Revurdering af tilskudsstatus for lægemidler med indhold af glucosamin (M01AX05)

Lægemiddelstyrelsen har marts-april 2011 modtaget bidrag fra følgende:

- Gigtforeningen
- Jordi Monfort, professor, spansk reumatolog
- Laboratoires Expanscience
- Orifarm Generics A/S
- Pharma Nord ApS (2 bidrag)

Lægemiddelstyrelsen
Den 25. maj 2011

ULLA KIRKEGAARD MADSEN

Fra: Inger Hove-Andersen [ihoveandersen@gigtforeningen.dk] på vegne af Lene Witte [lwitte@gigtforeningen.dk]

Sendt: 17. marts 2011 12:33

Til: ULLA KIRKEGAARD MADSEN

Emne: VS: Revurdering af tilskudsstatus for glucosamin

Sent to GoPro Portal: -1

Kære Ulla Kirkegaard Madsen

Tak for den fremsendte mail vedrørende revurdering af tilskud til glucosamin. Gigtforeningen har ikke særlige synspunkter i forbindelse med denne faglige vurdering.
Gigtforeningen har noteret, at der ikke foreligger undersøgelser, som dokumenterer en effekt, der begrunder denne type behandling på lægefagligt grundlag.

Internationalt er der også etableret konsensus om ovenstående. Vi er dog opmærksomme på, at der er mange - også fagfolk – som anser behandlingen for berettiget uanset den manglende evidens.

Med venlig hilsen

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ULLA KIRKEGAARD MADSEN

Fra: ULLA KIRKEGAARD MADSEN
Sendt: 25. maj 2011 14:22
Til: ULLA KIRKEGAARD MADSEN
Emne: The Danish Medicines Agency begins ad hoc reassessment of reimbursement status of glucosamine (M01AX05)

Sent to GoPro Portal: 0


Bruyere


Letters


Rapid Response
ɔmmentary to BMJ_ta-Analysis BMJ 201 from BMJ Editor...

-----Oprindelig meddelelse-----
Fra: Jordi Monfort Faure [mailto:JMonfort@parcdesalutmar.cat]
Sendt: 18. marts 2011 13:30
Til: medicintilskud
Emne: The Danish Medicines Agency begins ad hoc reassessment of reimbursement status of glucosamine (M01AX05)

Dear Sirs/Dear Madams,
Let me first introduce myself, I am Dr. Jordi Monfort; a Professor of Medicine at Universitat Autonoma de Barcelona since 2007 and practicing Reumathologist in Barcelona, Spain, with almost 17 years experience in Osteoarthritis research field; trained in Canada with Professors Pelletier, who are leading Osteoarthritis research worldwide.
I am an active member of the Spanish Rheumatologist National Society (SER) and the Osteoarthritis Research Society International (OARSI). Also I am a member of the Spanish Medicines Agency's scientific advisory committee board for osteoarthritis, and also I was in the expert's panel assessing the EMA's approval for Glucomed in 2006. I have been aware that the Danish Medicines Agency is beginning a reassessment of the reimbursement status of glucosamine, mainly due to two studies published recently (Wilkens JAMA 2010, Wandel BMJ 2010). I am little concerned that these two articles, which I further explain below, could be the main cause of this reassessment, with the consequent impact that this could have, firstly for the Danish osteoarthritic patients and for the overall European patients. First of all, it should be borne in mind that the EU approved indication for glucosamine is symptomatic treatment of knee osteoarthritis, the importance of a study assessing the effect of glucosamine in degenerative lumbar osteoarthritis (Wilkens JAMA 2010), can be considered, but definitely it cannot be used to support the reimbursement assessment of the product in the approved indication, knee osteoarthritis. Regarding the meta-analysis published by Wandel et al, I would like to bring to your attention a letter recently posted on the British Medical Journal (BMJ) website by the BMJ Deputy Editor on this meta-analysis. In it, the BMJ Deputy Editor explained that in view of the controversy raised by the article and the criticism received, the BMJ editors and statistical advisers discussed and analyzed it further at their Annual Review Meeting. At the meeting it was decided that the following statements in the article:
*"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."
*"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"
were not directly supported by the data by their meta-analysis. Thus, the Journal decided not to support these statements from the article, asserting that they were not directly based on the article's results and do not add usefully to it.
Another interesting fact to consider was the conflict of interest declared at the end of the present letter. It explained that the BMJ's senior statistics editor declared before the post publication review meeting, that he was well acquainted with and had recently been involved in research with two of the article's authors. Hence he did not comment during the review meeting. Overall, I believe the BMJ had officially rejected some of the conclusions of the study, the ones you had considered for the reassessment of the reimbursement and put in doubt the objectivity of one of the statistical editors of the article. Moreover, the results of the Wandel network meta-analysis clearly contrast to the recommendations of international (OARSI) and European (EULAR) Societies who classify glucosamine with the highest evidence level, 1A. I have

attached in the present message this letter from the BMJ's Deputy Editor, which you will also find in the following link:
http://www.bmj.com/content/341/bmj.c4675.full/reply#bmj_el_242776
Apart from this letter from the Deputy Editor, you will also find in this link the many other rapid responses (more than 20) that have been published in the BMJ website against this article. Additionally to the online rapid responses, 3 Letters to the Editor have also been published in the print edition of the BMJ. I also attach them for your information. On the other hand, another review of this controversial article contradicting its conclusions, has also been recently published (Bruyère O. Large review finds no clinically important effect of glucosamine or chondroitin on pain in people with osteoarthritis of the knee or hip but results are questionable and likely due to heterogeneity. Evid Based Med. 2011 Jan 11). I have also attached it for your consideration. Hoping this information can be of your interest, I remain at your disposal.

Kind regards,

Jordi Monfort

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

OVERVIEW OF THE DISCUSSION

Marketing Authorization Holder:
Laboratoires Expanscience,
10, Avenue de l'Arche,
92400 COURBEVOIE - FRANCE

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

OVERVIEW OF THE DISCUSSION

On March 3rd, 2011, the Danish Medicines Agency (DMA) started a procedure or reassessment of the reimbursement status of Glucosamine on the grounds of a clinical study (GAIT study) that called into question the efficacy of glucosamine for the alleviation of painful osteoarthritis (8). This was recently highlighted in a study of patients with CLBP arthritis (35) and in conclusion of a meta-analysis (34) suggesting health authorities not to grant reimbursement for glucosamine.

Consequently, the Danish Medicines Agency has decided to initiate ad hoc reassessment of glucosamine-containing medicines. In view of the arguments developed by the DMA, the MAH, Expanscience, wants to present the scientific arguments likely to offer an alternate view of the three publications on glucosamine taken into account by the DMA, by proposing an in-depth discussion of all methodological and scientific issues that may modify the relevance of those 3 studies or analysis.

The present document is an overview of the arguments developed by the MAH. A comprehensive and detailed review of the three documents is, in addition presented in a separate report. For easier finding of related references, the two documents have the same list of literature references, with the same numbering.

1. Discussion of the GAIT study.

This NIH-sponsored trial compared 6-month treatments with Glucosamine (G), Chondroitine (C), the G + C combination, Celecoxib (Cx) or placebo (P) in 1583 patients with knee OA. At the end of the treatment period, no significant difference was shown between any of the DMOAD groups and P, with respect to the primary and secondary outcomes. In Cx-treated patients, only the rates of patients with a pre-specified 20% change of the WOMAC pain scale were significantly different from P.

In all groups, including the Cx one, there was an insignificant effect on WOMAC mean changes. These results were also remarkable with respect to the very high magnitude of the placebo effect (around 60%).

The stratified analysis according to baseline severity revealed however a significant trend toward efficacy in patients with moderate to severe initial pain, inconclusive due to the small sample size in this stratum, also insignificant in Cx-treated patients, for most patients. A potential bias should explain the major placebo effect is that patients: those with previous DMOAD treatments could be included, while it had been shown that their activity could continue over long period after treatment withdrawal.

In agreement with the authors of the study, who expressed themselves in the discussion of the paper (8), the limits of their research, being notably due to the selection of patients with a "too light" symptomatology and/or a very high placebo response, it must be considered that the GAIT study remains inconclusive and is not relevant to evoke the lack of efficacy of the tested interventions, notably glucosamine.

2. Discussion of the meta-analysis by Wandel

This meta-analysis was performed by a team of mainly Swiss searchers involved in the field of rheumatology and social and preventive medicine (34). Even though a number of meta-analyses had already been published about the efficacy of glucosamine, notably those of the Cochrane Collaboration (30, 31, 32), the authors judged that the previous analyses gave conflicting results and therefore decided to perform the ultimate meta-analysis on those medicinal products, that should provide definitive responses on those questions.

However, the authors did not fully detailed the rationale that could have justify their analysis, except by a limited reference to their own experience. They did not, notably, explain in what extent the previous meta-analyses and/or studies did not answer the main question of efficacy (despite they had been accepted by European Health Authorities for the registration of Glucomed and considered in several international guidelines [27, 37]).

The results of their analysis was published in a paper in the BMJ that aroused a high number of reactions amongst the community of rheumatology experts and in many clinicians. The main reasons of the criticism resulting of that study concern almost all the aspects of their work, that are summarized hereafter.

a. The authors had not an individual critical view of each study included in their analysis, in order to determine which studies had the best or worst relevance and why. That very important step was not done. This resulted in the mixing up of relevant well-done studies and of inconclusive biased studies, such as GAIT, despite the highlight of limitations by the authors themselves. This is a major issue in the construction of this meta-analysis, notably because of the significant "weight" of the GAIT study, in term of the large sample size the study account for (32 to 80% according to the comparisons).

Therefore, it is clear that the authors included in their meta-analysis, several inconclusive studies, notably the GAIT study, as well as the studies by McAlindon or Rozendaal. If biased studies are taken into account in a meta-analysis without making any balance of their quality, therefore the results of the meta-analysis will necessarily be flawed and then inconclusive.

b. The method used by Wandel, i.e. the "network MA" is mainly dedicated to the multiple comparisons of several interventions studied separately in various studies. With respect to the main objective of the analysis (to clarify conflicting results regarding the efficacy of G, C and G+C vs placebo, there was no need to implement such a complex method in order to provide a definitive response on glucosamine and chondroitin efficacy vs placebo. But, as far as the method was implemented, an interesting response regarding the effectiveness vs active interventions (celecoxib and paracetamol) could have been obtained, but the authors decided not to perform those comparison.

c. The MA by Wandel did not meet some of the main basic principles of any meta-analysis :

- the studies included are not homogeneous in term of populations, in term of medications under study, in term of treatment regimen (treatment duration notably) and also in term of efficacy outcomes. The Wandel MA did not comply with any of these conditions, while:
  - Patients with different OA sites were included in the same analysis (knee, hip and spine),
  - Different glucosamine salts were used, between studies, but also within a single study, without ant demonstration of equivalence of study regimens,
  - Different dosages and daily posology were used across or within a study,

- Studies with fundamentally different objectives were pooled : very short and medium term trials (irrelevant for the assessment of DMOAD efficacy – minimal 6 months – see EMA guidelines) focusing on the symptomatic efficacy and long term studies (2 – 3 years) focusing on anatomical structures improvement.
- For those two main therapeutic schemes, the efficacy outcomes are not the same and the studies powered for concluding about one outcome (e.g. pain) will not provide accurate results with respect to the other outcome (e.g. JSW changes).

– the set of included studies is not comprehensive and that's prevent from improving statistical power of previous analyses and from offering a new view on the question.

d. The authors mixed up different "pain" symptomatic outcomes (pain at rest, on walking …) but also mixed criteria such as the Lequesne index (no pain outcome was studied in at least one study included in the analysis). In order to succeed in mixing the parameters they performed back transformations from effect sizes.

This results in an apparent abuse for the labeling of the main outcome of their analysis : the parameter named "pain intensity measured on VAS" is for most of studies a pure mathematical construction, which does not –qualitatively- correspond to the original experimental data.

e. The baseline values of efficacy outcomes was not taken into account. This is not adequate at least for the assessment of pain scores changes (19), while a similar magnitude of improvement (i.e. 0.9 on a 10 cm VAS) is not supposed to have the same clinical meaningfulness in patients with a < 4 pain value at baseline vs patients with severe pain (e.g. > 7 on VAS).

In addition, expectations regarding the pain improvement are quite different in symptomatic studies, where it is the main objective, and in anatomical structures studies, where the pain is to be "restrained" to an acceptable level, in order to avoid patient drop-outs.

f. A very significant number of available studies (around 75%) were excluded of the whole of trials possibly interesting for the analysis on the quasi-exclusive ground of sample size. The authors actually decided to only include studies with treatment groups ≥ 100 patients. But this decision cannot be justified while the authors chose an arbitrary and unusual hypothesis of clinically significant effect size.

The choice of this effect size threshold seems to be unaware of the reality of the values evidenced for major drug interventions in OA (19): paracetamol, "despite" being the universally recognized first line drug treatment in OA, has an effect size < 0.20 (36), while reviews on the effectiveness of NSAIDs in OA revealed effect size between 0.15 and 0.39 for pain treatment in OA (1). Therefore, one of the main basis for the "construction" of the meta-analysis is clearly irrelevant and makes any further conclusion highly questionable, while changing the ES threshold would have change the minimum number of patients per group and then the number of analysed studies.

g. Despite those issues in their analysis, the authors erroneously concluded about the lack of reduction in joint pain and the lack of impact on narrowing of joint space by glucosamine. They also overstepped the actual results of the meta-analysis in concluding that : "*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 relevance of this part of the conclusion was denounced by the BMJ's editorial board after a post-publication review. Actually, the BMJ's deputy director stated that two sections of Wandel's paper needed formal comments. He considered that the assertions (i) In the abstract : "*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*" and (ii) in the discussion: " *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*" were not directly supported by the data.

As finally stated by Reginster, Altman and Hochberg (20), "*the major limitations of Wandel and colleagues analysis do not support the strong negative conclusions and are harmful to patients: rejecting an effective agent is both inappropriate and a disservice to the community*."

In conclusion, the method implemented by Wandel et al. the network meta-analysis is probably applied in a quite satisfactory manner, but the rationale for choosing this method is not adequately justified, notably by the lack of documented discussion of previously published meta-analyses.

Furthermore, this method was applied on inadequate study data, with respect to their nature (patients, indication, OA site, drug nature, dosage and regimen, treatment duration and efficacy outcomes), to their quantity (non justified exclusion of around 75% of available studies) and –how much important- to their quality (inclusion of inconclusive studies, the limitations of which were mentioned by their authors or appeared quite evident).

The present document provides clear arguments to show that several studies on glucosamine are much biased. Their conclusions are hence to be considered as not allowing to provide a definitive information relating to the glucosamine efficacy.

Study authors are generally objective enough to mention the flaws and biases in the publication's discussion, but those limitations are never used to refrain the impact of the conclusions and the whole actual results remain available to any scientist, notably those interested in performing meta-analyses.

3. Discussion of the study of chronic low back pain study by Wilkens

This study was performed by a Norvegian team, that aimed to assess the symptomatic efficacy of Glucosamine in the 6-month treatment of patients with chronic low back pain and degenerative lumbar osteoarthritis (35).

It is to be stressed right away, that this study is irrelevant for the assessment of the glucosamine efficacy in the frame of the product's official indications, because chronic low back pain and/or lumbar OA are not mentioned in the glucosamine SPC, no MA having been granted for those indications.

Yet, the official EMA guidelines clearly states with respect to the study of drugs in osteoarthritis that the assessment of efficacy must be evaluated separately in each individual OA site, no extrapolation being accepted from the efficacy at one OA site to another one.

Therefore, the study by Wilkens cannot be considered in the field of the glucosamine MA in Denmark.

In addition, should this study be viewed as a Phase III-like study designed to establish the Glucosamine effectiveness in this "new" indication, then the results could not be taken into account for several methodological reasons:

- the rationale for assessment of glucosamine efficacy in CLBP is not adequately justified because this clinical entity involves other anatomical structures that the only vertebral cartilage, e.g. the intervertebral disk and the para-vertebral elements. Glucosamine is not expected to have a direct effect on those latter structures.
- the participation of patients in the study was triggered by advertisement that should include a financial motivation for some of them. This may interfere with the patient assessment of its own symptoms,
- the efficacy outcomes did not include any pain-specific clinical assessment. Only a CLBP-specific scale (RMDQ) was studied which, although being validated, does not take specifically into account the pain dimension of symptoms, which is the main target of Glucosamine as regards its symptomatic effectiveness.
- finally, the effectiveness of the tested interventions may have been seriously impaired by the authorized use of any concomitant therapy aiming at pain relief: pain killers, NSAIDs, common analgesics but also physiotherapy, chiropraxis, manipulations, massages, all those interventions being possibly administrated without any limitation of nature, dose, regimen or duration. Yet, while no pain threshold was required at inclusion, patients were likely to experience very slight pain at baseline and it seems quite impossible to evidence the analgesic effect of a medicinal product in patients who do not suffer.

4. 0verall conclusion

The glucosamine MAH present here several evidences towards the lack of relevance of most data used to anticipate a possible reassessment of reimbursement status of Glucomed. In view of the number of issues shown in each of the three mentioned references, the MAH expresses its formal reserves regarding the relevance of those works and of the need to go further in the reassessment procedures on those grounds. Therefore the MAH asks the Danish Medical Agency to maintain the present status of Glucomed, while the proposed document are not likely to modify, in any extent, the previously defined therapeutic profile of the drug and therefore its reimbursement status.

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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

OVERALL DISCUSSION

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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

EXECUTIVE SUMMARY

On March 3rd, 2011, the Danish Medicines Agency (DMA) started a procedure or reassessment of the reimbursement status of Glucosamine on the grounds of a clinical study (GAIT study) that called into question the efficacy of glucosamine for the alleviation of painful osteoarthritis (8). This was recently highlighted in a study of patients with CLBP arthritis (35) and in conclusion of a meta-analysis (34) suggesting health authorities not to grant reimbursement for glucosamine. Consequently, the Danish Medicines Agency has decided to initiate ad hoc reassessment of glucosamine-containing medicines. In view of the arguments developed by the DMA, the MAH, Expanscience, wants to present the scientific arguments likely to offer an alternate view of the three publications on glucosamine taken into account by the DMA, by proposing an in-depth discussion of all methodological and scientific issues that may modify the relevance of those 3 studies or analysis.

1. Discussion of the GAIT study.

This NIH-sponsored trial compared 6-month treatments with Glucosamine (G), Chondroitine (C), the G + C combination, Celecoxib (Cx) or placebo (P) in 1583 patients with knee OA. At the end of the treatment period, no significant difference was shown between any of the DMOAD groups and P, with respect to the primary and secondary outcomes. In Cx-treated patients, only the rates of patients with a pre-specified 20% change of the WOMAC pain scale were significantly different from P.

In all groups, including the Cx one, there was an insignificant effect on WOMAC mean changes. These results were also remarkable with respect to the very high magnitude of the placebo effect (around 60%). The stratified analysis according to baseline severity revealed however a significant trend toward efficacy in patients with moderate to severe initial pain, inconclusive due to the small sample size in this stratum, also insignificant in Cx-treated patients, for most patients. A potential bias should explain the major placebo effect is that patients: those with previous DMOAD treatments could be included, while it had been shown that their activity could continue over long period after treatment withdrawal.

In agreement with the authors of the study, who expressed themselves in the discussion of the paper (8), the limits of their research, being notably due to the selection of patients with a "too light" symptomatology and/or a very high placebo response, it must be considered that the GAIT study remains inconclusive and is not relevant to evoke the lack of efficacy of the tested interventions, notably glucosamine.

2. Discussion of the meta-analysis by Wandel

This meta-analysis was performed by a team of mainly Swiss searchers involved in the field of rheumatology and social and preventive medicine (34). Even though a number of meta-analyses had already been published about the efficacy of glucosamine, notably those of the Cochrane Collaboration (30, 31, 32), the authors judged that the previous analyses gave conflicting results and therefore decided to perform the ultimate meta-analysis on those medicinal products, that should provide definitive responses on those questions.

However, the authors did not fully detailed the rationale that could have justify their analysis, except by a limited reference to their own experience. They did not, notably, explain in what extent the previous meta-analyses and/or studies did not answer the main question of efficacy (despite they had been accepted by European Health Authorities for the registration of Glucomed and considered in several international guidelines [27, 37]).

The results of their analysis was published in a paper in the BMJ that aroused a high number of reactions amongst the community of rheumatology experts and in many clinicians. The main reasons of the criticism resulting of that study concern almost all the aspects of their work, that are summarized hereafter.

1. The authors had not an individual critical view of each study included in their analysis, in order to determine which studies had the best or worst relevance and why. That very important step was not done. This resulted in the mixing up of relevant well-done studies and of inconclusive biased studies, such as GAIT, despite the highlight of limitations by the authors themselves. This is a major issue in the construction of this meta-analysis, notably because of the significant "weight" of the GAIT study, in term of the large sample size the study account for (32 to 80% according to the comparisons).

Therefore, it is clear that the authors included in their meta-analysis, several inconclusive studies, notably the GAIT study, as well as the studies by McAlindon or Rozendaal. If biased studies are taken into account in a meta-analysis without making any balance of their quality, therefore the results of the meta-analysis will necessarily be flawed and then inconclusive.

2. The method used by Wandel, i.e. the "network MA" is mainly dedicated to the multiple comparisons of several interventions studied separately in various studies. With respect to the main objective of the analysis (to clarify conflicting results regarding the efficacy of G, C and G+C vs placebo, there was no need to implement such a complex method in order to provide a definitive response on glucosamine and chondroitin efficacy vs placebo. But, as far as the method was implemented, an interesting response regarding the effectiveness vs active interventions (celecoxib and paracetamol) could have been obtained, but the authors decided not to perform those comparison.

3. The MA by Wandel did not meet some of the main basic principles of any meta-analysis :

- the studies included are not homogeneous in term of populations, in term of medications under study, in term of treatment regimen (treatment duration notably) and also in term of efficacy outcomes. The Wandel MA did not comply with any of these conditions, while:
  - Patients with different OA sites were included in the same analysis (knee, hip and spine),
  - Different glucosamine salts were used, between studies, but also within a single study, without ant demonstration of equivalence of study regimens,
  - Different dosages and daily posology were used across or within a study,
  - Studies with fundamentally different objectives were pooled : very short and medium term trials (irrelevant for the assessment of DMOAD efficacy – minimal 6 months – see EMA guidelines) focusing on the symptomatic efficacy and long term studies (2 – 3 years) focusing on anatomical structures improvement.
  - For those two main therapeutic schemes, the efficacy outcomes are not the same and the studies powered for concluding about one outcome (e.g. pain) will not provide accurate results with respect to the other outcome (e.g. JSW changes).
- the set of included studies is not comprehensive and that's prevent from improving statistical power of previous analyses and from offering a new view on the question.

4. The authors mixed up different "pain" symptomatic outcomes (pain at rest, on walking …) but also mixed criteria such as the Lequesne index (no pain outcome was studied in at least one study included in the analysis). In order to succeed in mixing the parameters they performed back transformations from effect sizes.

This results in an apparent abuse for the labeling of the main outcome of their analysis : the parameter named "pain intensity measured on VAS" is for most of studies a pure mathematical construction, which does not – qualitatively- correspond to the original experimental data.

5. The baseline values of efficacy outcomes was not taken into account. This is not adequate at least for the assessment of pain scores changes (19), while a similar magnitude of improvement (i.e. 0.9 on a 10 cm VAS) is not supposed to have the same clinical meaningfulness in patients with a < 4 pain value at baseline vs patients with severe pain (e.g. > 7 on VAS).

In addition, expectations regarding the pain improvement are quite different in symptomatic studies, where it is the main objective, and in anatomical structures studies, where the pain is to be "restrained" to an acceptable level, in order to avoid patient drop-outs.

6. A very significant number of available studies (around 75%) were excluded of the whole of trials possibly interesting for the analysis on the quasi-exclusive ground of sample size. The authors actually decided to only include studies with treatment groups ≥ 100 patients. But this decision cannot be justified while the authors chose an arbitrary and unusual hypothesis of clinically significant effect size.

The choice of this effect size threshold seems to be unaware of the reality of the values evidenced for major drug interventions in OA (19): paracetamol, "despite" being the universally recognized first line drug treatment in OA, has an effect size < 0.20 (36), while reviews on the effectiveness of NSAIDs in OA revealed effect size between 0.15 and 0.39 for pain treatment in OA (1). Therefore, one of the main basis for the "construction" of the meta-analysis is clearly irrelevant and makes any further conclusion highly questionable, while changing the ES threshold would have change the minimum number of patients per group and then the number of analysed studies.

7. Despite those issues in their analysis, the authors erroneously concluded about the lack of reduction in joint pain and the lack of impact on narrowing of joint space by glucosamine. They also overstepped the actual results of the meta-analysis in concluding that : "*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 relevance of this part of the conclusion was denounced by the BMJ's editorial board after a post-publication review. Actually, the BMJ's deputy director stated that two sections of Wandel's paper needed formal comments. He considered that the assertions (i) In the abstract : "*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*" and (ii) in the discussion: " *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*" were not directly supported by the data.

As finally stated by Reginster, Altman and Hochberg (20), "*the major limitations of Wandel and colleagues analysis do not support the strong negative conclusions and are harmful to patients: rejecting an effective agent is both inappropriate and a disservice to the community*."

In conclusion, the method implemented by Wandel et al. the network meta-analysis is probably applied in a quite satisfactory manner, but the rationale for choosing this method is not adequately justified, notably by the lack of documented discussion of previously published meta-analyses.

Furthermore, this method was applied on inadequate study data, with respect to their nature (patients, indication, OA site, drug nature, dosage and regimen, treatment duration and efficacy outcomes), to their quantity (non justified exclusion of around 75% of available studies) and –how much important- to their quality (inclusion of inconclusive studies, the limitations of which were mentioned by their authors or appeared quite evident).

The present document provides clear arguments to show that several studies on glucosamine are much biased. Their conclusions are hence to be considered as not allowing to provide a definitive information relating to the glucosamine efficacy.

Study authors are generally objective enough to mention the flaws and biases in the publication's discussion, but those limitations are never used to refrain the impact of the conclusions and the whole actual results remain available to any scientist, notably those interested in performing meta-analyses.

3. Discussion of the study of chronic low back pain study by Wilkens

This study was performed by a Norvegian team, that aimed to assess the symptomatic efficacy of Glucosamine in the 6-month treatment of patients with chronic low back pain and degenerative lumbar osteoarthritis (35).

It is to be stressed right away, that this study is irrelevant for the assessment of the glucosamine efficacy in the frame of the product's official indications, because chronic low back pain and/or lumbar OA are not mentioned in the glucosamine SPC, no MA having been granted for those indications.

Yet, the official EMA guidelines clearly states with respect to the study of drugs in osteoarthritis that the assessment of efficacy must be evaluated separately in each individual OA site, no extrapolation being accepted from the efficacy at one OA site to another one.

Therefore, the study by Wilkens cannot be considered in the field of the glucosamine MA in Denmark.

In addition, should this study be viewed as a Phase III-like study designed to establish the Glucosamine effectiveness in this "new" indication, then the results could not be taken into account for several methodological reasons:

1. the rationale for assessment of glucosamine efficacy in CLBP is not adequately justified because this clinical entity involves other anatomical structures that the only vertebral cartilage, e.g. the intervertebral disk and the para-vertebral elements. Glucosamine is not expected to have a direct effect on those latter structures.
2. the participation of patients in the study was triggered by advertisement that should include a financial motivation for some of them. This may interfere with the patient assessment of its own symptoms,
3. the efficacy outcomes did not include any pain-specific clinical assessment. Only a CLBP-specific scale (RMDQ) was studied which, although being validated, does not take specifically into account the pain dimension of symptoms, which is the main target of Glucosamine as regards its symptomatic effectiveness.
4. finally, the effectiveness of the tested interventions may have been seriously impaired by the authorized use of any concomitant therapy aiming at pain relief: pain killers, NSAIDs, common analgesics but also physiotherapy, chiropraxis, manipulations, massages, all those interventions being possibly administrated without any limitation of nature, dose, regimen or duration. Yet, while no pain threshold was required at inclusion, patients were likely to experience very slight pain at baseline and it seems quite impossible to evidence the analgesic effect of a medicinal product in patients who do not suffer.

4. 0verall conclusion

The glucosamine MAH present here several evidences towards the lack of relevance of most data used to anticipate a possible reassessment of reimbursement status of Glucomed. In view of the number of issues shown in each of the three mentioned references, the MAH expresses its formal reserves regarding the relevance of those works and of the need to go further in the reassessment procedures on those grounds. Therefore the MAH asks the Danish Medical Agency to maintain the present status of Glucomed, while the proposed document are not likely to modify, in any extent, the previously defined therapeutic profile of the drug and therefore its reimbursement status.

DISCUSSION OF THE PUBLICATIONS

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 (8). This was recently highlighted in a Norwegian study of patients with chronic low back pain and lumbar arthritis (35). 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 (34).

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."

In view of the arguments developed by the Danish Medical Agency (DMA), the MAH, Expanscience, wants to present the scientific arguments likely to offer an alternate view of the publications on glucosamine. The main part of the present report will therefore consist of an in-depth discussion of the three papers listed by the DMA.

2. Discussion of the Glucosamine clinical trials / meta-analysis used by the DMA.

2.1. Discussion of the GAIT study (Clegg, 2006)

2.1.1. Reminder on material and methods

The GAIT study is a very important trial sponsored by the National Institute of Health aiming at the rigorous evaluation of glucosamine and chondroitine sulfate, alone and in combination, in the symptomatic treatment of patients with osteoarthritis of the knee. A total of 1583 patients with knee OA were to receive daily for 6 months : 1500 mg of glucosamine, 1200 mg of chondroitin sulfate, both treatments, or celecoxib 200 mg or placebo. Patient groups were stratified according to the severity of knee pain (mild [N = 1229] vs. moderate to severe [N = 354]). Efficacy outcomes included WOMAC scores, either as a 20% decrease in knee pain from baseline to week 24 (primary outcome) or mean changes from baseline to Week 24 endpoint of each subscore and normalized total score. Secondary outcomes also included various scales measuring the extent of disability (HAQ) and global assessments by the patient and the physician.

2.1.2. Main results of the GAIT study

2.1.2.1. Results in the whole population

In patients treated with either SYSADOA, the only significant differences vs placebo were observed for the combined OMERACT-OARSI response in the Glucosamine + Chondroitin group (p = 0.02). In patients of the "positive control" group, only the primary outcome (20% decrease of WOMAC pain score) and the derived secondary outcomes (OMERACT-OARSI response and 50% decrease in WOMAC pain score) were significantly different from placebo. But most of the mean WOMAC scores (total score and subscores, except function) were not modified significantly in celecoxib-treated patients.

2.1.2.2. Results in patients with moderate to severe pain at baseline

In the stratum of patients with moderate to severe pain at baseline, the global improvement was of greater magnitude in all groups, but, due to limitations in sample size in this subgroup (only 22% of the total randomized population), significant differences were not reached for all parameters, in all groups.

However it is noticeable that most WOMAC-derived parameters were significantly different from placebo, as were the patient's global assessments in the Glucosamine + Chondroitin treated patients. In the same moderate-severe pain subgroup, the results with celecoxib did not reach statistical significance for the primary outcome, nor any other secondary parameter, except the OMERACT-OARSI response ($p = 0.03$).

2.1.3. Discussion of the 6-month results

The great magnitude of the placebo effect and the lack of efficacy of an FDA-approved NSAID for OA pain, celecoxib, in those patients who were the most severely affected, reveal significant biases that obviously mask the real effect of treatments under study.

Those biases are probably in relation with a highly placebo-responder population.

But other likely explanations can also be anticipated: patients previously treated with either treatment under study could be included in the study, without prior wash-out. Under the hypothesis of the prolonged efficacy of SYSADOA, a carry-over effect of previous treatments during the study cannot be precluded.

In the paper discussion, the study authors themselves, have stressed the limitations of their study, which evidences a clinical effect of borderline significance, in patients with moderate to serious OA, treated with glucosamine, in spite of a significant placebo effect.

2.1.4. Long-term (2 years) results

The GAIT study was prolonged in the 572 patients who satisfied the radiographic criteria for the assessment of structural changes of the knee joint (25).

A total of 357 patients, totalling 581 evaluable knees, were included in the analysis. The mean difference from placebo in JSW loss was 0.153 mm in glucosamine-treated patients, the greater value compared to chondroitin, combination or celecoxib.

A separate analysis was performed according to the KL grade. It evidenced a trend toward a significant improvement, relative to placebo, especially in glucosamine-treated patients where the difference in JSW changes exceeded 0.2 mm.

2.1.5. Discussion of the long-term (2 years) results

Despite the limitations due to the development of JSW "natural" changes, the small number of subjects, as well as the high variability of JSW measurements, this long-term part of the GAIT tended to confirm the long-term structural effect of glucosamine.

Those results may be put in line with those observed in the analysis of very long term data (i.e. after a mean 8-year follow-up period) obtained from two glucosamine 3-year studies (5). This analysis evidenced a reduction in the proportion of patients needing total hip replacement by 57% in those treated with glucosamine (6.3%), compared to placebo (14.5%, p = 0.024). The corresponding effect size is 0.4, and can be considered as quite clinically significant, while the significance between thee two groups was confirmed by the Kaplan-Meier survival analysis, with a significant difference at the Log Rank test (p = 0.026).

Furthermore, a pharmaco-economic evaluation was performed over the year prior to the follow-up period. This analysis evidenced a reduction of most OA-related interventions with glucosamine: the direct cost of analgesics and NSAIDs was divided by two, compared to placebo (108 € per glucosamine-treated patient vs 204 € in the placebo group).

All other expenses were reduced in the group of patients treated with glucosamine (visits to practitioners or specialists, paramedical exams, X-rays, gastroscopies…) thus resulting in a significant (p = 0.024) reduction by about 50% of overall expenses in glucosamine-treated patients (292 €) vs placebo-treated patients (605 €), i.e. a 313 € saving.

2.1.6. Conclusion

In agreement with the author's discussion of the results, the assessment of glucosamine efficacy after a 6 month treatment in knee OA patients remains inconclusive at the end of the GAIT study, despite major efforts were made to obtain high-quality reliable data. This was due to a very high placebo effect that resulted in masking the true effects of the tested treatments. The positive control treatment group (celecoxib) only evidenced marginal significant efficacy, mainly on the primary outcome, but not on all WOMAC-derived parameters including mean subscores and total.

The effectiveness of DMOAD interventions appeared somewhat greater in patients with moderate to severe pain at baseline, but differences were not all significant due to the insufficient number of subjects in this subgroup. However, in this subgroup, all efficacy outcomes but one, were not significantly modified in celecoxib-treated patients.

The long-term (2 years) assessment of structural changes tended to confirm the therapeutic interest of glucosamine in patients with JSW loss changes about 0.2 mm lower than that measured under placebo.

In total, the GAIT study cannot be considered as a "negative" study with respect to glucosamine symptomatic efficacy. This study remained inconclusive, even though better results were observed in patients with moderate to severe pain at baseline.

2.2. Discussion of the Low back pain study (Wilkens, 2010)

As far as this study is considered as one of the triggering factor for the decision of reassessment, it is very important to mention several discrepancies in relation with its relevance.

2.2.1. Indication under study

First of all, the indication "chronic low back pain" (CLBP) is not an official indication of Glucosamine, when considering the SPC edited at the end of the European registration procedure. The only recognized indication is : "*Relief of symptoms in mild to moderate osteoarthritis of the knee".*

This is of importance while it is commonly stated that –generally speaking, as well as specifically in patients with osteoarthritis-, the demonstration of efficacy (or lack of efficacy) on one specific joint does not allow for extrapolation of efficacy to one or more additional joints (27). The reciprocal proposition is naturally true, i.e. the lack of efficacy at one joint level (for instance the spine) does not allow for extrapolation of the same lack of efficacy at another joint level (for instance the knee).

In other words, it can be considered that the results of the study by Wilkens has no relevance for the assessment of Glucosamine efficacy in the field of its natural and official indication: knee osteoarthritis.

2.2.2. Pharmacological rationale for Glucosamine effectiveness in CLBP

The authors proposed using Glucosamine in this indication, on the basis of its anatomical long term effect on the cartilage and secondarily of its anti-inflammatory effect in human OA chondrocytes, under the hypothesis that such effects should be sufficient to result in an improvement of the pain-related disability (main efficacy criterion in that study).

However, the intervertebral joint is a particular one, in the sense that it includes a particular anatomical element, which plays a major role in the joint function: the intervertebral disc. Therefore, the rationale for glucosamine efficacy in the indication of this study in incomplete because the product is not supposed to have an effect on two components involved in the clinical development of CLBP: the intervertebral disk and the non articular paravertebral structures (muscles and tendons).

2.2.3. Patient recruitment methods

Patients were selected through referral by GP's, physiotherapists, chiropractors, as well as self-referral based on one newspaper advertisement. In the context of marketing of glucosamine, which can be obtained either as a reimbursed drug or as a purchased food supplement, the motivation of patient for participating in the study could be purely financial. And this could also interfere in their assessment while the lack of efficacy could result in study discontinuation and therefore in free drug supply termination.

2.2.4. Potential role of multiple uncontrolled concomitant therapies of CLBP

As regards the protocol itself, it can be considered that some of its methodological specificities did not allow for an "easy" demonstration of the effect on "pain-related" disability. Of course, it is commonly agreed upon the major role of disability as a valuable assessment criterion. But in the case of evaluation of glucosamine efficacy, the major impact is expected on the symptomatic efficacy. Actually, in order to assess the analgesic effect of an intervention (glucosamine in this particular case), the patients are supposed to have pain, at the maximal acceptable level, to be able to actually perceive the analgesic effect.

Yet, it is to be emphasized that, in the Wilkens study, patients were allowed to take any sort of concomitant therapies, including pain killers, NSAIDs, usual analgesics, but also any type of LBP therapy, e.g. physiotherapy, manipulations, massages, without any planned restriction.

In those conditions, it may be supposed that patients naturally tended to use all interventions in such a way their pain will be reduced at the "minimal level". This particular protocol characteristics is likely to have considerably reduced the sensitivity level of the comparison between glucosamine and placebo.

Furthermore, in its official indication, the main target of glucosamine is "the relief of symptoms", i.e. mainly pain. But the primary outcome measure used in that study is the 24-item Roland Morris Disability Questionnaire, which is not directly focused on pain intensity, but only as an indirect reflection of pain. No secondary criterion evaluated pain changes according the reference method of Huskisson VAS. It can then be considered that the primary outcome used in that study is only an indirect criterion that is not in line with the official indication of glucosamine and its previously shown clinical profile.

2.2.5. Evidence of several limitations of the study by the authors of the study

Finally, several of these restrictions were raised by the authors themselves in the paper's discussion. They actually and very honestly stated that :

- *The inclusion criteria for the present trial may have selected patients with LBP who were not receptive to glucosamine*
- *LBP studies are faced with a diagnostic challenge and several possible classification methods. Alternative inclusion criteria might have provided a more glucosamine-receptive population.*
- *Glucosamine may be more effective in other body articulations than in the lumbar spine.*
- *The location and severity of OA disease may be important for the efficacy of glucosamine*
- *Trial limitations require attention. First, free participation, including study treatment and visits, and the focus on glucosamine may attract a certain type of patients with specific personality traits toward trial settings and glucosamine that could affect the out come. Second, adjunctive management was permitted, which may have influenced outcome. Third, adherence was assessed by capsule counts. This may have caused bias owing to increased study awareness and the number of capsules might have been altered by capsule dumping. Fourth, although the capsule counts indicated that more than 80% of the capsules were consumed, the dose-response for glucosamine might require higher adherence to demonstrate efficacy.*

2.2.6. Conclusion

As far as the results of the study by Wilkens et coll. could be considered as negative with respect to the efficacy of Glucosamine on the disability in patients with CLBP, the conclusion cannot be taken into account because :

- they refer to a clinical indication that does not belong to the Glucosamine official indications,
- they were observed in patients who could receive multiple uncontrolled concomitant treatments (drugs, physiotherapy, massages…) that were likely to reduce the sensitivity of the comparison,

- the selection of the patient population did not take into account their initial pain (no pain threshold was required at study entry) and the "minimal" RMDQ score was rather low (quoted 3 out of 24 items).
- the primary outcome is only dedicated to the assessment of disablement. It does not directly take into account the pain intensity.
- the authors themselves emphasized several major limitations of their study.

2.3. Discussion of the Wandel meta-analysis (2010)

The publication of the meta-analysis by Wandel and his colleagues (34) provoked a number of reactions, mainly criticisms due to the choices made for that analysis. Several items approached in the following discussion are referring to those reactions, which were published as rapid response letters in the British Medical Journal. In order to simplify the search of those references they are gathered in a single document that is appended to the present report and is referred as a single reference (3) to, except otherwise specified.

2.3.1. Discussion of the very principle of "yet one additional" meta-analysis on Glucosamine in osteoarthritis

One of the first subject of discussion about this publication was the very principle of this meta-analysis, i.e. was a new meta-analysis on glucosamine necessary, in view of the great number already performed on the subject ?

Actually, several meta-analyses had already been published about glucosamine effect in the treatment of osteoarthritis. Those analyses were performed either by international or European scientific or regulatory organisations, or by the independent Cochrane collaboration, as well as several individual scientific groups. Globally, those meta-analyses provided rather homogeneous results, allowing, notably for the registration of the product in many countries and for the publication of therapeutic guidelines in the management of osteoarthritis, by several scientific organisation, such as OARSI and EULAR.

Rationale of the meta-analysis

While no new relevant data is available in the Wandel analysis when compared to those previous pieces of work, the rationale for performing this new meta-analysis is questionable.

In view of the paper's introduction, it can be felt that the major triggering factor of this work is of economic nature and the authors consider that this statement needs further confirmation of the therapeutic role of the two drugs, glucosamine and chondroitine.

But they primarily justified their analysis by the "conflicting" effectiveness of both drugs, that should be related to studies of poor quality and/or small sample sizes.

In order to establish a basis of the conflicting effectiveness of glucosamine, the authors mentioned three publications (15, 13, 33), consisting of a "self-reference" to previously recommendations in the management of osteoarthritis (13), and of two meta-analyses published by the same team (15, 33).

Owing to the number of publications on the therapeutic role of glucosamine in osteoarthritis, it is surprising that the authors did not mention several other publications that should have established the claimed "conflicting randomised trials". They did not, notably, explain in what extent the previous meta-analyses and/or studies did not answer the main question of efficacy (despite they had been accepted by European Health Authorities for the registration of Glucomed and considered in several international guidelines [27, 37]).

However, in their previous paper, the authors stated interestingly (13) that "*Risk factors for incidence and progression of osteoarthritis vary considerably according to the type of joint*." and that "*one of the guiding principles to the management of OA is to base patient management on the severity of pain, disability and distress, and not on the severity of joint damage or radiographic change*".

Despite considered by Wandel as of conflicting efficacy, the therapeutic interventions depicted here (13) by his co-workers, are considered to present with small to moderate effect sizes in meta-analyses and are therefore still valuable for patients and clinically relevant for physicians. Is this statement consistent with the objective of the present meta-analysis by Wandel ?

The two other references that are supposed to establish the conflicting character of Glucosamine efficacy are the Glucosamine meta-analyses by MacAlindon (15) and Vlad (33). The selection of those two references is surprising because :

- only five studies were included in the meta-analysis of McAlindon vs 20 studies in the 2005 version of the Cochrane-sponsored meta-analysis (31).
- the same was true for the Vlad meta-analysis, which included only 15 glucosamine studies all taken into account in the Cochrane meta-analysis.

If the authors considered that the Cochrane meta-analysis was not valid, this should have been mentioned and the differences between the two considered analyses and the Cochrane one should have been discussed, in showing, notably what are the specific qualities of the McAlindon and Vlad analyses.

The main specificity found for those two meta-analyses is to have been performed by the same team (McAlindon is author of the two papers) and to raise a lot of questions about the quality of industry-sponsored trials.

One example of a partial demonstration of this issue was shown in the paper by McAlindon. For the authors, there is a clear effect of the quality of trials on the level of demonstrated efficacy.

This was supposed to be ascertained in showing that pooled effect sizes were substantially higher among lower-quality (i.e. industry-sponsored) compared with higher-quality trials. For glucosamine, the pooled effect for trials with a quality score below the median was 0.7 ($_{95\%}$CI = 0.4 - 1.0) vs 0.3 ($_{95\%}$CI = 0.1 - 0.5) for trials with a quality score above the median. For chondroitin, the pooled effect for trial with a quality score below the median was 1.7 ($_{95\%}$CI = 0.7-2.7) vs 0.8 ($_{95\%}$CI = 0.6-1.0). But this conclusion is only true in the context of the mentioned comparison with a posteriori definition of a cut-off point, here chosen as the median. It is well known that changing the cut-offs may completely change the conclusion of this type of analysis.

Furthermore when approaching this question through another statistical method, the conclusions are diametrically opposed.

Actually, if the hypothesis of the authors was true, it must be supported by the evidence of a statistical relationship between the efficacy level (assessed as the effect size) and the trial quality (assessed by the Jadad score or similar).

The study of the correlation between the two parameters (extracted from the McAlindon publication) that was presented in the context of the Glucosamine-HCl French transparency dossier, (efficacy effect size vs quality score) strongly suggest that these two parameters are not correlated, with $R^2 = 0{,}0893$ (see hereafter).

In other words, contrary to the hypotheses of the authors mentioned above, for a given effect size level, studies of any quality level can be found, and vice versa, the studies with the lowest quality scores are not those with the highest effect sizes.

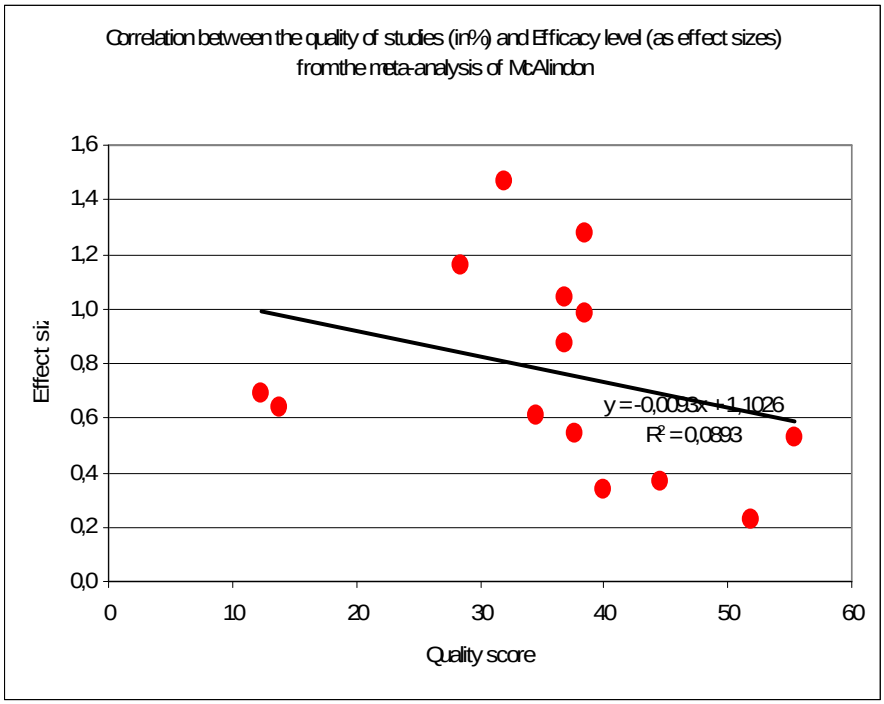

Figure 1: Analysis of the correlation between the efficacy results (effect size) and the quality of the study (Jadad score) in clinical studies published in the meta-analysis of McAlindon (15)

Finally, it can be considered that the authors did not provide objective and comprehensive data about Glucosamine studies, in order to validate the basic hypothesis of their meta-analysis. With respect to glucosamine, they only referred to 3 papers, including one self-reference to a general recommendations for the management of OA and two partial meta-analyses (15, 33), whereas at least two more recent and more complete, comprehensive and independent reviews had been already published (31, 32).

2.3.2. Discussion of the objectives and the choice of a particular statistical method of meta-analysis: the network meta-analysis

When considering the first lines of the paper abstract, the objective of the meta-analysis of Wandel et al. seems quite simple: "*to determine the effect of glucosamine, chondroitin, or the two in combination on joint pain and on radiological progression of disease in osteoarthritis of the hip or knee*."

First, this meta-analysis takes into account both knee osteoarthritis and hip osteoarthritis. Pooling the two indications in the same analysis is not pertinent because hip OA is not a validated indication for most brands of glucosamine.

In addition, the authors themselves unambiguously stated that : "*Risk factors for incidence and progression of osteoarthritis vary considerably according to the type of joint*." (13).

Besides, the wording of the objective let suppose that there was no previous information for the determination of glucosamine effect, but the paper introduction should lead to "correct" the study objective as a "confirmatory analysis" of glucosamine efficacy in view of pre-existing conflicting results. Therefore the implicit place of this meta-analysis should be that of an "arbitrator" who will decide if previously published conclusions were valid or not (even though they were confirmed and validated, notably, by European regulatory authorities).

Therefore, in order to play this role, it seems pertinent that authors implement their analysis using undisputed methods, in order to provide results that should not raise any discussion and permit to obtain a definitive conclusion on the question of glucosamine efficacy.

Generally speaking (10), the objectives of a meta-analysis are : (i) to increase the statistical power in demonstrating a therapeutic effect, (ii) to obtain the optimal accuracy in determining an effect size and (iii) to have a comprehensive view of the results, especially in case of discrepancy.

Is the meta-analysis by Wandel likely to meet, partly or totally those objectives ? It is clear that it will not.

1) increasing statistical power supposes to increase the number of studies and/or subjects, compared to single trials analyses or to previous meta-analyses. The meta-analysis by Wandel does not fulfil this condition. On the contrary, the authors restricted the number of analyzed studies, which is supposed to reduce statistical power, compared to previous more comprehensive analyses (31, 32).

2) improving the calculation of effect size is not an objective (and not a result as well) of the Wandel network meta-analysis. On the contrary, this method performs several back transformations of studied variables and changes the usual thresholds for the interpretation of effect size according to Cohen's classification (9).

3) no global view of the situation regarding discrepancies can be expected from this meta-analysis while all the "small studies", i.e. with group sizes < 100 patients per arm were excluded from the analysis. This cut-off was defined because it is supposed to be consistent with the demonstration of an effect size arbitrarily fixed to 0.4, which does not correspond to any usual threshold values as defined by Cohen (see development of this issue hereafter)

In addition, playing the role of an arbitrator supposes to use undisputed methods, notably in terms of compliance with regulatory guidelines. Actually it is not the case for the network meta-analysis (MA), the role of which being mainly to permit indirect comparisons of products tested separately in different trials (e.g. one study compared A vs B, another study compared B vs C, the network MA will provide an estimation of the A vs C comparison). But considering several A vs B trials, it is not a specificity of network MA to provide additional information, compared to "traditional" meta-analysis, of the A vs B global difference !

To provide a complete statement on glucosamine efficacy did not require such a complex model.

Conversely, as far as the authors decided to implement this method for their analysis, it is very surprising that they did not choose to provide additional information about two "positive" control groups, i.e. patients treated with paracetamol (from the GUIDE study, by Herrero-Beaumont [12]) and patients treated with celecoxib (from the GAIT study, by Clegg [8].

The specificities of the network meta-analysis could have fully play their role in showing the differences between glucosamine, placebo and those two positive control interventions. But doing so could also have revealed some discrepancies of the meta-analysis, such as, for instance the lack of difference between the celecoxib positive control and placebo…

2.3.3. Discussion of the criteria of selection of studies included in the meta-analysis

For Wandel and colleagues, the main factor likely to differentiate the relevance of clinical studies is the number of patients per arm. Their hypotheses were based on the significance of a 1 cm active vs placebo differences in pain intensity on a 10 cm visual analog scale. They consider that this difference corresponds to a "small to moderate effect size"[1] of 0,40, with a 80% power, in a bilateral situation at p = 0.05. Their calculations result in a minimum sample size of 100 patients per arm. In fact, those calculations were not performed specifically for that meta-analysis but were extrapolated from those done in another analysis aiming at showing the negative role of "small" clinical studies in meta-analyses (17).

The choices made for the definition of this selection criterion is highly questionable for many reasons.

1) Such a systematic exclusion of a great number of clinical studies, goes against the basic principles of any meta-analysis, that is exhaustiveness. For the authors, including the so-called "small studies" may be misleading. But it is generally accepted that excluding available studies may have the same result. In the particular case of glucosamine studies in knee OA, the Wandel meta-analysis only included 6 studies, out of the 25 that were analysed in the latest update of Cochrane Collaboration (32). This means that Wandel excluded "at least" 76% (19/25) of potentially interesting studies !

2) The determination of theoretical value for the calculation of the valid number of subjects has been made using the cut-offs values as defined by Cohen for psychometric assessments. Those cut-offs, disregarding their relevance in the field of osteoarthritis assessment, were 0.2, 0.5 and 0.8, with respective "verbal" correspondence of small, moderate and large effects. But Wandel decided not to fully comply with the usual thresholds and to only consider a significant effect size value of 0.4 to define the minimal sample size of patients groups.

[1] Note : Referring to the Cohen's classification, small to moderate effect size is between 0.2 and 0.79

Actually, this 0.4 value is to be considered as purely arbitrary in the field of osteoarthritis.

- First, because the "clinically relevant" effect, even if small is defined by a 0.2 effect size value, which probably should have resulted in smaller minimal sample size and then in the inclusion of a greater number of studies.

- Second, because the clinical meaningfulness of the effect size values in osteoarthritis does not correspond to those defined by Cohen. For instance, as stated by Pelletier (19), paracetamol is recommended for the initial treatment of symptomatic osteoarthritis by the European League of Associations of Rheumatology and the Osteoarthritis Research Society International, yet its effect size for pain is < 0.20,

The only other exclusion criterion was the use of a therapeutic dose < 1500 mg glucosamine. But the authors do not specify if they considered the glucosamine base, or the salt dose, that may be quite different.

Finally, the main and quasi-unique inclusion criterion in the meta-analysis is the number of patients per group, which was arbitrarily determined to 100. This results in the exclusion of 19/25 of the trials available for glucosamine knee OA, in the latest version of the Cochrane Collaboration meta-analysis. This very high rate of exclusion is questionable in view of the theoretical bases of a meta-analysis. As such, it may hamper the relevance and impact of the meta-analysis conclusions.

2.3.4. Discussion of the outcome measures in the meta-analysis and their assessment times

The authors selected two outcomes in their analysis: the main one was the absolute value of pain intensity reported at any of the time windows they defined as relevant : 0 and then every 3 month, until 21 months with an additional time ≥ 22 months.

This methods raises several significant issues.

- First, the choice of the –absolute- value of pain intensity, i.e. disregarding the baseline pain intensity, may be misleading because, as discussed by Pelletier et al. (19), a change of same magnitude, e.g. 1 cm on a 10 cm VAS, has not the same clinical relevance in patients with severe pain at baseline (> 7 cm on a 10 cm VAS) and in patients with slight of moderate baseline intensity (< 4 cm on a 10 cm VAS).
- Second, in some studies, the assessment criteria may not include either the primary or secondary selected outcomes. For instance, it is particularly the case for the study by Noack (16) in which the only reported assessment criterion is the Lequesne index, that cannot be considered as a pure pain intensity assessment. Actually, Wandel refers to a previous paper published by the same team (13), that "suggest" the hierarchy of pain-related outcomes used in their meat-analyses. However, using the total Lequesne index score as a pain oucome is questionable, because the questions of the score directly focusing on pain represent only a maximum of 3 points out of 24, other items being more dedicated to the assessment of functional impairment.
- The relevance of the back transformation allowing to obtain "pain intensity on VAS" from total score of the Lequesne index is also difficult to establish, while, finally, it is impossible to have an objective view of the "content" of the newly generated main efficacy outcome. In other words, the multiplication of extrapolations and transformations result in a gap between the original, actual assessment (pain at rest, pain on movement, WOMAC pain score, Lequesne index and so on) and the main outcome in the network meta-analysis (ambiguously labeled in tables and figures "pain intensity measured on visual analog scale"). It is to be noticed that, in their meta-analyses, the Cochrane statisticians did not mix fundamentally different efficacy criteria and reported separately the results for pain scales and for combined scales (Lequesne or WOMAC).

– Third, the time windows under study were quite wide, while limited to 4 weeks (here quoted as "up to 3 months") in some studies (16) and up to 36 months or more, in some other studies (18, 21) being there quoted as "more than 22 months".

Pooling so different studies in terms of treatment duration is quite troublesome because the authors mixed up studies with different objectives (short and medium term as symptomatic studies vs long-term as "anatomical" studies), different initial hypotheses and different primary outcomes. But they decided to consider an unique primary outcome for all studies (even though it was a secondary one in individual studies). Some authors considered that this was a "nonsense" (28). By using this time-window classification, the authors decided to purely and simply "erase" (by mixing all data over 22 months) the long term results (up to 3 years) of 2 studies which accounted for more than 400 patients. By selecting the analysis of most available timepoints in each study, the author obtained a very heterogeneous matrix. Using an endpoint analysis with carry-forward and reducing the number of windows, should have increased the number of patients in each time window.

It is also to be emphasized that the European Guidelines have stated that the assessment of the symptomatic effect of SYSADOA should be evaluated after a minimal treatment duration of 6 months, while the effect on anatomical changes can only be evaluated after two years (27). Therefore, to perform multiple assessments of efficacy parameters in the 0 – 6 months period does not seem adequate in view of regulatory recommendations.

2.3.5. Discussion of the quality assessment of studies in the meta-analysis

Three criteria were used by Wandel to characterize good quality trials : allocation concealment, blinding and adequacy of analyses.

With respect to the role of allocation concealment, it is to be emphasized that it became rather recently a key criterion. A literature search of the term (Pubmed) "allocation concealment" returns 861 references, the first of which published in 1984, but the second one in 1994, with a clear increase in the occurrence of the term from 2000 onwards (831 references). This observation is to explain that papers published before 2000 were not systematically checked for the presence / absence of allocation concealment. This can be explained by the fact that it was generally confounded with double-blinding.

This is notably the case for the Noack study, that was published in 1994 and probably did not care about the need to report this "additional" quality criterion.

In addition, Wandel and colleagues made a mistake in reporting a quotation "unclear" for allocation concealment in the Reginster study, while it is clearly reported in page 252, 2nd paragraph "*The principal investigator was provided with individual envelopes, each containing patient codes, thus concealing treatment assignment*".

The same was true in the same study, with respect to blinding, the mention of "double-blind" being repeated in several parts of the paper.

2.3.6. Discussion of data collection and statistical analysis methods.

Wandel and colleagues implemented a rather complex method as the "network meta-analysis". Again, it is necessary to emphasize that this "network" specificity of analysis became only "necessary" by the author's will to perform cross-comparisons between glucosamine, placebo and also chondroitin and the combination of the two products (this latter group being only provided by the GAIT study).

In order to try to answer to the simple question relating only to glucosamine, such a complex model would not have been necessary and the meta-analysis would probably have been different.

A detailed discussion of the methodological issues was published by Helg (3) in the number of rapid responses let after the publication of the paper by Wandel. The considerations of Helg are somewhat long and complex, although being of great accuracy and relevance. They are provided in full in the appended document that summarizes all BMJ rapid responses (3).

In the same document, Giacovelli (3) also pointed out several issues in the statistical analysis and reported the conclusions of independent master methodologists about that technique : "Unfortunately, their statistical methods are so complex that many are mystified by whether the conclusions make sense".

2.3.7. Discussion of some specific studies included in the meta-analysis

2.3.7.1. Discussion of the study by McAlindon

Out of the 7 clinical studies included in the network meta-analysis for glucosamine, one of them published by McAlindon (14) was considered of special interest in view of the major biases and flaws it apparently contents.

In its introduction, McAlindon expresses an "evident" statement, that is, *osteoarthritis trials are burdensome and costly, especially in pursuit of modest effect sizes*.

Should the efforts made in a clinical study be now tailored according to the magnitude of the anticipated effect size ?

Of course not, and it is probably the contrary, greater efforts are to be agreed, if there is some potential conflict in the quality of the results, notably due to other "negative studies" or to an effect of small magnitude.

This it is particularly the case of the McAlindon study.

Actually, in view of saving up some money, McAlindon developed a special methodology, entirely based on the Internet follow-up of the study. Right at the beginning, the glucosamine study included in the Wandel meta-analysis was initially considered by McAlindon as a pilot study, to test the feasibility of online clinical trials by performing a "prototypical" double-blind study.

Methods

The methods implemented in this protocol by McAlindon are unusual ones according to the following characteristics.

1) the patients were exclusively recruited by their response, via Internet, to an advertisement. By itself this method is likely to result in selection biases, as well as, in the follow up, in assessment biases. Actually, for many patients with OA, glucosamine is not a free product and the aim to obtain a free treatment for over 3 months may be a strong incitation for some patients. Similarly, the risk to loose the benefit of a free treatment in case of withdrawal may encourage patients to report better efficacy, whatever the intervention they receive.

2) The detail of the procedure for validating the inclusion of a patient is unclear. Of course, it seems quite clear that the whole inclusion is made over the Internet, without even one consultation of a physician. Even under the hypothesis of selecting (how ?) patients with a high level of education that will allow them to complete easily the whole procedure, there is absolutely no possible control on the veracity and consistency of data, directly recorded by the patients. Possible errors in diagnosis and presence of contra-indication or precaution for use cannot be ruled out by this method. But the main question remains the way by which factual results were checked by the investigator(s?). How could he verify and quote the presence of X-ray or MRI signs ? This point remains very questionable while considering the absence of any study-related medical contact.

Furthermore, the study is probably not in full compliance with Good Clinical Practice, especially regarding the lack of information of –at least- the patient's GP, the lack of on-site study monitoring and the lack of "original" hand-written CRF.

3) Another major issue of the study is related to the study treatments. In its initial phase, the active study treatment was glucosamine sulphate given as 500 mg capsules (496 mg after control). The daily dosage was 3 capsules daily, i.e a total 1500 mg daily dose of glucosamine sulfate. But due to manufacturer withdrawal, the study treatment was changed during the course of the study, after the 162nd inclusion, i.e., after 79% of the total randomised population had been included. The study treatment was then switched to glucosamine hydrochloride, given as 1500 mg glucosamine-HCl powder in sachets, once daily. Considering the differences in purity between the sulfate and the hydrochloride salts, the glucosamine-base daily doses were as different as 957 mg in 3 divided dose for the sulfate vs 1250 mg in a single daily dose for the hydrochloride.

It is quite unusual to change the tested drug during a clinical study, and to change simultaneously the total daily dose and the daily regimen. Such method is likely to disqualify the entire study, or at least, the part of the subjects included after the switch to the Glucosamine-HCl formulation. This is necessary while the patients treated by the two different regimen were not –a priori- in the same conditions.

Another characteristic of the protocol was to allow the unrestricted use of analgesics, i.e. paracetamol, in mean doses of 1845 mg daily in the Glucosamine group and 1309 mg daily in the placebo group. The use of such concomitant treatments is recognized by the authors as a potential factor that could have masked a beneficial effect of glucosamine.

In conclusion, this pilot study should not be qualified for being entered in any meta-analysis, notably that of Wandel. This is motivated by the very particular Internet-driven trial follow-up, without any contact between patients and investigator(s), and also by using two different active intervention formulation, in different daily dosages and different regimen, in two successive patient subgroups, and without any attempt to demonstrate that both study regimens were equivalent, notably through a bioequivalence study.

2.3.7.2. Discussion of the study by Rozendaal

The study published by Rozendaal (23, 24) that was included in the meta-analysis of Glucosamine was dedicated to the assessment of efficacy in patients hip OA.

Disregarding the previously mentioned non compliance of that indication with official indication of Glucosamine in Europe, that study cannot be considered as adequate for the assessment of efficacy in hip OA patients. Actually, the authors accepted to include patients with OA of slight severity as shown by the Kellgren-Lawrence index, stage 1. This was the case in about one half of included patients, thus resulting in a major decrease in the sensitivity of the comparison. Actually, it is clearly recommended by EMA guidelines (27) to include only patients with KL grades 2 and 3, because in the presence of very slight anatomical (i.e. radiological) joint lesions, it becomes almost impossible to evidence an objective effect.

This major discrepancy in inclusion criteria renders the study partially or fully invalid, as stated by Theodosakis (29).

2.3.8. Discussion of the results of the network meta-analysis

Not surprisingly in view of the biases evidenced at the "methods" level of the analysis, its results are considered as showing "*no clinically relevant effect of chondroitin, glucosamine or their combination on the perceived pain*" (…) and "*the effects on minimal width of joint space were small, again clinically irrelevant* (…)".

It is interesting to emphasize that those conclusions are made in the context of the authors initial hypothesis of clinical relevance (ES = 0.4), which was obviously overestimated. When considering the "facts", despite considerable dilution of relevant effect due to the inclusion of biased studies, the authors however report a "traditional" p value revealing a "conventional" significance at the 0.05 level for the "perceived pain" criterion.

But, the authors considered that this significance is irrelevant, while being masked by the lack of clinical significance. But, again, this opinion is to be viewed in the context of the particular hypotheses of their analysis.

It is to be noticed that authors reject the relevance of traditional statistical significance as regards the significant effect on perceived pain, but emphasizes the lack of statistical significance as regards the effects on JSW.

Generally speaking, the multiple reactions of researchers and clinicians against the publication by Wandel, mainly concerned the "method" section of the publication.

However, some authors considered it was necessary to present and discuss the results in a different way.

In his commentary on the publication (7) Bruyere notably:

- remarked that, despite statistically significant, though modest, ES on pain decrease, differences compared with placebo on a 10 cm VAS were significant, but of –0.4 cm (95% credible interval –0.7 to –0.1) for glucosamine (ie, below the –0.9 cm threshold for putative clinical relevance). The saving in JSW changes with glucosamine was 0.2 mm (0.3–0.0), of comparable magnitude to chondroitin but considered small by the authors.
- emphasizes on mixing up quite different studies, that results in an increase in heterogeneity : Thus, heterogeneity rises to 63% when expressed as I-squared values in a conventional meta-analysis. This is not appropriately discussed by Wandel and colleagues, since they claim low heterogeneity but they used, instead, a minimally informative prior distribution with emphasis on high heterogeneity. He also stresses that when others (22) limited the analysis to the three long-term trials of prescription glucosamine sulphate 1500 mg once a day in knee osteoarthritis,1 heterogeneity was absent and pain ES was 0.27 according to conventional techniques and 0.34 with the authors' Bayesian approach. This is clinically relevant, higher than with paracetamol (ES = 0.14) and in line with non steroidal anti-inflammatory drugs (ES = 0.29).

Bruyere then concluded that : "*This additional meta-analysis is biased by poor trial selection and does not change the existing evidence despite the use of a complex methodology that does not modify the previous results.*

The conclusions by Wandel and colleagues are in disagreement with all international and European guidelines, which unanimously recommend the use of prescription chondroitin and glucosamine sulphate. This research should not change the current practice in this respect"

2.3.9. Conclusion

The meta-analysis published by Wandel and colleagues is presented by authors as the ultimate work in this field, supposed to definitely solve the question of the "conflicting" effectiveness of glucosamine and chondroitin, by using a sophisticated and complex method of analysis: the network meta-analysis.

However, the rationale supposed to justify this meta-analysis appears somewhat partial and does not meet the basic principles of this statistical technique :

- the "conflicting" nature of glucosamine efficacy is not ascertained by a comprehensive analysis and discussion of previous scientific consensus and meta-analyses,
- the meta-analysis by Wandel:
  - is not able to increase the statistical power, because of the lack of new data,
  - cannot improve the estimation of the treatment effect sizes, because of mixing up the studies outcomes, the assessment times, the indication and because using a lot of approximations and back transformations,
  - is not able to bring any new view on the question, because of the exclusion of about 75% of glucosamine available data, thus being totally in contradiction with the principle of comprehensiveness of a meta-analysis.

The authors justified using the network meta-analysis because they wanted to make cross-comparisons between glucosamine, chondroitin and placebo. Not only the interest of cross-comparisons is not evident, but while implementing the method, they decided to exclude of their cross-comparisons two positive controls present in two studies : paracetamol and celecoxib.

The authors also decided to exclude the vast majority of the available studies on the quasi-exclusive ground of patient groups size. Referring to an arbitrary and unusual effect size threshold (0.4), they chose a minimal sample size of 100 patients per group.

On the contrary, the authors decided to maintain in their analysis, several studies the characteristics of which makes questionable their inclusion in a meta-analysis that is supposed to deal with homogeneous information:

- inclusion of one very short term (1 month) study, not meeting the regulatory criteria for assessment of SYSADOA,
- inclusion of (only) one study in the treatment of hip OA, while this is not an official indication of glucosamine (disregarding the major bias in this study by including a majority of KL stage 1 patients),
- inclusion of one irrelevant (prototypical) study (McAlindon) in which two different formulations of glucosamine, in different daily dosages and different regimen, were attributed to the same treatment group,

The main outcomes defined for the meta-analysis are heterogeneous, while under an unique term of "pain intensity measure on VAS", the authors used by back transformation, different quotations of pain (at rest, on walking, on movement etc…) or of composite scales such as the Lequesne index (of which the pain component cannot be extracted). Furthermore, the assessment times were unnecessarily multiplied; on the contrary, the authors decided to purely and simply erase the times between 22 and 36 months by pooling them into a unique class > 22 months, despite some studies brought relevant data in those long-term 36-months time windows.

With respect to the quality of studies, the authors reported erroneous "bad" quotation of at least one important study.

Finally, despite large efforts of authors to present their meta-analysis as the ultimate work in this field, the restriction of included studies to a very small part of available data, the mixing-up of studies of quite different characteristics, in term of indication, objectives, treatment duration, nature of treatments .. maintain the results of this study in the "scholar" position defined by the BMJ editorial board (3), and refrain to grant to its conclusion any sound relevance with respect to the glucosamine effectiveness.

Despite the number of issues of their analysis, the authors not only erroneously concluded about the lack of reduction in joint pain and the lack of impact on narrowing of joint space by glucosamine, but they largely overstepped the actual conclusions of their meta-analysis when they stated:

"*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 relevance of this part of the conclusion was denounced by the BMJ's editorial board after a post-publication review, and the BMJ's deputy director stated that two sections of Wandel's paper needed a special and formal mention. The editorial board considered that the assertions (i) in the abstract : "*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"* and (ii) in the discussion: " *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*" were not directly supported by the data.

3. Overall conclusion

The reassessment of the reimbursement status of glucosamine by the Danish Medicine Agency has been triggered on the grounds of three publications, including two clinical studies: the "GAIT" study in knee osteoarthritis and the study by Wilkens in chronic low back pain, as well as one recent meta-analysis (Wandel).

In view of the significant issues raised in each of these works, the MAH asks the DMA not to take it into account for the following reasons :

1. The results of the GAIT study were observed in a very particular population characterized by their unusual level of placebo response (around 60%) thus notably explaining the insignificant effect on WOMAC mean scores, of the "positive control" group, treated with celecoxib, considered as a NSAID of undisputed efficacy. Even though this placebo effect considerably reduced the sensitivity of the comparison between the tested treatments and placebo, a significant trend was observed in patients with moderate to severe pain. The results of the 2-year part of the study was also difficult to interpret globally, due to the lack of validation of initial hypotheses (great variability, too low number of subjects, JSW loss lower than expected). But a positive trend was observed for glucosamine in patients with a baseline KL grade 2 severity.

The potential long-term interest of glucosamine was confirmed in the presentation of the very long term results (mean 8 years) of 2 studies, that evidenced a significant increase in the time to the first total hip prosthesis and a significant reduction of medical and paramedical costs in patients treated with glucosamine.

2. The study by Wilkens & coll. cannot be taken into account, because it was performed in patients with chronic low back pain, which is not an official indication of glucosamine. European guidelines unambiguously states that the assessment of an intervention in the treatment of osteoarthritis is to be shown for each OA site and that the demonstrated efficacy (or lack of) at one OA site is not a systematic indicator of efficacy at another OA site. And that's especially true for CLBP, the pathogenic mechanism of which not being totally related to OA lesions. In addition, this study is biased by the authorised use of any concomitant OA treatment, including NSAIDs, analgesics, pain-killers, but also massages, physiotherapy, manipulations etc… that were very likely to considerably reduce the sensitivity of the comparison, which, in addition did not even include a "dedicated" specific pain assessment.

3. The meta-analysis of Wandel & coll. presents with a great number of issues that resulted in numerous negative reactions of rheumatology experts. It can be reproached to the authors that the principle of "another meta-analysis" on glucosamine is not adequately justified by the discussion of many other published analyses, often more complete and validated by European regulatory authorities as well as international scientific associations (notably the most recent Cochrane collaboration meta-analyses). The meta-analysis by Wandel would like to reconcile the only and very fragmentary results they present as "conflicting". But this goal cannot be reached when considering, at least, some of the numerous issues present in their analysis.

This "new" meta-analysis did not include any new data, when compared to other available well-done meta-analyses. On the contrary this meta-analysis is the occasion to eliminate a vast majority of the whole of glucosamine published studies (at least 75%).

Second this meta-analysis used a very complex statistical method : "network meta-analysis", which was not necessary to evidence the efficacy of each treatment compared to placebo. However, its main theoretical interest could have been valuable in presenting the comparisons vs positive controls (paracetamol and celecoxib). But the authors did not include those comparisons in their analysis.

Finally the authors mixed up in their analysis studies with quite heterogeneous characteristics in terms of indications, treatment duration, assessment criteria etc., some of them with evidence of major quality issues.

For all those reasons, the conclusions of this meta-analysis clearly overstep its possibilities while not only it does not bring any new relevant information compared to previously available works, but also, it draws irrelevant conclusions not related with the analysis results.

In conclusion, the glucosamine MAH present here several evidences towards the lack of relevance of several data used to anticipate a possible reassessment of reimbursement status of Glucomed. In view of the number of issues shown in each of the three mentioned references, the MAH expresses its formal reserves regarding the relevance of those works and of the need to go further in the reassessment procedures on those grounds. Therefore the MAH asks the Danish Medical Agency to maintain the present status of Glucomed, while none of the proposed document is likely to modify in any extent the previously defined therapeutic profile of the drug and therefore its reimbursement status.

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Odense, 2011.04.06

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Att: Ulla Kirkegaard Madsen

Re: "Ad hoc revurdering af tilskudsstatus for glucosamin" – Orifarm point of view for the coming review.

Dear Ulla Kirkegaard Madsen,

Thank you for giving us the opportunity to provide our input and point of view to the upcoming review of the glucosamine reimbursement status.

You point out in your letter that recent evidence published indicates that the efficacy of glucosamine should be questioned.

The most recent update (11 Nov 2008) of the Cochrane Review[1] concluded that pooled results excluding the industry (Rottapharm) sponsored studies failed to show benefit in pain and WOMAC function while the studies evaluating the Rottapharm preparation showed that glucosamine was superior to placebo in the treatment of pain and function impairment resulting from symptomatic osteoarthritis.

The Cochrane review shows that heterogenicity in the results of published studies is large. This has amplified the discussion of possible bias in industry-sponsored studies on glucosamine. Also the specific findings in studies performed using glucosamine manufactured by Rottapharm have led to a discussion of the impact of the source of glucosamine active substance on the efficacy.

Glucosamine sulphate; newly published clinical trials

We would like to draw your attention to clinical trials of glucosamine sulphate published since the most recent update (11 Nov 2008) of the Cochrane Review.

We have compiled a list of published reports examining the clinical efficacy of glucosamine sulphate in *placebo*-controlled clinical trials in osteoarthritis patients. Note that 'placebo-control' was not a strict requirement for inclusion in the Cochrane analysis as comparative studies were allowed (see Towheed et al. (2005), 'Types of studies' section). However, we believe a placebo-controlled trial is the optimum method to ascertain the effects of glucosamine sulphate therapy. Furthermore, two of the post-Cochrane update, non placebo-controlled comparative studies that we found in the literature, compared a non conventional treatment therapy (hydrolyzed collagen or a Chinese medical recipe) against glucosamine sulphate therapy. These studies thus do not give a clear indication of the effect of glucosamine sulphate therapy.

All of the listed reports have quality standards that meet the quality criteria described for studies included in the Cochrane Review update (see Towheed et al. (2005), Table 1). An initial survey of the

[1] (Towheed, T.E., Maxwell, L, Anastassiades, T.P, Shea, B, Houpt, J, Robinson, V, Hochberg, M.C and Wells, G. (2005). Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*)

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Pubmed/MEDLINE and journal sources contained in the Scirus comprehensive science-specific search engine yielded the following studies:

Bruyere, O., Pavelka, K, Rovati, L.C, Gatterova, J, Giacovelli, G, Olejarova, M, Deroisy, R and Reginster, J.Y. (2008). Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. *Osteoarthritis Cartilage*, **16**, 254-260.

Chopra, A., Saluja, M, Tillu, G, Venugopalan, A, Sarmukaddam, S, Raut, A.K, Bichile, L, Narsimulu, G, Handa, R and Patwardhan, B. (2011). A Randomized Controlled Exploratory Evaluation of Standardized Ayurvedic Formulations in Symptomatic Osteoarthritis Knees: A Government of India NMITLI Project. *Evid Based Complement Alternat Med*, **2011**, 12 pages.

Frestedt, J.L., Walsh, M, Kuskowski, M.A and Zenk, J.L. (2008). A natural mineral supplement provides relief from knee osteoarthritis symptoms: a randomized controlled pilot trial. *Nutr J*, **7**, 9 pages.

Giordano, N., Fioravanti, A, Papakostas, P, Montella, A, Giorgi, G and Nuti, R. (2009). The efficacy and tolerability of glucosamine sulphate in the treatment of knee osteoarthritis: A randomized, double-blind, placebo-controlled trial. *Current Therapeutic Research*, **70**, 185-196.

Petersen, S.G., Saxne, T, Heinegard, D, Hansen, M, Holm, L, Koskinen, S, Stordal, C, Christensen, H, Aagaard, P and Kjaer, M. (2010). Glucosamine but not ibuprofen alters cartilage turnover in osteoarthritis patients in response to physical training. *Osteoarthritis Cartilage*, **18**, 34-40.

Scholtissen, S., Bruyere, O, Neuprez, A, Severens, J.L, Herrero-Beaumont, G, Rovati, L, Hiligsmann, M and Reginster, J.Y. (2010). Glucosamine sulphate in the treatment of knee osteoarthritis: cost-effectiveness comparison with paracetamol. *Int J Clin Pract*, **64**, 756-762.

Wilkens, P., Scheel, I.B, Grundnes, O, Hellum, C and Storheim, K. (2010). Effect of glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis: a randomized controlled trial. *JAMA*, **304**, 45-52.

In all of these studies, except for Chopra et al. 2011 and Wilkens et al. 2010, a positive effect is reported for glucosamine sulphate in patients with knee osteoarthritis. Wilkens et al. 2010 investigates the effect of glucosamine in chronic low back pain and degenerative lumbar osteoarthritis, effect on knee osteoarthritis is not included in this study.

Glucosamine sulphate: Does efficacy depend on the manufacturer of the active substance?

It has been pointed out that the efficacy of glucosamine sulphate could be different when produced by different manufacturers and that the products on the Danish market are not among the products with proven efficacy. We would like to emphasize that glucosamine sulphate is a well-defined chemical substance with specified quality and purity. Therefore glucosamine sulphate supplied from different manufacturers should be considered to be equivalent with regards to efficacy and safety.

It is generally recognized that whether different formulations containing the same quantity of the same active substance derivative are therapeutically equivalent or not depends solely on the properties of the formulation. Hence in our opinion there is no reason to consider the active substance source when evaluating the evidence regarding the efficacy of products containing glucosamine sulphate.

All glucosamine containing preparations on the Danish market have been approved on basis of bibliographic applications claiming well-established use, meaning that the efficacy and safety is well-known and well-

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described. Thus, and in accordance with the EC directive regarding medicinal products for human use (2001/83/EC as amended) it is not necessary to provide results of clinical trials for the specific product in a marketing authorisation application, when it can be demonstrated that the active substance involved has been in well-established use within the community for at least ten years with recognised efficacy and an acceptable level of safety. On the basis of the above mentioned details the studies published for glucosamine sulphate is valid for the glucosamine sulphate containing tablets on the Danish market including Glucosamin Copyfarm.

General bias in industry sponsored clinical trials?

It has been suggested that the industry sponsored glucosamine clinical trials might be biased.

In general such a view on industry sponsored clinical trials should raise concern as an extensive framework of regulations, guidelines and approval procedures surrounds the conduct of clinical trials, and the vast majority of the clinical trials providing evidence of the efficacy and safety on medicinal products are industry sponsored. Therefore such a view would undermine the basis for the approval and maintenance of marketing authorisations for all medicinal products.

Thus, the reliability of the results from the given clinical trials for glucosamine efficacy should be based only on the quality of the design and conduct of the trial and not on whether the trial was sponsored by the industry or by public means. Therefore we find that the results of the glucosamine studies sponsored by Rottapharm should not be disregarded when evaluating the overall evidence of the efficacy and safety of treatment with glucosamine sulphate.

Orifarm point of view on the future reimbursement status of Glucosamin "Copyfarm" film-coated tablets

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. However 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 current reimbursement on glucosamine is limited to: PARTH (*PARTH Pensionister. Lindring af symptomer ved let til moderat osteoartrose.*). According to the approved summary of product characteristics for Glucosamin Copyfarm it is recommended that the efficacy of the product for the individual patient is evaluated after 2-3 months of treatment. If the patient's symptoms is not relieved the treatment should be reconsidered.

Since there is most substantial evidence for the efficacy of glucosamin sulphate on symptoms of osteoarthritis in the knees we find that reimbursement status could be restricted to relief of symptoms of mild to moderate osteoarthritis in the knees. The reimbursement should take into account that glucosamine sulphate is efficient in relieving those symptoms in some but not all patients. Therefore the efficacy and the access to reimbursement should still be determined on individual patient basis by the physician 2-3 months after initiation of treatment and continuously when renewing the prescription for Glucosamin Copyfarm.

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We hope you find this information helpful in your continued analysis of the reimbursement status for Glucosamin Copyfarm and we welcome further communication with the agency in this regard.

Best regards

Orifarm Generics A/S, (Copyfarm A/S)

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Vejle, 4. april 2011

Vedr.: Journal nr. 2011023887 – Glukosamin Pharma Nord

Hermed følger svar på Lægemiddelstyrelsens brev af 2. marts 2011, omkring revurdering af tilskudsstatus for glukosamin. Brevet er således et udtryk for Pharma Nords synspunkter, som bedes medtaget i Medicintilskudsnævnets vurdering af tilskudsstatus for lægemidlet "Glukosamin Pharma Nord" - hvor Pharma Nord ApS er indehaver af markedsføringstilladelsen.

Vi anerkender Medicintilskudsnævnets opfordring til revurdering af glukosamins tilskudsstatus – på baggrund af de nævnte randomiserede kliniske forsøg[1] - men finder det afgørende at man foretager en nuanceret gennemgang af det videnskabelige grundlag for glukosamin, således der tages højde for det anvendte produkt (glukosamin form, råvare/færdigvare og fremstillingsmetode), metode / population, samt kvalitet af publikationen – og at dette ses i sammenhæng med den terapeutiske indikation[2], som Glukosamine Pharma Nord har. Det samme gør sig således gældende ved gennemgang af den nylige metaanalyse[3] (BMJ Meta), som Lægemiddelstyresen henviser til i ovennævnte brev af 2. marts.

Der findes, som allerede anerkendt i paneuropæiske registreringer, solid dokumentation for at krystalinsk glukosamin sulfat (anvendt i Glukosamine Pharma Nord) "lindrer symptomer ved let til moderat osteoartrose i knæet" - som er indikationen på "Glukosamin Pharma Nord" - og vi accepterer, at det videnskabelige grundlag for symptomlindring ved let til moderat osteoartrose i andre led, på nuværende tidspunkt, kan betvivles. Vi mener derfor at fortsættelse af tilskud til glukosamin produkter bør ses i sammenhæng med den terapeutiske indikation.

Vælger Medicintilskudsnævnet at se på BMJ Meta, er det nødvendigt at "rense" denne publikation for studier, som ikke har relevans i forhold til Glukosamin Pharma Nord og dettes indikation. BMJ Meta behandler 7 studier på glukosamin, hvoraf kun 3 studier (Reginster 2001, Pavelka 2002 og Herrero-Beaumont 2007):

(1) er udført med et produkt (krystalinsk glukosamin sulfat) som betragtes bioækvivalent til Glukosamin Pharma Nord[4]
(2) er gennemført på en population som kan sammenlignes med den danske.
(3) er af den nødvendige længde for demonstration af effekt, af et langsomt virkende, symptomlindrende lægemiddel, som glukosamin.

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1 Clegg et al., Glucosamine, chondroitine sulfate and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006 Feb 23;354(8);795-808.
Wilkens et al. Effect of Glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis: a randomized controlled trial. JAMA. 2010 Jul 7;304(1):45-52

2 Glukosamin Pharma Nords terapeutiske indikation er, i modsætning til de fleste andre produkter på det danske marked, specificeret på osteoartrose i knæet – og ikke osteoartrose, generelt.

3 Wandel et al. Effects of glucosamine, chondroitine, or placebo in patients with osteoarthritis of hip or knee: network metaanalysis. BMJ. 2010 Sep 16;341:c4675.

4 Kontakt Pharma Nord for dokumentation.

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De øvrige er enten af meget kort varighed (Noack 1994), gennemført på andre led end knæ (Rozendaal 2008) eller gennemført med produkter og/eller råvarer der ikke kan betragtes bioækvivalente til Glukosamin Pharma Nord[5], på populationer[6] der ikke kan sammenlignes med den danske (McAlindon 2004, Clegg 2006).

Opsummering:
Vi anerkender at der findes grundlag for vurdering af tilskudsstatus for produkter med generel terapeutisk indikation "lindring af symptomer ved let til moderat osteoartrose" - men at man bør bevare tilskudsstatus for produkter med terapeutisk indikation "lindring af symptomer ved let til moderat osteoartrose i knæet".
Vi mener at det er nødvendigt med en nuanceret gennemgang af det videnskabelige grundlag for glukosamin og lindring af symptomer ved let til moderat osteoartrose – hvorved der bør tages højde for hvilke former for glukosamin der er anvendt, hvilke metoder og i hvilke populationer, set i sammenhæng med indikationens bredde.

Med venlig hilsen,

Jørgen Dam
Pharma Nord ApS

5 Produkter baseret på Glukosamin HCl og/eller udefinerede kvaliteter, der ikke har dokumenteret effekt. Jf. bl.a. Towheed el al., Glucosamine therapy for treating osteoartritis. Cochrane database rev. 2009;2:CD002946, som konkluderer at bl.a. Glukosamin HCl ikke har dokumenteret effekt.

6 Ifølge Population & Societies, 455, April 2009 har danske kvinder gennemsnitligt BMI under 24 og mænd under 25,5. Til sammenligning var gennemsnitligt BMI i patienter fra McAlindon et al. 2004 og Clegg et al. 2006, henholdsvis højere end 31,0 og 31,8. Ligeledes viste det europæiske GUIDE studie at de europæiske osteoartrose patienter havde BMI på 27,7. Mærkbart højere BMI gør det alt andet lige svære at vise symptomlindrende effekt af en hvilket som helst lægemiddel i behandling er osteoartrose.

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Vedr.: Journal nr. 2011023887 – Ledamin

Hermed følger svar på Lægemiddelstyrelsens brev af 2. marts 2011, omkring revurdering af tilskudsstatus for glukosamin. Brevet er således et udtryk for Pharma Nords synspunkter, som bedes medtaget i Medicintilskudsnævnets vurdering af tilskudsstatus for lægemidlet "Ledamin" - hvor Pharma Nord ApS er indehaver af markedsføringstilladelsen.

Vi anerkender Medicintilskudsnævnets opfordring til revurdering af glukosamins tilskudsstatus – på baggrund af de nævnte randomiserede kliniske forsøg[1] - men finder det afgørende at man foretager en nuanceret gennemgang af det videnskabelige grundlag for glukosamin, således der tages højde for det anvendte produkt (glukosamin form, råvare/færdigvare og fremstillingsmetode), metode / population, samt kvalitet af publikationen. Det samme gør sig således gældende ved gennemgang af den nylige metaanalyse[2] (BMJ Meta), som Lægemiddelstyresen henviser til i ovennævnte brev af 2. marts.

Der findes, som allerede anerkendt i paneuropæiske registreringer, solid dokumentation for at krystalinsk glukosamin sulfat (anvendt i Ledamin) "lindrer symptomer ved let til moderat osteoartrose i knæet" - og vi accepterer, at det videnskabelige grundlag for symptomlindring ved let til moderat osteoartrose i andre led, på nuværende tidspunkt, kan betvivles. Vi mener derfor at fortsættelse af tilskud til glukosamin produkter bør ses i sammenhæng med den terapeutiske indikation, og er opmærksomme på, at dette kan nødvendiggøre en variationsansøgning på Ledamin, hvor vi ansøger om ny indikation[3], hvis Ledamin i fremtiden skal være tilskudsberettiget.

Vælger Medicintilskudsnævnet at se på BMJ Meta, er det nødvendigt med en nuanceret gennemgang af denne publikation. BMJ Meta behandler 7 studier på glukosamin, hvoraf kun 3 studier (Reginster 2001, Pavelka 2002 og Herrero-Beaumont 2007):

(1) er udført med et produkt (krystalinsk glukosamin sulfat) som betragtes bioækvivalent til Ledamin[4]
(2) er gennemført på en population som kan sammenlignes med den danske.
(3) er af den nødvendige længde for demonstration af effekt, af et langsomt virkende, symptomlindrende lægemiddel, som glukosamin.

De øvrige er enten af meget kort varighed (Noack 1994), gennemført på andre led end knæ

1 Clegg et al., Glucosamine, chondroitine sulfate and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006 Feb 23;354(8);795-808.
Wilkens et al. Effect of Glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis: a randomized controlled trial. JAMA. 2010 Jul 7;304(1):45-52

2 Wandel et al. Effects of glucosamine, chondroitine, or placebo in patients with osteoarthritis of hip or knee: network metaanalysis. BMJ. 2010 Sep 16;341:c4675.

3 Nuværende terapeutisk indikation for Ledamin er "Lindring af let til moderat osteoartrose", mens andre glukosamin produkter har "Lindring af let til moderat osteoartrose i knæet".

4 Kontakt Pharma Nord for dokumentation.

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(Rozendaal 2008) eller gennemført med produkter og/eller råvarer der ikke kan betragtes bioækvivalente til Glukosamin Pharma Nord[5], på populationer[6] der ikke kan sammenlignes med den danske (McAlindon 2004, Clegg 2006).

Opsummering:
Vi anerkender at der findes grundlag for vurdering af tilskudsstatus for produkter med generel terapeutisk indikation "lindring af symptomer ved let til moderat osteoartrose" - men at man bør bevare tilskudsstatus for produkter med terapeutisk indikation "lindring af symptomer ved let til moderat osteoartrose i knæet".
Vi mener at det er nødvendigt med en nuanceret gennemgang af det videnskabelige grundlag for glukosamin og lindring af symptomer ved let til moderat osteoartrose – hvorved der bør tages højde for hvilke former for glukosamin der er anvendt, hvilke metoder og i hvilke populationer, set i sammenhæng med indikationens bredde.

Med venlig hilsen,

Jørgen Dam
Pharma Nord ApS

5 Produkter baseret på Glukosamin HCl og/eller udefinerede kvaliteter, der ikke har dokumenteret effekt. Jf. bl.a. Towheed el al., Glucosamine therapy for treating osteoartritis. Cochrane database rev. 2009;2:CD002946, som konkluderer at bl.a. Glukosamin HCl ikke har dokumenteret effekt.

6 Ifølge Population & Societies, 455, April 2009 har danske kvinder gennemsnitligt BMI under 24 og mænd under 25,5. Til sammenligning var gennemsnitligt BMI i patienter fra McAlindon et al. 2004 og Clegg et al. 2006, henholdsvis højere end 31,0 og 31,8. Ligeledes viste det europæiske GUIDE studie at de europæiske osteoartrose patienter havde BMI på 27,7. Mærkbart højere BMI gør det alt andet lige svære at vise symptomlindrende effekt af en hvilket som helst lægemiddel i behandling er osteoartrose.