-articular (IA)) and 3 studies used GH.

[1] GS studies included both hip and knee OA while GH studies included only knee OA

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Using a meta-analysis of RCTs in which GS *or* GH were used (including post-2006 studies), an ES=0.46 was determined which the authors termed a "moderate symptomatic efficacy". However, there was significant heterogeneity of outcomes and considerable evidence of publication bias in this analysis.

Considering the results of GS and GH separately, the OARSI study concludes that the ES for pain reduction was 0.58 for GS but insignificant for GH, ES=-0.02. The outcomes of GS trials were determined to be very heterogeneous and there was indication of significant publication bias. When the analysis of GS trials was limited to RCTs of high quality, then ES is 0.29, there is no evidence of publication bias but heterogeneity remained significant.

Considering only RCTs performed after the publication of the consolidated standards for reporting clinical trial statement, the results become homogeneous, there is no evidence of publication bias but efficacy is smaller as ES was only 0.13.

The calculated ES for pain of 0.58 for GS is considered 'moderate' [2] and compares favourably to other pharmacological, non-pharmacological or surgical treatment modalities examined in the OARSI study using a criteria of 'best of evidence for efficacy' and the highest Level of Evidence category, Ia. It is similar to the ES for pain calculated for IA corticosteroid (ES=0.58) and IA hyaluronic acid (ES=0.60) and only two other treatments, opioids (ES=0.78) and chondroitin sulphate (ES=0.75) have a better ES for pain than GS.

2.4 Comment on the Latest Reviews of Glucosamine Efficacy

Although the Cochrane Review did not show any benefit of glucosamine using the WOMAC indices for pain, function or stiffness, the Review did state that glucosamine was better than placebo when outcomes were evaluated by a combined severity index of pain/discomfort, maximum distance walked and daily activities (Lequesne Index).

The British Health Technology Assessment concluded that GS showed some clinical effectiveness in the treatment of knee OA. The report concluded that the evidence in support of GS effectiveness was greater than the evidence of support for other preparations of glucosamine, chondroitin or combination therapy. The authors of the Health Technology Assessment suggest that future clinical studies of glucosamine should use GS as they saw no evidence for a clinical effect of GH.

The discrepancy between GS and GH was also seen in the OARSI study (part III) which reported very different ES pain scores for GS (0.58) and GH (-0.02). This unadjusted ES value for GS, although considered moderate, is better than other OA treatment options. Consideration of possible confounding factors, accordingly, results in a reduction in the magnitude of the calculated ES value but still remains above 0.13.

3. Post-Review Meta-Analyses of Glucosamine Studies

Two recent studies of glucosamine trials have used the technique of meta-analysis or 'network' meta-analysis in an attempt to resolve the issue of glucosamine efficacy. Both studies have generated a great deal of comment and criticism in the form of published editorials, letters to the editor and on-line rapid responses.

[2] ES=0.2 is considered small, ES=0.5 is moderate and ES>0.8 is a large effect

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The meta-analysis of Vlad et al. [4] analyzed 15 [3] randomized, double-blind, placebo controlled trails of glucosamine (GS or GH) trials for pain from OA of the hip or knee in an attempt to explain the heterogeneity of the various trials.

The conclusions of this study are that heterogeneity in these trials was larger than would be expected by chance, that GH is not effective and effect sizes were consistently higher in trials with industry involvement. The authors indicated that different glucosamine preparations, inadequate allocation concealment and industry bias could potentially explain the noted differences in effects sizes and heterogeneity.

Critiques of the Vlad study propose several alternate explanations of the glucosamine meta-analysis results of Vlad et al. and propose that quality and trial design issues are more likely explanations of differences in the glucosamine trials.

A lengthy critique of the Vlad study is provided by Reginster [5]. Reginster proposes that study design and drug quality issues are more likely responsible for the differences in the glucosamine trials that an inferred industry bias. Reginster proposes that the differentiating factor between studies demonstrating a positive effect and those that do not are due to a variety of quality related issues and not the presence or absence of industry involvement. Thus, the three industry sponsored trials [6-8] do demonstrate efficacy because the study drug used was a high quality, prescription form of the drug used in Europe and that the trial designs (i.e., dose, duration and outcome analysis) were also of high quality. In other words, the industry sponsorship of the trial is incidental to the quality parameters. More specifically, he argues that there are three trials included in the Vlad analysis that have detrimental quality and/or trial design issues including being underpowered. Performing a meta-analysis of the three trials mentioned above, which were all high-quality, recent studies of knee OA, Reginster produced results that were extremely homogenous with an effect size that was ≥0.33 for all WOMAC and Lequesne parameters examined and is of the same magnitude as seen in other OA treatments.

The network meta-analysis of Wandel et al. [9] is another recent meta-analysis study of glucosamine trial data that produced a great deal of comment, criticism and exposure in the popular media [10, 11]. This was a network meta-analysis study of 10 [4] large scale (>200 patients) randomized controlled trials in patients with knee or hip OA that compared glucosamine, chondroitin or glucosamine plus chondroitin with placebo alone. The aim was to determine the effect of glucosamine, chondroitin, or the two in combination on joint pain and on radiological progression of disease in knee or hip OA.

The conclusions of this study were that compared to placebo, glucosamine, chondroitin, and their combination do not result in a relevant reduction in joint pain or have an impact on narrowing of joint space. Health authorities and health insurers should not cover the costs of these preparations, and new prescriptions to patients who have not received treatment should be discouraged.

The two major critiques of the Wandel study can be summarized as follows.

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[3] Trials ranged from 24-630 subjects, duration of 4-156 weeks reported from 1980 to 2006. GS was used in 12 trials, 2 used GH and 1 used both. Industry funding was reported for 11 trials and 13 used industry supplied study drug.

[4] There were 6 glucosamine *vs.* placebo trials of 101-111 subjects per treatment from 1994 to 2008. 'Glucosamine' was used in 2 trials GS was used in 3 trials, and GH and GS used 1 trial. The 4 arm GAIT study of approx. 300 subjects per arm used GH in the glucosamine containing arms.

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First, the results are dependent on the particular studies included in the network analysis. Most notable are claims that studies using GH or OTC dietary supplement or other non-pharmaceutical grades of GS should not be included in the network analysis. A similar claim for exclusion is made for doses of GS less than the recommended dose of 1500 mg qd or for indications other than knee OA.

The second major critique is that the criteria used in the Wandel study to establish a clinical relevance, namely 0.9 cm for the pain scale and >0.39 for ES, are not valid. It was noted that a 0.9 cm difference for severe (>7) pain is clinically different than for pain of <4 and it was noted that the baseline pain for some of the included trials was only 2.5 cm and that it was unlikely to decrease by >0.9 cm [12] Several persons questioned the raising of the ES threshold in the Wandel study to 0.39 from the traditional value of 0.2. Furthermore, it was noted that ES values for conventional OA treatments such as paracetamol, NSAIDs and celecoxib calculated in other studies were 0.14, 0.29 and 0.13, respectively; all far below the 0.39 threshold, but very near the 0.17 ES for glucosamine calculated in the Wandel network meta-analysis study.

The level of controversy and criticism of the Wandel study prompted the editors of the BMJ to re-examine the paper at a Post Publication Review Meeting. The editor confirmed that the criticisms raised in the rapid responses mainly address the selection and inclusion of studies and the assumptions made by the authors in their modelling analyses. They concluded that these criticisms continue the debate but do not negate the findings of the study. The editors judged that the authors of the article gave an accurate and suitably cautious account of this study's findings, strengths, and limitations and noted that the authors were particularly thorough and transparent in reporting their methods and justifying their assumptions.

However, the BMJ editors decided that the following statements in the discussion section and the abstract of the article were *not* directly supported by their data.

"Coverage of costs by health authorities or health insurers for these preparations and novel prescriptions to patients who have not received other treatments should be discouraged."

and

"Health authorities and health insurers should not cover the costs of these preparations, and new prescriptions to patients who have not received treatment should be discouraged"

3.1 Comment on the Latest Meta-Analyses of Glucosamine Efficacy

Although the more notable meta-analyses of Vlad [4] and Wandel [9] are generally not supportive of a favourable efficacy for glucosamine, several investigators have vigorously challenged the assumptions and conclusions of these MA studies. It has been demonstrated that MA outcomes can vary greatly depending on the criteria used to include or exclude studies. Using logical criteria for inclusion, Reginster has shown that extremely homogenous results with an effect size of the same magnitude as seen in other OA treatments can be produced. Others have argued that the grading criteria used by Wandel et al. are not appropriate and that the reported ES value of 0.17 judged to be not significant by the criteria used by Wandel is actually quite in agreement with ES values for conventional OA treatments reported in other studies.

4. Post-review studies

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A survey of the post-Cochrane Review literature for placebo-controlled randomized controlled trials (RCTs) demonstrates that there are recent clinical trials that continue to indicate a beneficial effect of glucosamine sulphate (GS) in patients with knee osteoarthritis (OA).

The studies of Frestedt [12] and Giordano [13] each indicated a measurable reduction in pain and improvement in functioning associated with GS treatment. The study of Bruyere [14] indicated that treatment of knee OA patients with GS, for at least a year, may reduce the incidence of future joint replacements. The recent study of Petersen [15] showed that GS therapy, when combined with exercise, decreased the levels of one (and perhaps two) markers of cartilage degradation indicating a physiological effect that may be the result of improvements in OA symptoms. Of the studies in knee OA patients, only the study of Chopra [16] did not demonstrate a beneficial effect of GS. A summary of the statistically significant results of GS administration in these studies is provided in Table 1.

Table 1 Statistically Significant ($P \leq 0.05$) Results in 'Post-Cochrane' Studies: Within Glucosamine Sulphate Group or *vs.* Placebo

Study	Daily GS Dose (mg)[d]	Number of GS patients	Duration of Treatment	Diagnosis of Patients	Statistically Significant Outcome (P≤0.05); Within GS Group	Statistically Significant Outcome (P≤0.05); PBO *vs.* GS
Bruyere et al. 2008	1500	144	≥12 months	KOA	na	57% decrease in TJR
Chopra et al. 2011	1000	35	16 weeks	KOA	None	None
Frestedt et al. 2008	1500	19	12 weeks	KOA	WOMAC pain -12.6 [0] Activity Score -10.6 [0] WOMAC total -10.8 [0] 6MWD +56 feet	WOMAC pain; (PBO -2.9; GS -12.6) [0 n]
Giordano et al. 2009	1500	30	12 weeks	KOA	Rest and motion VAS pain, W-TPS, W-TSS, W-TPFS, Decreased NSAID use [0]	Rest and motion VAS pain, W-TPS, W-TSS, W-TPFS, Decreased NSAID use [0]
Petersen et al. 2010	1500	12	12 weeks	KOA	13% decrease in serum COMP	13% decrease in serum COMP
Wilkens et al. 2010	1500	125	6 months	LBP or lumbar OA	None	None

na; not applicable, nd; not determined, GS; Glucosamine sulphate, PBO; placebo, OA; osteoarthritis, KOA; knee osteoarthritis, LBP, lower back pain, TJR; total joint replacement, WOMAC; Western Ontario and McMaster Universities, 6MWD; six minute walking distance, VAS; Visual Analogue Scale, W-TPS; WOMAC total pain score, W-TSS; WOMAC total stiffness score, W-TPFS; WOMAC total physical function score, NSAID; nonsteroidal anti-inflammatory drugs, COMP; cartilage oligomeric matrix protein.

Using a transformed scoring system, where negative values indicate improvement and positive values indicate worsening of symptoms. Only the improvement in WOMAC pain score differed significantly among all groups (p = 0.009 ANCOVA), however, differences in WOMAC pain scores at baseline also differed significantly among groups (p = 0.039 ANCOVA).
Evaluations performed at baseline, 4, 8, 12, 16, 20 and 24 weeks. Listed outcomes achieved statistical significance for at least one evaluation.
1500 mg GS is equivalent to 1200 mg glucosamine.

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4.1 Comment on the Most Recent Studies of Glucosamine Efficacy

The heterogeneity in the results of the post-Cochrane studies described in this report is indicative of the varied results of glucosamine studies.

In all of the studies involving knee OA, a positive effect is reported for glucosamine sulphate except for the Chopra et al. study [16]. No positive effect was reported in the Wilkens et al. study [17], however, the patient population was different from the other studies and consisted of chronic low back pain (LBP) and degenerative lumbar OA patients. The Bruyere et al. [14] and Wilkens et al. [17] studies had more than 100 subjects in the GS treatment group while the other 4 were small studies with between 12 to 35 subjects in the GS treatment groups.

Limiting the analysis to subjects with knee OA who were administered 1500 mg GS per day for at least 12 weeks, the results are uniformly positive. Although this is an admittedly small collection of studies representing a small number of subjects, they do provide an indication of a possible clinical benefit for GS (*not* GH) therapy in a selected patient population (knee OA) of at least 12 weeks duration of approximately 1500 mg per day.

5. Concluding remarks

It is difficult to reconcile the conflicting efficacy results of glucosamine clinical trials. Potential sources of the diversity in outcomes in these clinical trials can be explained by the unorthodox drug development history of glucosamine. Most other drugs are usually discovered, formulated and developed into a pharmaceutical drug therapy by a single company that follows a linear well-defined path from discovery to approval. Through this process factors such as drug quality, formulation, dosage, length of therapy and therapeutic indication(s) are determined or optimized by a clear, straight forward and routine process of modern drug development. A single drug company who has proprietary and patented control of the drug under development is in control of the entire highly regulated process.

Glucosamine, however, was independently developed by numerous non-commercial and commercial entities in Europe and North America. As glucosamine was developed as a nutritional supplement in the US, the manufacturing standards required for pharmaceutical drugs did not apply and thus the quality and bioequivalence of different preparations varied greatly [18]. In Europe where drug quality standards were more rigorous, different formulations (GH or GS) of glucosamine at different doses and dosing schedules have been used in clinical trials.

When looking at the entire history of glucosamine clinical trials it has been said that efficacy results are no longer uniformly positive as the first encouraging results were not found consistently in later studies. However, efficacy results can *not* be said to be uniformly negative either.

Although the results of the most recent Cochrane Review have been interpreted as being negative, the Review did report positive results when outcomes were measured by the Lequesne Index. In addition, the British Health Technology Assessment concluded that GS showed some clinical effectiveness in the treatment of knee OA and that the evidence for the efficacy of GS was much greater than the evidence for the effectiveness of GH, chondroitin or combination therapy. Finally, the OARSI study reports unadjusted ES values for GS that are 'moderate' and small but significant ES values in subgroup analyses.

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Contributing further to the confounding of glucosamine results are factors such as investigator bias and study quality, heterogeneity in the affected subject population (i.e., differences in severity or length of disease), different indications (knee OA vs. hip OA), significant placebo effects and a small or modest anticipated beneficial effect of glucosamine therapy. Several factors each individually contributing a small degree of diversity, can make it difficult to compare individual trials to each other. This problem is magnified when one attempts to make generalized conclusions regarding the overall efficacy of glucosamine or when studies must be grouped together, for example, in a meta-analysis study.

This critical question was addressed by Vlad and colleagues [19] in their response to criticism [5] of the inclusion of several clinical trials in their meta-analysis study [4]. The authors of the Vlad study stated that they had followed standard conventional meta-analysis techniques to pre-specify liberal inclusion criteria and that this method was the best way to prevent intentional or unintentional biases from influencing which trials are included or excluded from the analysis. Although this is indeed most likely correct, it must also be mentioned that these inclusion techniques were developed in the framework of the traditional drug development process which is itself an inherently homogenous process. Thus, 'casting a wide inclusion criteria net' for clinical trials of a drug developed in the traditional drug development process is quite different from casting a wide net for glucosamine clinical trials; a drug that was developed in a disorganized drug development environment.

The debate surrounding the results and conclusion of the Wandel et al. study [9] can also be attributed to a similar cause, i.e., the results of any analysis are directly dependent on the data chosen to be analyzed. Valid arguments exist for the inclusion or exclusion of any specific data set.

An alternative selection approach to that used by Wandel is described by Reginster [19] who argues that for a drug such as glucosamine, the analysis should be performed with the same substance, (i.e., only GS) formulation, and dosage to avoid the inherent problems of heterogeneity introduced by the various manufactures of glucosamine that have variable PK/PD properties.

The OARSI Treatment Guideline Committee [3] has stated its preferred comparison method. The committee favours pooling of all available trial data for each modality of therapy in order to facilitate comparisons of ES across treatments based on the published MAs. Further comparisons should be made using the same criteria, rather than applying different quality criteria for inclusion of trials in the MAs for different modalities of therapy. For example, MA of all trials for GS showed significant efficacy for pain relief with a moderate ES (ES=0.61, 95% CI 0.28, 0.95), whereas in a sub-group analysis of trials judged to have adequate allocation concealment, efficacy was not apparent (ES=0.04, 95% CI -0.09, 0.17). The committee recommends the former inclusive method rather than the latter procedure that excludes studies for a reason that is specific or particular to an individual treatment modality.

Whichever selection procedure is most appropriate, it is certain that the results derived from any particular meta-analysis study is critically dependent on which studies are included or excluded in the analysis.

The survey of the post-Cochrane Review literature demonstrates that there are recent clinical trials that indicate a beneficial effect of GS in patients with knee OA. The studies of Frestedt [12] and Giordano [13] each indicated a measurable reduction in pain and improvement in functioning associated with GS treatment. The study of Bruyere [14] indicated that treatment of knee OA patients with GS, for at least a year, may reduce the incidence of future joint replacements. The recent study of Petersen [15] showed that

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GS therapy, when combined with exercise, decreased the levels of one or two markers of cartilage degradation indicating a physiological effect that may be the result of improvements in OA symptoms. Of the studies in knee OA patients, only the study of Chopra [16] did not demonstrate a beneficial effect of GS.

Although the efficacy results for GS are not uniformly positive they are also not uniformly negative and positive results can be found in studies performed after the most recent Cochrane Review using the sulphate form of glucosamine, at a daily dose of 1500 mg for the specific indication of knee OA.

Glucosamine in relation to alternative pharmacological treatments

The scientific documentation for the efficacy of glucosamine sulphate is complex and the effect sizes are small. This is a common finding for treatment of osteoarthritis.

In Denmark paracetamol is recommended as the treatment of first choice for weak to moderate pain, including pain associated with osteoarthritis. Use of specific NSAIDs for pain associated with osteoarthritis are recommended with reservation and in special cases. The National Board of Health recommends treatment with paracetamol as first choice and suggests using NSAIDs in case of lack of efficacy of paracetamol [20]. The efficacy of the various NSAIDs is superior to that of paracetamol. However, paracetamol is the treatment of first choice because of the better safety profile compared to the NSAIDs. According to the Cochrane Institute [21] the effect of paracetamol for overall pain in osteoarthritis using multiple methods demonstrated a statistically significant reduction in pain (SMD -0.13, 95% CI -0.22 to -0.04), which is similar to the effect seen for glucosamine.

The small overall effect sizes seen for paracetamol and glucosamine may be reflecting that paracetamol as well as glucosamine is efficient for some patients but not for all. Since the efficacy of paracetamol as well as glucosamine for the treatment of symptoms in osteoarthritis is of similar magnitude doctors should have equal access to prescribe either medicinal product as first choice on equal terms with regards to the reimbursement status.

Conclusion

We disagree with the opinion of "Medicintilskudsnævnet" regarding changing the reimbursement status from "Generelt klausuleret tilskud" to "Ikke generelt tilskud".

Taking into consideration all relevant published clinical trials we find that there is substantial documentation showing that glucosamine sulphate does have an effect on symptoms of osteoarthritis primarily in the knees. Furthermore, glucosamine sulphate has an excellent safety profile. The efficacy of glucosamine and paracetamol in the treatment of symptoms in osteoarthritis in the knee are of similar magnitude. It is preferable that patients are treated with glucosamine or paracetamol rather than with NSAID for symptom relief as treatment with NSAID carry an increased risk of adverse reactions which may negatively impact the health of the patient and increase the risk of costly hospital admissions.

Since there is substantial evidence for the efficacy of glucosamin sulphate on symptoms of osteoarthritis in the knees and since the glucosamine safety profile is superior to other pharmacological treatments, patients

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with osteoarthritis in the knees should continue to have access to glucosamine treatment with reimbursement.

However, since the evidence for the efficacy of glucosamine for treatment of osteoarthritis located to other joints than the knee is weak, we suggest that the reimbursement status for products containing glucosamine sulphate for oral use should be "Generelt klausuleret tilskud" for the indication symptom relief for mild to moderate osteoarthritis in the knee. The dosage recommendations in the approved summary of product characteristics for Glucosamin Copyfarm takes into account that glucosamine sulphate is efficient for symptom relief in some but not all patients as treatment should be reevaluated after 2-3 months.

The suggested restriction of the reimbursement status together with the recommendations in the approved summary of product characteristics ensure that only patients for which glucosamine has sufficient effect has access to reimbursement on a long-term basis.

Best regards

Orifarm Generics A/S (Copyfarm A/S)

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Attachments:
Efficacy of Glucosamine – Brief Overview. TFS Trial Form Support. August 2011.

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16. august 2011

Vedr.: Nævnets revurdering af tilskudsstatus for lægemidler i ATC gruppe M01AX05

Hennning Bliddal og Robin Christensen, Frederiksberg Hospital, Parker Instituttet har i artiklen: "Glucosamin til osteoartrose: bordet fanger?" i Rationel Farmakoterapi, marts 2011 vurderet at der ikke i Danmark er tilgængelige præparater af typen glucosaminsulfat der har terapeutisk effekt.

Det er vi ikke enige i.

Forfatterne nævner at der kun er et glucosaminsulfat der har kunnet påvise en effekt og det er glucosaminsulfat fra firmaet Rottapharm/Madaus. Præparatet (Handelsnavn: DONA) forhandles ikke i Danmark.

Producenten BlueBio der fremstiller Dolenio har udfærdiget et White Paper der påviser at Dolenio glucosaminsulfats aktive substans er identisk og i samme mængde som i DONA.

Der er altså et glucosaminsulfat tilgængeligt i Danmark, der har terapeutisk effekt.

Vi henstiller til nævnet at denne information indgår i nævnets revurdering af tilskudsstatus for Dolenio glucosaminsulfat.

White Paper vedlagt.

Med venlig hilsen
Pharmazan Pharmaceutical ApS

Jens Otto Tram
Adm. Direktør

A Whitepaper to establish that the composition of Dolenio and Dona are equivalent

and they offer similar patient benefits and outcomes

Objective: To establish an understanding that the Salts forming the qualitative composition of Dolenio and Dona are similar

Method: Compare documents available in the public domain for the composition, and pharmaco dynamic properties and therapeutic indications to identify similarities.

Discussion: Dolenio is a registered medicine in all the 27 EU markets with Denmark as the RMS country. Dolenio is a once daily coated tablet form

Dona is a registered medicine in EU and is available as a powder form to be reconstituted into a oral solution.

Comparison: **Quantitative comparison of contents and inference**

Criterion	DONA	DOLENIO
Composition	each sachet contains: crystalline glucosamine sulphate sodium chloride 1884 mg equivalent to glucosamine sulphate 1500 mg sodium chloride 384 mg excipient: Sodium 151mg	each tablet contains 1884.60 mg glucosamine sulphate sodium chloride corresponding to 1500 mg glucosamine sulphate corresponding to 1177.50 mg glucosamine excipient: Sodium 151 mg

From the above comparison we infer the following

1. The forms of delivery are different – Dona being a powder form and Dolenio being a tablet
2. The main ingredient in both the products is Glucosamine Sulphate Sodium Chloride approximately equivalent to 1884 mg.
3. Both the products claim proven equivalence through pharmaco kinetic studies of 1500 mg of Glucosamine Sulphate and approximately 1178 mg of Glucosamine respectively.
4. Both products claim an excipient sodium content of 151 mg.

Comparison of the therapeutic uses

Criterion	DONA	DOLENIO
Indication	Treatment of symptoms of Osteoarthritis, i.e., pain and functional limitation	Relief of symptoms in mild to moderate osteoarthritis of the knee

From the above comparison we infer the following

1. The broad indication the product treats is Osteoarthritis
2. In case of Dona, the indication covers all forms of Osteoarthritis, and the symptoms are clearly defined as pain and functional limitation
3. In case of Dolenio, the indication is very specific going to the extent of stating in mild to moderate osteoarthritis of the knee.
4. Nonetheless the broad indiciations are the same for both the products

Comparison Efficacy and compliance

Criterion	DONA	DOLENIO
Efficacy	Dona has been extensively studied in more than 20 double blind studies and found to be effective in the treatment of indications of Osteoarthritis of the Knee. It also acts as a comparison standard for other Glucosamine sulphate all glucosamine products on the whole	The product was filed based on a bibliography application with the DKMA using many studies on Glucosamine Sulphate (many studies done on Dona itself)
Compliance	Once daily	Once daily

By Inference

- Since the clinical studies relevant to both products are similar and the bibliography approach was accepted by the medical authorities, it is safe to assume the products are similar in constitution.
- Both products are given as once daily treatments.

Comparison of the source of raw material:

Criterion	DONA	DOLENIO
Special Warnings	since glucosamine is obtained from shellfish, patients who are allergic to shellfish should exercise caution in the use of product	must not be used in patients who are allergic to shellfish as the active ingredient is obtained from shellfish

By Inference

- Since both the products give a special warning to people allergic to shell fish, claiming that the respective glucosamines are derived from processed shellfish, it is safe to assume that both products are sourced from shellfish.

Comparison of the Pharmaco therapeutic group:

Criterion	DONA	DOLENIO
Pharmaco therapeutic group and properties	product for the the treatment of osteoarthritis (product for musculoskeletal system - ATC code: M01AX05) The mechanism of action of glucosamine sulfate in osteoarthritis is unknown. However, glucosamine is a normal constituent of the polysaccharide chains of cartilage matrix and synovial fluid glucosaminoglycans. In vitro and in vivo studies have shown that glucosamine sulfate stimulates the synthesis of physiological glycosaminoglycans and proteoglycans by chondrocytes and of hyaluronic acid by synoviocytes. *(We have given only an excerpt of this portion for the sake of argument here)*	other anti-inflamatory and anti-rheumatic agents, non-steroids ATC Code: M01AX05 Glucosamine is an endogenous substance, a normal constituent of the polysaccharide chains of cartilage matrix and synovial fluid glucosaminoglycans. In vitro and in vivo studies have shown glucosamine stimulates the synthesis of physiological glycosaminoglycans and proteoglycans by chondrocytes and of hyaluronic acid by synoviocytes

By Inference

- Since both the products give a special warning to people allergic to shell fish, claiming that the respective glucosamines are derived from processed shellfish, it is safe to assume that both products are sourced from shellfish.
- The Pharmaco therapeutic properties of both the products are also similar.

Conclusions: In terms of the Qualitative composition, therapeutic usages, efficacy and classification of therapeutic group, both Dona and Dolenio are equivalent.

Sources:

- *Dolenio Public assessment report – Scientific discussion on Dolenio (Glucosamin) DK/H/1580/001/MR*
- *Dolenio SPC*
- *Dona SPC updated on the 17th November 2011 downloaded from http://www.medicines.ie/printfriendly document.aspx?documentid=39909companyid=193(1of8) [4/16/2011 4:38:16PM]*
- *These sources are attached as copies in this document.*

LÆGEMIDDEL STYRELSEN

25. august 2010

PRODUKTRESUMÉ

for

Dolenio, filmovertrukne tabletter

0. D.SP.NR.
22554

1. LÆGEMIDLETS NAVN
Dolenio

2. KVALITATIV OG KVANTITATIV SAMMENSÆTNING
En filmovertrukket tablet indeholder 1884,60 mg glucosaminsulfatnatriumchlorid svarende til 1500 mg glucosaminsulfat eller 1178 mg glucosamin.

Hjælpestof: Natrium 151 mg.
Alle hjælpestoffer er anført under pkt. 6.1.

3. LÆGEMIDDELFORM
Filmovertrukne tabletter.

Hvide til råhvide, ovale og bikonvekse filmovertrukne tabletter med delekærv på den ene side.
Delekærven er der, for at tabletten kan deles, så den er nemmere at sluge, ikke for at kunne dosere to halve tabletter.

4. KLINISKE OPLYSNINGER

4.1 Terapeutiske indikationer
Symptomlindring ved mild til moderat slidgigt i knæet.

4.2 Dosering og indgivelsesmåde
Voksne:
En tablet daglig

Glucosamin er ikke indiceret til behandling af akutte smertefulde symptomer. Lindring af symptomer (især smertelindring) kan først forventes at indtræffe efter adskillige ugers behandling og i nogle tilfælde efter endnu længere tid. Hvis der ikke ses symptomlindring efter 2-3 måneder, bør fortsat behandling med glucosamin genovervejes.

Tabletterne kan tages uafhængigt af måltiderne.

Yderligere oplysninger til særlige befolkningsgrupper:
Ældre:
Der er ikke foretaget særlige undersøgelser med ældre, men ud fra klinisk erfaring er dosisjustering ikke påkrævet ved behandling af ældre patienter, der i øvrigt er raske.

Børn og unge:
Dolenio bør ikke anvendes til børn og unge under 18 år på grund af utilstrækkelig dokumentation for sikkerhed og virkning.

Nedsat nyre- og/eller leverfunktion:
Der kan ikke gives dosisanbefalinger til patienter med nedsat nyre- og/eller leverfunktion, idet der ikke er foretaget undersøgelser med denne gruppe.

4.3 Kontraindikationer

- Dolenio må ikke anvendes af personer med skaldyrsallergi, da det aktive indholdsstof er udvundet fra skaldyr.
- Overfølsomhed over for det aktive stof eller over for et eller flere af hjælpestofferne.
- Børn under 2 år.

4.4 Særlige advarsler og forsigtighedsregler vedrørende brugen

Lægen bør konsulteres for at udelukke tilstedeværelsen af ledsygdomme, hvor anden behandling bør komme i betragtning.

Hos patienter med nedsat glucosetolerance skal blodsukkeret og evt. insulinbehov monitoreres før behandlingen initieres og periodisk under behandlingen.

Hos patienter med en kendt risikofaktor for kardiovaskulær sygdom anbefales monitorering af lipidtal i blodet, idet der er rapporteret om hyperkolesterolæmi i nogle få tilfælde hos patienter, der blev behandlet med glucosamin.

Der foreligger en rapport om forværrede astma symptomer efter begyndelse på glucosaminbehandling (symptomerne forsvandt ved seponering af glucosamin). Astmapatienter, der begynder på glucosaminbehandling, bør derfor være opmærksomme på en potentiel forværring af astma symptomer.

Dette lægemiddel indeholder 6,52 mmol (eller 151 mg) natrium pr. dosis. Dette bør tages i betragtning ved behandling af patienter, som er på natriumfattig diæt.

4.5 Interaktion med andre lægemidler og andre former for interaktion

Der er rapporteret om øget effekt af coumarin antikoagulanter (f.eks. warfarin) ved samtidig behandling med glucosamin. Patienter i behandling med coumarin antikoagulanter skal derfor monitoreres tæt ved initiering og afslutning af behandling med glucosamin.

Samtidig behandling med glucosamin kan forøge absorptionen og serumkoncentrationen af tetracykliner, men den kliniske relevans af denne interaktion er sandsynligvis begrænset.

Pga. begrænset dokumentation om potentielle lægemiddelinteraktioner med glucosamin, skal man generelt være opmærksom på ændret respons eller koncentration af lægemidler, der indtages samtidigt.

4.6 Graviditet og amning

Graviditet:
Data for anvendelse af glucosamin til gravide er utilstrækkelige. Der findes kun utilstrækkelige data fra dyreforsøg. Dolenio bør ikke anvendes til gravide.

Amning:
Der findes ingen data om udskillelse af glucosamin i modermælk. Indtagelse af glucosamin i ammeperioden anbefales derfor ikke, da der ikke findes sikkerhedsdata for barnet.

4.7 Virkninger på evnen til at føre motorkøretøj eller betjene maskiner

Ikke mærkning.
Der er ikke foretaget undersøgelser af virkningen på evnen til at føre motorkøretøj eller betjene maskiner.
Hvis der forekommer svimmelhed eller sløvhed, anbefales bilkørsel eller betjening af maskiner ikke.

4.8 Bivirkninger

De hyppigst forekommende bivirkninger ved behandling med glucosamin er kvalme, mavesmerter, fordøjelsesbesvær, forstoppelse og diarré. Desuden er hovedpine, træthed, udslæt, hudkløe, og rødmen rapporteret. De rapporterede bivirkninger er sædvanligvis milde og forbigående.

Systemorganklasse i henhold til MedDRA	**Almindelig (≥1/100 til <1/10)**	**Ikke almindelig (≥1/1.000 til ≤1/100)**	**Meget sjælden (< 1/10.000), ikke kendt (kan ikke estimeres ud fra forhåndenværende data)**
Nervesystemet	Hovedpine Træthed		Svimmelhed
Luftveje, thorax og mediastinum			Astma/forværring af astma
Mave-tarmkanalen	Kvalme Mavesmerter Fordøjelsesbesvær Diarré Forstoppelse		Opkastning
Hud og subkutane væv		Udslæt Kløe Rødme	Angioødem Nældefeber

Systemorganklasse i henhold til MedDRA	Almindelig (≥1/100 til <1/10)	Ikke almindelig (≥1/1.000 til ≤1/100)	Meget sjælden (< 1/10.000), ikke kendt (kan ikke estimeres ud fra forhåndenværende data)
Metabolisme og ernæring			Utilstrækkelig kontrol af diabetes mellitus Hyperkolesterolæmi
Almene reaktioner og reaktioner på administrationsstedet			Ødem/perifert ødem

Der er rapporteret tilfælde af hyperkolesterolæmi, forværring af astma og utilstrækkelig kontrol af diabetes mellitus, men årsagssammenhængen er ikke fastslået.

Dolenio kan forårsage forhøjet leverenzymniveau og i sjældne tilfælde gulsot.

Patienter med diabetes mellitus
Blodglucosekontrol forværredes hos patienter med diabetes mellitus. Frekvensen er ikke kendt.

4.9 Overdosering

Tegn og symptomer på utilsigtet eller tilsigtet overdosering med glucosamin kan omfatte hovedpine, svimmelhed, desorientering, artralgi, kvalme, opkastninger, diarré eller forstoppelse.

I tilfælde af overdosering med glucosamin skal behandlingen seponeres og symptomatiske tiltag skal iværksættes efter behov.

I kliniske undersøgelser oplevede 1 ud af 5 raske unge forsøgspersoner hovedpine efter infusion af op til 30 mg glucosamin.

Yderligere et tilfælde af overdosering er blevet rapporteret hos en 12-årig pige, som tog 28 g glucosaminhydrochlorid oralt. Hun udviklede artralgi, opkastninger og desorientering. Patienten kom sig uden følgevirkninger.

4.10 Udlevering

HF

5. FARMAKOLOGISKE EGENSKABER

5.0 Terapeutisk klassifikation

ATC-kode: M 01 AX 05
Andre non-steroide antiinflammatoriske og antirheumatiske midler.

5.1 Farmakodynamiske egenskaber

Glucosamin er et endogent stof, en almindelig bestanddel af polysakkaridkæden i bruskmatrix og glycosaminoglycaner i synovialvæske. *In vitro*- og *in vivo*-forsøg har påvist, at glucosamin stimulerer syntesen af fysiologiske glykosaminoglycaner og proteoglycaner ved hjælp af chondrocytter og af hyaluronsyre ved hjælp af synoviocytter.

Virkningsmekanismen for glucosamin er ukendt.
Perioden indtil respons kan ikke fastsættes.

5.2 Farmakokinetiske egenskaber

Glucosamin er et relativt lille molekyle (molekylærmasse 179), som let opløses i vand og er opløselig i hydrofile, organiske opløsningsmidler.

Oplysninger om farmakokinetikken ved glucosamin er begrænset. Den absolutte biotilgængelighed er ukendt. Distributionsvolumen er ca. 5 liter, og halveringstiden efter intravenøs indgift er ca. 2 timer. Ca. 38 % af en intravenøs dosis udskilles uomdannet med urinen.

Glucoaminsulfats ADME-profil (absorption, distribution, metabolisme og ekskretion) hos mennesker er ikke fuldstændigt klarlagt.

5.3 Prækliniske sikkerhedsdata

D-glucosamin har lav akut toksicitet.

Der findes ikke data fra dyreforsøg omhandlende toksicitet efter gentagne doser, reproduktionstoksicitet, mutagenicitet eller karcinogenicitet. Resultater fra *in vitro*- og *in vivo*-forsøg i dyr har vist, at glucosamin nedsætter insulinudskillelsen og giver insulinresistens, sandsynligvis ved hjælp af glukokinasehæmning i betacellerne. Den kliniske relevans er ukendt.

6. FARMACEUTISKE OPLYSNINGER

6.1 Hjælpestoffer

Tabletkerne
Povidon K30
Macrogol 4000
Magnesiumstearat
Hypromellose
Titandioxid (E171)
Talcum

Overtræk
Propylenglycol
Polysorbat 80

6.2 Uforligeligheder
Ikke relevant.

6.3 Opbevaringstid
3 år.

6.4 Særlige opbevaringsforhold
Dette lægemiddel kræver ingen særlige forholdsregler vedrørende opbevaringen.

6.5 Emballagetyper og pakningsstørrelser
HDPE-beholder med HDPE-skruelåg.
Alu/PVC/PVDC blisterpakninger.

Pakningsstørrelser:
20, 30, 60 og 90 filmovertrukne tabletter i HDPE beholder med HDPE skruelåg.
4, 10, 20, 30, 45, 60, 90 filmovertrukne tabletter i Alu/PVC/PVDC blisterpakninger.

Ikke alle pakningsstørrelser er nødvendigvis markedsført.

6.6 Regler for destruktion og anden håndtering
Ingen særlige forholdsregler.

7. INDEHAVER Af MARKEDSFØRINGSTILLADELSEN
Blue Bio Pharmaceuticals Limited
5th Floor, Beaux Lane House
Mercer Street Lower
Dublin 2
Irland

Repræsentant
Pharmazan Pharmaceuticals ApS
Kilde Allé 22, 1 sal
3600 Frederikssund

8. MARKEDSFØRINGSTILLADELSESNUMMER (NUMRE)
37024

9. DATO FOR FØRSTE MARKEDSFØRINGSTILLADELSE
20. september 2006

10. DATO FOR ÆNDRING AF TEKSTEN
25. august 2010