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Review
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Review

Health Technology Assessment (HTA) evidence, regulatory classification and reimbursement of medicine: the case of glucosamine

Parnnaphat Luksameesate and Suthira Taychakhoonavudh*

Department of Social and Administrative Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand

*Correspondence: Suthira Taychakhoonavudh, Department of Social and Administrative Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, 254 Phayathai Road, Patumwan, Bangkok 10330, Thailand. Tel: +66-2-218-8386 to 90, +6681-848-0384; Email: suthira.t@chula.ac.th, suthira.tay@gmail.com

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Abstract

Objectives To examine the relationship among Health Technology Assessment (HTA) evidence, regulatory classification and reimbursement of health products using glucosamine as a case study. Data of HTA evidence, regulatory classification and reimbursement of glucosamine from 13 countries were extracted from official government websites and peer-reviewed journal articles. Role and responsibility of HTA in each country along as well as the regulatory approval process and reimbursement status of health products were reviewed. The case of glucosamine was then analysed to explore the regulatory classification, reimbursement and its HTA evidence from past to present.

Key findings For regulatory classification, we found that glucosamine is classified as either medicine (9 from 13 countries) or a dietary supplement (4 from 13 countries) depends on where glucosamine is seeking its market approval. Reimbursement also differs among the countries. We summarized the key factors that could be the cause of these variations. First, the clinical evidence of glucosamine is still in question especially its efficacy and as a results its cost-effectiveness. This evidence is important for policy consideration. Secondly, different level of HTA approach in each healthcare system and country context effect on how HTA evidence is utilized and synthesized. Lastly, company's strategic positioning is the first key stakeholder to decide whether their product would be registered as medicine or dietary supplement.

Summary The variation of HTA evidence in a diverse healthcare system affects regulatory classifications and reimbursement. This can result in different levels of patient access to health products.

Keywords osteoarthritis; glucosamine; Health Technology Assessment (HTA); regulatory classification; reimbursement

Introduction

'Health products' is a broad term that describes substances, including medicines, dietary supplements and cosmetics, used for prevention, diagnosis and treatment of diseases and health problems.[1] Most countries require health products to be registered with the individual country's regulatory agency as a first step before these products can be commercially available in the healthcare market. Health Technology Assessment (HTA) has been used as a tool to inform policy and decision-making processes within the healthcare systems. It also plays an important role throughout the health

product life cycle, from the regulatory classification to reimbursement. The regulatory classification determines different levels of rigour for regulations required to approve various medicines. This includes medicine approvals required in both pre-clinical and clinical studies to prove the efficacy, safety and quality of potential products. Medicines must go through an intensive review process while other products, such as dietary supplements, have lower degrees of rigour for approval such that manufacturers only need to notify the existing regulatory agency. Regulatory classification also determines the reimbursement status since many insurance payers refuse to reimburse products that do not provide a reasonable threshold of positive effect. Consequently, products such as dietary supplements are not reimbursed by health insurance payers and access to these health products may be limited.

There are products that are not easily categorized; one such product is glucosamine, an alternative treatment for knee osteoarthritis (OA). The use of the product is controversial since there is insufficient evidence proving efficacy and cost-effectiveness. This has resulted in a variation of regulatory classification and reimbursement around the globe. The objective of this study is to examine the relationship among the HTA evidence, regulatory classification and reimbursement of health products using glucosamine as a case study. The scope of the case study will include the following countries: Australia, Canada, Denmark, France, Ireland, Norway, the UK, the USA, the Philippines, Singapore, Spain, Sweden and Thailand, which were chosen based on available data from official government websites and peer-reviewed journal articles. Role and responsibility of HTA in each country along as well as the regulatory approval process and reimbursement status of health products were reviewed. The case of glucosamine was then analysed to explore the regulatory classification, reimbursement and its HTA evidence from past to present.

What is HTA evidence and how to use it?

HTA is a systematic research process that analyses and evaluates evidence for the application of health technology.[2] The term *technology* is broadly described to include medicines, devices, procedures and healthcare system organization.[3] The aim of HTA is to inform health policy and reimbursement decision making for optimal use of limited resources.[4] HTA evidence incorporates all possible elements of the healthcare system, including marketing approval, health coverage, reimbursement and clinical guidelines.[4]

HTA is a multidisciplinary process that includes an assessment of the clinical, economic, ethical, organizational, societal and legal issues.[2] Clinical studies measure many different outcomes including the reduction of symptoms, side effects and patient-reported outcomes. Economic evaluation considers the relationship between cost and clinical benefits. This is frequently included as a factor for deciding to include a product in health coverage or for reimbursement.[3] Budget impact analysis is used for capturing a short-term financial impact on the overall healthcare system. The evidence from the HTA process is used to support policy decisions within healthcare systems.

Regulatory approval of health products

Regulatory approval of health products is needed to ensure that the product is safe, meets the standards of quality and produces effective results as indicated. However, different health products have different regulatory requirements due to the differences in impact on patient's health and community as well as the variation of regulatory agency either by country or by region.

The European Medicines Agency (EMA) and the US Food and Drug Administration (USFDA) are responsible for the regulation of health products approval in the European Union and the USA, respectively. According to EMA and USFDA guidelines, the evidence required to approve the new medicinal product includes information on the chemistry, manufacturing, and control (CMC) and evidence proving the safety and efficacy in animal models and humans. All data and evidence must be adequately investigated in a controlled environment. If the benefits of a new product outweigh the risks, it will receive approval from the regulatory agency, in this case, either the EMA or USFDA and can then be marketed commercially.

The process for dietary supplement approval in these countries is, however, less rigorous as the evidence and data required from the manufacturer include mainly safety data and whether the product is compliant with Current Good Manufacturing Practice (CGMP) regulations.[5, 6] The details of the new products' approval and how to categorize these products, whether as new medicines or dietary supplements, however, varies from country to country. Even though the classification is mostly straightforward, there are several products that could be classified into both medicinal and dietary supplement categories. In the end, the categorization depends on the petitioning company's strategic positioning on the regulatory classification, since this will determine different patients' access to health products.

Reimbursement of health products by health insurance payers

While regulatory approval of the health product ensures product availability in the market, access to health products is determined mainly by whether the product is affordable or not. Many countries are trying to achieve universal healthcare coverage to ensure that patients can access healthcare services and health products equally when needed. Universal healthcare coverage can be achieved through either public or private health insurance systems in which health insurance providers pay part or all of the healthcare expenditures incurred. For health products, health insurance providers reimburse only what is on the specific policy's reimbursement list. Health products are included on the list if the health insurance providers consider them appropriate therapeutic options. HTA is a widely used tool employed by health insurance providers to inform decisions of whether a product should be reimbursed by an insurer. However, the use of HTA evidence for reimbursement decisions varies globally due to differing HTA requirements and the various affordability, socioeconomic and political factors of each country.[7] Some countries, including Canada, Australia, the UK and the USA, use 'high-level' approaches of HTAs. The required elements of HTAs consist of clinical, epidemiological, economic and other factors not captured in clinical or economic elements.[8] Other countries, such as France, use 'low-level' approaches of HTAs wherein clinical evaluation is the only element required.[8] These differences can result in different categorizations of a single product across countries, which also impacts the reimbursement recommendation of that product in these countries.

The case of glucosamine: HTA evidence, regulatory classification and reimbursement status

Glucosamine has been used as an optional treatment for knee OA. Glucosamine has been reported to provide benefits to knee OA patients by modifying damaged cartilage, delaying the disease

progression and exerting mild anti-inflammatory properties.[9] Currently, there are mainly two forms commonly available on the market: glucosamine sulfate and glucosamine hydrochloride. These substances have a good safety profile in which only mild side effects have been found,[10] making glucosamine a widely used health product.[11]

The efficacy and cost-effectiveness of glucosamine is controversial as the HTA evidence has found glucosamine both an effective and ineffective treatment. As a result, variations in regulatory classifications, and reimbursement statuses have been found across the globe. For example, while considered medicine in Thailand, glucosamine is available in the USA only as dietary supplement.[12–14]

Current regulatory classification of glucosamine worldwide

Currently, all glucosamine products, including glucosamine sulfate and glucosamine hydrochloride, are widely available in healthcare markets worldwide. Variations in the classification as medicine or a dietary supplement are shown in Table 1. Of the 13 countries reviewed, we found that glucosamine is classified as a medicine in 9 countries (69% of the countries studied): Denmark, France, Ireland, Norway, Spain, the Philippines, Sweden, UK and Thailand. It is classified as a dietary supplement in the remaining four countries: Canada, the USA, Singapore and Australia. Interestingly, glucosamine is classified as either a medicine or a dietary supplement in the UK depending on its salt form and strength. Products containing more than 1500 mg of glucosamine sulfate (equivalent to glucosamine base 1178 mg) were reclassified as medicine in 2018 because the Medicines and Healthcare Products Regulatory Agency (MHRA) reviewed the updated evidence of glucosamine and found that 1500 mg per day of glucosamine sulfate showed a positive pharmacological effect.[15]

We found that, among the nine countries which classify glucosamine as medicine, glucosamine sulfate is classified as a medicine in all countries while glucosamine hydrochloride is classified as a medicine in only four countries: France, the Philippines, Spain and Sweden. This variation in the classification of glucosamine potentially occurs due to the production company's strategic positioning during the categorization process, as different companies may choose to submit the product as either medicine or dietary supplements when under review. This difference may also be due to the variation of opinions concerning which substances constitute medicines and dietary supplements between regulatory agencies in each country.

Reimbursement status of glucosamine by major health insurance payers

From our review, we speculate that the differences between glucosamine regulatory classification in each country have an impact on the reimbursement status worldwide as shown in Table 1. If it is classified as a dietary supplement, it may not be reimbursed by the national health insurance system, as shown by policy in Australia, Canada, the USA and Singapore. Moreover, the decision to reimburse glucosamine when classified as a medicine depends on the context of the national health insurance system of the country in question. Among the nine countries which classify glucosamine as medicine, the product is currently reimbursable in just four of those countries: France, the UK, Spain and Thailand.

Glucosamine was once reimbursable in Sweden, Denmark and Ireland, but in 2010, the Dental and Pharmaceutical Benefits Agency (TLV), a central government agency in Sweden, decided to remove glucosamine from the reimbursement scheme due to a high consumption rate without a demonstrable show of positive efficacy.[33] In 2011, the Reimbursement Committee and the Danish Medicines Agency had evaluated the evidence of efficacy and safety for glucosamine and decided to remove glucosamine from the reimbursement list as the evidence had not been strong enough to prove that glucosamine is more effective than a placebo.[34] The Health Service Executive (HSE), the public health and social care services of Ireland, removed glucosamine from the reimbursement list in 2012. One potential reason might have been that the National Centre for Pharmacoeconomics (NCPE) concluded that glucosamine sulfate was not a cost-effective therapy in the Irish healthcare setting.[35] However, glucosamine was prescribed free-of-charge to patients over the age of 70 as part of the National Shared Services Primary

Table 1 Regulatory classification and reimbursement status of glucosamine in selected countries

Glucosamine	Classification	Specific formulation	Reimbursement
Australia[16]	Dietary supplement	Any form and strength	No
Canada[17, 18]	Dietary supplement	Any form and strength	No
Denmark[19]	Medicine	Glucosamine sulfate 500, 750 and 1500 mg	Removed
France[20, 21]	Medicine	Glucosamine sulfate 1500 mg Glucosamine hydrochloride 750 mg	Yes
Ireland[22, 23]	Medicine	Glucosamine sulfate 500 mg	Removed
Norway[24, 25]	Medicine	Glucosamine sulfate 500 mg Glucosamine sodium sulfate 1500 mg	No
The Philippines[26, 27]	Medicine	Glucosamine sulfate 250, 750 and 1500 mg Glucosamine hydrochloride 750 mg	No
Singapore[28]	Dietary supplement	Any form and strength	No
Spain[29]	Medicine	Glucosamine sulfate 1500 mg Glucosamine hydrochloride 750 and 1500 mg	Yes
Sweden[30]	Medicine	Glucosamine sulfate 750 mg Glucosamine hydrochloride 750 mg	Removed
Thailand[13]	Medicine	Glucosamine sulfate 1500 mg	Yes1
The UK[31, 32]	Medicine	Glucosamine sulfate 1500 mg	Yes
	Dietary supplement	Any form and strength except glucosamine sulfate 1500 mg	No
The USA[12, 14]	Dietary supplement	Any form and strength	No

[1]Glucosamine is only reimbursable for Civil Servant Medical Benefit Scheme patients.

Care Reimbursement Service of the HSE in Ireland, a general medical services scheme.[36]

HTA evidence of glucosamine: developing evidence from past to present

Efficacy

Efficacy has been one of the most controversial aspects of glucosamine since the product was introduced to the market. The very first clinical studies were published almost 40 years ago in which the use of glucosamine had shown promising results for pain control, symptom improvement and slowed disease progression, but not with reducing the space loss of the knee joint itself. Lopes *et al.*[37] and Muller-Fabbender *et al.*[38] conducted randomized controlled trials (RCTs) to compare the medicinal effects of glucosamine sulfate to ibuprofen and they reported that glucosamine demonstrated a statistically significant positive change in patients' pain scores. Glucosamine was also shown to be as effective as ibuprofen for improving pain symptoms in knee OA patients. Reginster *et al.*[39] and Pavelka *et al.*[40] conducted RCTs which aimed to determine whether glucosamine sulfate could modify the progression of joint structural and symptom changes in knee OA patients when used as a long-term treatment. Results showed that long-term use of glucosamine sulfate slowed the progression of knee OA, but found no significant reduction in joint-space loss in both studies.[39, 40] However, studies conducted after these have shown contradictory results in which the use of glucosamine had no positive results on patients' outcome. Sawitzke *et al.*[41] concluded that no statistically significant difference in mean joint-space width loss existed in the glucosamine group when compared with the placebo group.

With these mixed results, a Cochrane systematic review of 25 RCTs with 4963 OA patients was conducted in 2005 by Towheed *et al.*[42] The review failed to find a consensus about the benefits of glucosamine for pain relief. Interestingly, subgroup analyses showed only crystalline glucosamine sulfate was significantly superior to the placebo in terms of pain relief and functional improvement. Subsequent studies have since shifted to the evaluation of different formulations of glucosamine. In 2004, McAlindon *et al.* performed RCT of glucosamine hydrochloride compared with a placebo. They reported that no significant difference in glucosamine therapeutic effects had been observed.[43] In 2006, the National Institutes of Health (NIH) published the results of the large trial, the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT). Results showed that glucosamine hydrochloride did not significantly reduce pain in knee OA patients.[44] Another study by Kawasaki *et al.*[45] examined the effects of glucosamine hydrochloride and concluded that it did not show a significant effect on OA progression when compared with a placebo. These studies, therefore, support the indication that some forms of glucosamine may lack a minimum threshold of medical benefit when used to treat knee OA.

Evidence for the use of glucosamine sulfate, however, reported positive results for knee OA treatment. Many studies have consistently shown that crystalline glucosamine sulfate demonstrates superior benefits over other formulations in terms of clinically relevant pain improvement and function limitation.[46–49] The substance has also been linked to a reduction in the risk of undergoing total joint replacement surgery. In a real-world observational study following knee OA patients who used crystalline glucosamine sulfate for 5 years, there was demonstrated a 57% reduction in the risk of total knee replacement surgery when compared with the placebo.[50] Additionally, crystalline glucosamine sulfate demonstrated benefits for delayed joint structural changes and reduced use of long-term non-steroid anti-inflammatory agents (NSAIDs) as was shown in the Pharmaco-Epidemiology of the GonArthroSis (PEGASus) study, which reported a significant reduction in NSAID use by 36%.[51]

Safety

Even if evidence of the efficacy of glucosamine is currently contested, the safety data of glucosamine have shown the substance to be consistently considered safe across all glucosamine formulations. A Cochrane review of 25 RCTs reported that there was no difference in the number of people who experienced side effects from using glucosamine. The side effects are all mild and mainly included abdominal pain, constipation, diarrhoea, nausea and skin rash.[42] In addition, a review of the effects of all glucosamine formulations on glucose metabolism in clinical trial data, including 3063 human patients, concluded that there were no adverse effects on blood, urine or faecal parameters; additionally, glucosamine did not affect glucose metabolism parameters.[52] However, it was found that patients allergic to shellfish should be cautious since glucosamine is extracted from shellfish.[53]

Cost-effectiveness

Cost-effectiveness results have become one of the most important aspects of HTA evidence, which impacts health policy decision making for medicine reimbursement. Evidence of glucosamine's cost-effectiveness has also been a controversial issue, as its efficacy has yet to be determined. It was shown that glucosamine would be deemed cost-effective only if a specific formulation was used. A total of five economic evaluation studies of glucosamine for knee OA treatment were conducted between the years 2008 and 2019 in the UK, Belgium and Thailand. Two studies concluded that glucosamine was cost-effective, while three studies found it not to be cost-effective. Of these studies, there was only one to use glucosamine hydrochloride and crystalline glucosamine sulfate. The other studies chose glucosamine sulfate as a comparator.

Several key characteristics of these studies are worth mentioning. The first key characteristic is the different glucosamine formulations. Three studies used glucosamine sulfate as an intervention[54–56], one study used glucosamine hydrochloride,[57] while another used crystalline glucosamine sulfate.[58] These evaluations of economic viability of glucosamine sulfate concluded mixed results. Scholtissen *et al.*[54] found that it was cost-effective over paracetamol and a placebo. Inconsistency with the two other studies by Black *et al.*[55] and Chaiyakunapruk *et al.*[56] showed that it might not be cost-effective at the willingness-to-pay threshold of their countries, the UK and Thailand, respectively. When glucosamine hydrochloride was considered for economic evaluation, the UK National Institute for Health and Clinical Excellence (NICE) guidelines (2008) did not recommend glucosamine as a treatment for OA knee patients because of a lack of cost-effectiveness.[57] The reason might be that glucosamine hydrochloride was the only licensed version of the product available in the UK at that time, and its medicinal efficacy was deemed poor.[44] The latest evidence by Bruyere *et al.* published in 2019 used crystalline glucosamine sulfate as a comparator. They concluded that it was cost-effective, while other formulations were not.[58] The second key characteristic lies with the choice of comparators. These studies used either a placebo or current care as a comparator. Interestingly, both the Black *et al.* and Chaiyakunapruk *et al.*'s studies showed that glucosamine lacked cost-effectiveness when compared with current care, but the other three studies found glucosamine to be more cost-effective when compared with a placebo.[54–58] Only Scholtissen *et al.*'s study compared paracetamol and glucosamine and showed that glucosamine sulfate was more cost-effective than paracetamol.[54] The last key characteristic involves the variety of

the treatment duration, including 6 months, 3 years and a lifetime horizontal. Black *et al.* and Chaiyakunapruk *et al.*[55, 56] used lifetime horizontals and found that under such conditions glucosamine may not be cost-effective. Thus, the choice of the glucosamine formulation along with the type of comparator used, and the length of time for studied treatment are all important factors for proving the potential cost-effectiveness of glucosamine as either a medical or supplemental treatment.

Discussion

HTA has become an important part of the healthcare system as a tool for diagnosis management, treatment and other interventions with the aim to promote a sustainable healthcare system. HTA implementation varies between countries, which enforce HTAs differently throughout the health product life cycle, from regulatory classification to reimbursement. The same health product can be classified as either medicine or a dietary supplement depending on the company's strategic positioning and the regulatory agency's consideration of the product's scientific evidence during review. Furthermore the 'high'- and 'low'-level approaches of HTA in each healthcare system and the context of each country also affect the utilization and synthesis of evidence and, as a result, policy recommendations. All the factors directly determine different levels of patient access to these health products.

Glucosamine is an interesting case study to explore the implementation of high and low HTA approaches in different healthcare systems across the world. Currently, all glucosamine products, including glucosamine sulfate and glucosamine hydrochloride, are widely available in the healthcare market as either medicine or a dietary supplement. Countries in the European Union tend to classify these substances as medicine, while in the USA, glucosamine is classified as a dietary supplement. The different regulatory classifications of glucosamine also impact the reimbursement status. It is noteworthy that glucosamine could be reimbursable in countries with low-level approaches to HTA, while in most countries with high-level approaches to HTA glucosamine is not authorized to be reimbursed. The reasons for policy variation found between countries seem to be that, since the introduction of the product into the market, glucosamine has produced mixed evidence concerning its efficacy and cost-effectiveness as a viable healthcare product. When conflicting evidence is applied to a diverse level approach of HTA in different healthcare systems, it is not unusual that variations of regulatory classifications and reimbursement statuses of such products would occur.

Yet, evidence exploring the efficacy and cost-effectiveness of glucosamine has increased in publication over the past 10 years. The turning point of the new research found that different glucosamine formulations affect efficacy in terms of clinical improvement, delayed disease progression, reduction of long-term use NSAIDs and decreased risk of undergoing total joint replacement surgery. Consideration of regulatory classifications, therefore, should be revisited based on updated resources. When different formulations are issued, policy decision-makers should consider them separately for optimal decision making. For example, in the UK products containing more than 1500 mg of glucosamine sulfate were reclassified as medicine in 2018.[15] Unlike dietary supplements, medicine must have proven quality, safety and efficacy. Agencies, healthcare practitioners and patients must be able to ensure a demonstrable positive effect for what the product is intended to treat. Regarding the differences in efficacy, economic evaluation results are used as important information for reimbursement and to consider changes in reimbursement and health coverage. It would be better if reimbursement status is also reevaluated when new studies and evidence present themselves so that patients can be able to access the most appropriate treatment available.

Conclusion

This review proposes to explain the correlation among HTA, regulatory classification and reimbursement status of health products using glucosamine as a case study to point out that when a health product is placed in a diverse healthcare system, this can result in different policy recommendations and patient access.

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Author Contributions

S.T. and P.L. conceived the conception of the study. P.L. reviewed data and prepared the draft of the article. S.T. revised and approved the final version of the article.

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Conflict of Interest

All authors declare that they have no conflict of interest.

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article.

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