LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Glucomed
Glucosamine hydrochloride

SE/H/560/01

This module reflects the scientific discussion for the approval of Glucomed. The procedure was finalised at December 13th, 2006. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Navamedic ASA submitted applications for mutual recognition of Glucomed, 625 mg, tablet on the basis of the marketing authorisation granted by Sweden on 4 August 2005.
The active substance is glucosamine hydrochloride.

The mutual recognition procedure started on 18 October 2005. The reference member state was Sweden and the concerned member states were Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Germany, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, The Netherlands, Poland, Portugal, Slovakia and United Kingdom and Norway and Iceland.

The mutual recognition procedure was referred to CMD(h) on 21 January 2006 due to serious public health concern raised by four member states. The issues concerned both clinical and quality documentation. In response to the quality concerns raised by one member state the company made commitments for changes in the specifications of the drug substance and some of the starting materials in the synthesis of the drug substance. These commitments were accepted during the CMD(h) procedure. The four member states maintained their major objections regarding the clinical issues, and the positive risk/benefit profile of glucosamine hydrochloride in this indication was questioned. In addition one further member state agreed with the major objections regarding the clinical issues. Sweden referred the reasons for disagreement to the EMEA on 31 March 2006. The procedure was initiated under Article 29 of the Community code on human medicinal products (Directive 2001/83/EC as amended).

Following discussion in CHMP in September 2006 the Committee concluded a referral procedure for Glucomed recommending the granting of a marketing authorisation for the relief of symptoms in mild to moderate osteoarthritis of the knee.

II. QUALITY ASPECTS

II.1 Introduction

Glucomed is presented in the form of tablets containing 625 mg of glucosamine which corresponds to 750 mg of the glucosamine hydrochloride. The excipients are hydroxypropylcellulose, low substituted hydroxypropyl cellulose, microcrystalline cellulose and magnesium stearate. The tablets are packed in/filled in PVC/PVDC-aluminium blisters or HDPE tablet containers with a silica gel desiccant in paper bags.

II.2 Drug Substance

Glucosamine hydrochloride does not have a monograph in the Ph Eur. Information on glucosamine hydrochloride has been supplied in the form of an ASMF.

Glucosamine hydrochloride is a white, crystalline powder which is soluble in water. The structure of glucosamine hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Glucomed 625 mg tablet is formulated using excipients described in the current Ph Eur, except for low substituted hydroxypropyl cellulose which is controlled according to USP. All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life and the storage conditions claimed in the SPC.

III. NON-CLINICAL ASPECTS

It can be concluded that there are deficiencies in the toxicological documentation for Glucomed. Glucosamine can, however, be regarded as a pharmaceutical product with well established medicinal use. According to revision 6 of the Note for Guidance on Products with well established medicinal use, reproductive toxicity and genotoxicity should be assessed. However, MPA has not considered the absence of genotoxic studies as a major issue due to the endogenous nature of the substance, and the absence of genotoxicity alerts.

No data regarding reproduction, embryonic or peri-/postnatal toxicity is available and lack of reproductive toxicity studies for an OTC product is considered unfavourable. The wording of section 4.6 of the SPC states that glucosamine should not be used during pregnancy and lactation.

IV. CLINICAL ASPECTS

IV.1 Introduction

In patients with mild to moderate osteoarthritis, in addition to physical exercise, paracetamol and NSAIDs are the only existing approved medicinal oral drug alternatives to obtain symptomatic relief of symptoms such as pain and stiffness. No curative or disease-modifying treatment exists, apart from surgery with arthroplasty.

Glucosamine was mainly introduced on the world-wide market as a food-supplement but with the aim to improve symptoms in patients with osteoarthritis or joint pain or function. These

products gained very high sales figures with a huge interest from patients, due to limitations in the existing alternatives to relieve the often debilitating pain in osteoarthritis.
Different views on glucosamine as a pharmaceutical substance or not, due to different interpretations of regulatory/legal systems have resulted in glucosamine being classified as a medicinal product in many regions of the world, and thereby restrictions for free sales. Within the EU, this difference between countries is evident.

Since 1980 many clinical studies of glucosamine have been performed, with varying scientific relevance and quality. These data have been scrutinised and discussed within several EU-applications for glucosamine. Glucosamine has been approved as a medicinal product in 22 EU countries. Many published reviews, national therapy recommendations and other publications have discussed and evaluated the robustness of efficacy data. However, safety in the performed studies and within reviews is uniformly positive, with AE reporting similar to placebo.

IV.2 Clinical efficacy

Published studies and reviews
Glucosamine containing pharmaceutical products (both hydrochloride and sulphate) have been evaluated based on bibliographical data. A Cochrane review was also performed with efficacy shown, in favour of glucosamine. Thereafter, some new studies have been published and also a recent update of the Cochrane review.

The following summarising tables describe the initially submitted study data considered as pivotal and also a table showing supportive studies.

Principal studies and their endpoints

Citation	**No. of GA treated patients**	**Treatment duration**	**Type of OA**	**Study endpoints**					
				WOMAC Index	**Lequesne's index**	**Ratings for pain. swelling and function**	**Pain diary**	**Joint-space width***	**Safety**
Double-blind placebo-controlled studies									
Reginster et al., 2001; Bruyere et al., 2002	106	3 years	Knee	X				X	X
Houpt et al., 1999	58	8 weeks	Knee	X			X		X
Noack et al., 1994	126	4 weeks	Knee		X				X
Hughes & Carr, 2002	80	24 weeks	Knee	X		X			X
Pavelka 2002	101	3 years	Knee	X	X			X	X
Double-blind active treatment controlled studies									
Qiu et al., 1998	88	4 weeks	Knee			X			X
Müller-Fassbender et al., 1994	100	4 weeks	Knee		X				X
Thie et al., 2001	21	90 days	TMJ			X			X
	In total, 680 patients								

*Radiographically determined mean joint-space width of the medial compartment of the tibiofemoral joint.

Supportive studies.

Citation	Number of patients	**Duration of treatment**	**Type of OA**
Crolle et al., 1980	15	21 days	Knee
Drovanti et al., 1980	40	30 days	General
Pujalte et al., 1980	10	6-8 weeks	Knee
D'Ambrosio et al., 1981	15	21 days	Knee
Vajarandul et al., 1981	28	5 weeks	Knee
Vaz et al., 1982	18	8 weeks	Knee
Tapadinhas et al., 1982	1208	13-99 days (open)	General
Vajranetra et al., 1984	108	14 weeks	Knee
Reichelt et al., 1994	79	6 weeks	Knee
Rindone et al., 2000	47	8 weeks	Knee
	In total, 1568 patients		

Other recently published studies are the GAIT study: "Glucosamine, Chondroitin sulphate, and the two in combination for painful knee osteoarthritis" New. Engl. J. Med.; Feb 23, 2006; vol 354 and "A multi-central, randomized, controlled clinical trial of glucosamine hydrochloride/sulfate in the treatment of knee osteoarthritis" Study by Qiu 2005.

IV.3 Discussion on the clinical aspects

In the evaluation procedures for medicinal glucosamine, bibliographical data from a number of studies have been evaluated. A modest efficacy has been shown in most studies. Two large well-conducted long-term 3-year studies have been performed. They indicate efficacy, however modest. Two Cochrane reviews indicate efficacy but somewhat more hesitant in the second review. As with all assessments based on published data, the risk for publication bias is recognised.

Safety in all the performed studies covering thousands of patients is reassuring and was comparable to placebo. Pharmacovigilance reporting, mainly from Sweden and Spain, does not indicate any new safety issues. The SPC covers the mainly mild side-effects reported in clinical trials, as well as post-marketing.

Efficacy in symptomatic relief of pain in osteoarthritis, of the existing alternatives, NSAIDs and paracetamol, is of similar magnitude as glucosamine (e.g. ref. review by Bjordal). The safety profiles are, however, inferior to glucosamine. When it comes to relative benefit and risk assessment, the influence of publication bias may be less.

Dose selection in this bibliographical application is made from experience from other related glucosamine products and the dose and posology chosen is the same as used in almost all performed studies, which seems appropriate.

Formal drug interaction studies have not been performed with glucosamine. Therefore, a general caution should be included in the SPC, 4.4. A few case reports on possible warfarin interactions have been found in pharmacovigilance reporting, and a warning is therefore included.

Within this referral procedure, a question was raised, whether Glucomed containing hydrochloride, is as effective as glucosamine containing sulphate. Glucosamine, however, is considered to be a very uncomplicated substance with a high solubility, and therefore, a comparative bioavailability study is not considered crucial for an approval. The comparative

study by Qiu 2005, however open, did not identify any efficacy differences between the two formulations.

We have concluded that glucosamine, both hydrochloride and sulphate, is efficacious for the symptomatic relief in patients with mild to moderate osteoarthritis. We have also concluded that safety is sufficiently shown, and that the safety profile is favourable with mainly mild gastrointestinal symptoms reported. However, glucosamine has been extensively used all over the world as a non-pharmaceutical product and therefore also limited knowledge of possible rare safety issues. Pharmacovigilance has resulted in some reports indicating an interaction potential with warfarin, and thereafter information has been added in the SPC text. This improved knowledge of the drug is of benefit to the patient, indicating that pharmaceutical use of glucosamine is justified, although the risk profile is very favourable.

Taken together, the efficacy data, although not uniformly positive, indicate efficacy in the symptom driven indication. The uniformly positive safety data, compared with existing alternatives for symptomatic relief in osteoarthritis, result in a positive risk/benefit for glucosamine.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed. The mutual recognition procedure was initiated before the date of entry into force of the new legislation.

The risk/benefit ratio is considered positive and Glucomed 625 mg tablet is recommended for approval.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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