

**Rapporteur's
Final Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

Glucosamine

Donacom and other trade names

Hard capsules 250 and 500mg, Coated tablets 250mg, Film-coated tablets 750mg, 1178mg powder for oral solution, Solution for injection 400mg

UK/W/008/pdWS/001

Marketing Authorisation Holder: Rottapharm Ltd

Rapporteur:	UK
Start of the procedure:	15 June 2009
Date of this report:	24 August 2009
Deadline for Rapporteur's AR (Day 70):	24 August 2009
Deadline for CMS's comments (Day 85):	8 September 2009
Date circulation of final preliminary PdAR (Day 89):	12 September 2009
Finalisation procedure (Day 90):	28 September 2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Donacom and other trade names
INN (or common name) of the active substance(s):	Glucosamine
MAH:	Rottapharm Ltd
Currently approved Indication(s)	Symptomatic relief of mild to moderate osteoarthritis of the knee.
Pharmaco-therapeutic group (ATC Code):	Drugs for treatment of musculoskeletal and joint diseases
Pharmaceutical form(s) and strength(s):	Hard capsules 250, 500mg Coated tablets 250mg Film-coated tablets 750mg 1178mg powder for oral solution Solution for injection 400mg

INDEX

Executive summary and recommendation

I. Introduction

II. Scientific discussion

II.1 Information on the pharmaceutical formulation used in the clinical studies

II.2 Non-clinical aspects

1. Introduction

2. Discussion of non-clinical aspects

II.3 Clinical aspects

1. Introduction

2. Clinical overview

3. Clinical studies

4. Discussion of clinical aspects

5. PSUR

6. Additional reference

III. Rapporteur's overall conclusion and recommendation

IV. Additional clarifications requested

EXECUTIVE SUMMARY

Glucosamine is a natural substance found in mucopolysaccharides, mucoproteins and chitin. It is found in relatively high concentrations in the joints used together with sulfates, for the biosynthesis of hyaluronic acid of the synovial fluid and of glycosaminoglycans of the fundamental substance of articular cartilage. Glucosamine is a hexosamine sugar and a basic building block for the biosynthesis of glycoprotein, glycolipids, hyaluronic acid, glycosaminoglycans and proteoglycans, which are important constituents of articular cartilage. The mechanism of action is not fully understood, but administration of glucosamine is believed to stimulate production of cartilage components and allow rebuilding of damaged cartilage. In vitro studies have found that glucosamine can increase mucopolysaccharide and collagen synthesis in fibroblast tissue. It also appears to activate core protein synthesis in human chondrocytes. It has also thought to have anti-inflammatory activities and inhibits the degradation processes of articular cartilage mainly due, as probably the metabolic activities themselves, to an inhibitory activity of the interleukin 1 (IL-1) effects.

Glucosamine (as sulphate and hydrochloride) has been widely available as a prescription medication for OA in the EU and as over-the-counter treatment for OA in the US and Europe, for many years. Currently in UK glucosamine hydrochloride has been authorised for the symptomatic relief of mild to moderate osteoarthritis of the knee.

The data package submitted by one MAH under article 45 of the Paediatric Regulation comprises 4 clinical studies including paediatric patients, together with a critical overview of these studies and one published article as literature reference. The MAH also submitted the currently approved SmPC and PIL for the licensed glucosamine sulphate product and the periodic safety update reports (PSURs) for the period 20 November 2003 – 31 March 2008 submitted for the renewal procedure.

The currently approved SmPC contains the following information regarding paediatric use

4.2 Posology and method of administration

Children and adolescents:

Glucosamine sulphate should not be used in children and adolescents below the age of 18 years (see 4.4).

4.4 Special warning and precaution for use

Glucosamine sulphate should not be used in children and adolescents under the age of 18 years since safety and efficacy have not been established.

The Company's view is that no change to the European SmPC texts is necessary as a consequence of the data presented.

RECOMMENDATION

Based on the review of the presented paediatric data the rapporteur considers that:

The presented data is insufficient to support a variation application to extend the use of glucosamine to the paediatric population.

For consistency between glucosamine containing products (as sulphate and hydrochloride) across the EU, it is recommended that all SmPCs and PLs contain the following statement:

4.2 Posology and method of administration

Children and adolescents:

Glucosamine should not be used in children and adolescents below the age of 18 years (see 4.4).

4.4 Special warning and precaution for use

Glucosamine should not be used in children and adolescents under the age of 18 years since safety and efficacy have not been established.

I. INTRODUCTION

On 6 May 2009, the MAH submitted 4 completed studies including paediatric patients for Glucosamine, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. Short critical expert overview has also been provided with an additional published article as literature reference. The MAH also submitted the currently approved SmPC and PIL for licensed glucosamine sulphate product and the periodic safety update reports (PSURs) for the period 20 November 2003 – 31 March 2008 submitted for the renewal procedure.

The MAH stated that the submitted paediatric data support the company's position that there is no anticipated use of glucosamine in the paediatric population and therefore no update of the SmPC is needed.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical studies

Glucosamine was Developed in the early 60's. Oral glucosamine is commonly used for the treatment of osteoarthritis although there is conflicting evidence as to its effectiveness. From a review of the literature and meta-analysis of the clinical trials in adults, studies reporting beneficial effects have generally used glucosamine sulphate.

Glucosamine based products have been authorised in many European countries. Among that, glucosamine has been registered through Mutual Recognition Procedure where Denmark is the RMS and Belgium, Cyprus, The Netherlands, Norway, Sweden and Slovakia are the Concerned Member States.

Different pharmaceutical forms have been used in the submitted clinical studies with dose adjustments by the clinical researchers.

II.2 Non-clinical aspects

1. Introduction

Non-clinical studies have not been provided or summarized by the MAH on glucosamine. It is noted that no literature review has been conducted by the MAH to identify preclinical studies relevant for the paediatric use of this drug.

2. Discussion on non clinical aspects

The benefit of glucosamine in patients with osteoarthritis is likely the result of a number of effects including its anti-inflammatory activity, the stimulation of the synthesis of proteoglycans and a trophic action towards articular cartilage. More recent studies have postulated that most of the above mentioned metabolic and anti-inflammatory effects may be due to an inhibition of the transductional intracellular signal to the IL-1 stimulation, one of the cytokines involved in the pathogenesis of osteoarthritis. There is no indication that these effects have been investigated in immature juvenile cartilage.

II.3 Clinical aspects

1. Introduction

The MAH submitted the following 4 clinical studies that included paediatric patients:

- A. Souschek K. **Efficacy of Glucosamine in juvenile osteochondrosis.** Ortopädische Praxis 1973; 9(11): 383-6.
- B. Böhmer D., Ambrus P., Szögy A., Haralambie G. **Chondropathia patellae of young Sportsmen.** Therapiewoche 1982; 32(41), 4897-4901
- C. Tapadinhas M.J., Rivalal.C., Bignamini A.A. **Oral glucosamine sulphate in the management of arthrosis: report on a multi-centre open investigation in Portugal.** Pharmatherapeutica 1982; 3(3): 157-68
- D. Rovati L.C., Giacobelli G., Setnikar I. **A multicenter clinical trial on the efficacy and tolerability of glucosamine sulphate (DONA) in the treatment of osteoarthritis.** Confidential report 1989

2. Clinical overview

The MAH has provided a brief critical expert statement as part of the submission package. The clinical studies are briefly summarised along with brief information of the product. Based on the data included in this review, the MAH concludes that

“...Glucosamine cannot be used in paediatric population as no incidence of osteoarthritis has been demonstrated in the age range provided by the Regulation. This is supported also by the lack of further evidence in the literature data. The Company considers that the actual Summary of Product Characteristics properly reflect the current knowledge on the use of Glucosamine and no modification of the target population is requested.”

3. Clinical studies

Efficacy of Glucosamine in juvenile osteochondrosis.

Souschek K. Ortopädische Praxis 1973; 9(11): 383-6.

This appears to be a rather old paper that reviews the use of glucosamine in paediatric patients affected by chondropathia patellae, Scheuermann’s disease and Schlatter’s disease.

The author does not provide much information regarding this observational study apart from the table below:

DIAGNOSIS	PATIENTS							TREATMENT					RESULTS			
	Total	Slight	Moder.	Severe	Age	Sex		ROUTE		DOSAGE		Dura- tion weeks	Very Gd.	Good	Moderate	Unsat.
						H.	F.	Oral	Oral+ im	Oral	im					
Chondropathia patellae	50	22	25	3	21 11-38	29	21	25	25	3x1	10 X 5 ml	16	14	26	9	1
Scheuermann's disease	20	6	12	2	17 12-21	15	5	8	12	3x1	10-15 X 5 ml	24	2	15	2	0
Schlatter's disease	8	2	6	0	17 15-22	8	0	6	2	3x1	15 X 5 ml	16	5	2	-	1
TOTAL	78												21	43	11	2

A total number of 78 patients were included in the study, of which 50 treated for chondropathia patellae, aged range 11-38y (mean = 21 y), 20 treated for Scheuermann’s disease, aged 12-21y (mean = 17 y) and 8 treated for Schlatter’s disease, aged 15-22y (mean = 17 y). The treatment Glucosamine

was a combination of oral and intramuscular administration of glucosamine (Dona 200) in different dosing regimes and duration of 16 to 24 weeks depending on the underlying disease. The author concluded that although the number of patients was relatively small to permit a significant result to be calculated, a good therapeutic outcome was observed in 82% of the patients. The treatment appeared to be well tolerated and no side-effect was reported.

Assessor's Comment

This paper does not contain fundamental information on the study design. It is a very old study and the author has not provided detailed information regarding the methods used to select or evaluate the patients. The sample size is very small and the design of the study limits the significance of the positive findings.

In the assessor's opinion, this study is too limited to offer robust evidence on the efficacy of glucosamine in paediatric conditions associated with degeneration of the articular cartilage.

Chondropathia patellae of young Sportsmen.

Böhmer D. et al Therapiewoche 1982; 32(41), 4897-4901

➤ **Methods**

- Objective
Investigate the effect of glucosamine sulphate in patients with chondropathia patellae after sports.
- Study design
Not clearly identified but there was no placebo group.
- Study population /Sample size
68 patients were included in the study including 51 males age 19.3 +/- 6.6 years and 17 females age 18.9 aged +/- 5.9 years. Diagnosis was confirmed clinically and radiologically when appropriate and only patients that fitted that Bentley phases I-III were included in the study.
- Treatment
The patients received 500mg glucosamine sulphate 3 times daily for 40 days and then 250mg of glucosamine sulphate 3 times daily for further 90-120 days. Sports' training was restricted drastically and patients were instructed to self-massage both knee joints regularly.
- Assessment criteria
The assessment criteria are not very clearly presented but include evaluation of patient's pain at rest, walking, standing and sitting, pain during movement and evaluation findings during palpitation such as patella friction sounds, displacement or pressure pain and facet pain.
- Statistical Methods
Not specified

➤ **Results**

In 52 out of 68 patients (76.5%), a complete regression of symptoms was noted. After 4 to 5 months full sports' training could be resumed. Also at a follow-up of 12 months after the conclusion of treatment, no recurrence of chondropathia patellae could be ascertained. In 2 patients an allergic reaction was noted (2.9%).

Assessor's Comment

This is a very interesting study to evaluate the effects of glucosamine in young patients; however there are several limitations. It is a very old study conducted in adolescents and young adult patients with chondropathia patellae after sports. In theory this group represent a population that could benefit from treatment with a drug that improved cartilage quality and strength. However the diagnosis of the condition is often obscure particularly if it is not based on MRI or arthroscopic findings. Patello-femoral pain syndrome (PFPS) is the common term currently used to describe adolescents and young adults with pain behind or around the patella and crepitations, provoked by ascending or descending stairs, squatting, prolonged sitting with flexed knees, running and cycling. In the literature there is some agreement that PFPS is a term to be applied only to people with retropatellar pain in which no cartilage damage is evident. Although it is considered to be a self-limiting condition, when approaching PFPS as a cartilage problem, pharmacotherapy may focus on chemically disrupting the destructive enzymatic processes or aid constructive processes by providing nutrients for cartilage repair. In the literature, evidence for the effect of glucosamine is conflicting and merits further investigation. In this study, the author has not provided detailed information regarding the paediatric cohort in this study as the results are presented as a total. A control group of patients with the condition was not available and the efficacy outcomes should be reviewed with caution.

In the assessor's opinion, this is a very limited study which does not offer robust evidence on the effect of glucosamine sulphate in adolescents with chondropathia patellae.

Oral glucosamine sulphate in the management of arthrosis: report on a multi-centre open investigation in Portugal.

Tapadinhas M.J. et al Pharmatherapeutica 1982; 3(3): 157-68

➤ **Methods**

- Objective
Investigate the effect of glucosamine sulphate in the treatment of arthrosis
- Study design
Not clearly identified. A total of 252 doctors across Portugal participated in the study that covered three quarters of a year (Sept 1980 to May 1981).
- Study population /Sample size
1208 patients were included in the study including 516 males and 692 females ranging in age from 16 to 84 years (mean 54.2 years). 52.1% of the patients reported one or more concomitant condition including more commonly cardiovascular disorders, obesity, gastrointestinal conditions or depressive neurosis. The location of the arthrosis and the sex and age characteristics of the patients are summarized below

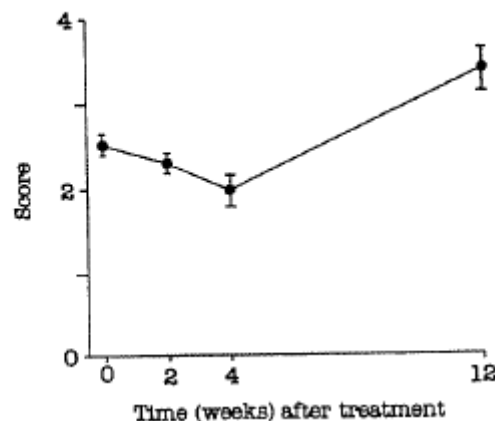
Site	No. (%) patients	Sex		Age (years)	
		Male	Female	Mean (±S.D.)	Range
Vertebral column	376 (31)	143	233	53.1±10.0	16 to 75
Shoulder/elbow	87 (7)	47	40	52.8± 9.0	30 to 68
Hip	213 (18)	122	91	55.9± 8.5	33 to 72
Knee	425 (36)	153	272	54.8± 9.0	20 to 83
Tibio-tarsal	30 (3)	17	13	53.2± 9.3	33 to 74
Small joints	36 (3)	21	15	52.3± 9.9	30 to 84
Polyarticular	41 (3)	13	28	55.8±10.2	32 to 70

- **Treatment**
The patients received 500mg glucosamine sulphate 3 times daily over a period of 50.3 +/- 14.4 days (range 13 to 99 days). In 16.1% of the patients an anti-inflammatory agent or analgesic or both were also used for a period of time.
- **Assessment criteria**
Before the start of the treatment and then after 2 weeks, after 3 to 4 weeks and after 6 to 8 weeks of treatment, the investigating doctors would score the intensity of pain at rest, on standing and on exercise as well as the intensity of limited active and passive movements. Similar recording was attempted in a period of 2 to 12 weeks after the end of the treatment.
- **Statistical Methods**
Data was processed using a paired t-test. Frequency distributions were tested according to the Fisher's or the χ^2 -test as applicable.

➤ Results

- **Efficacy results**
The investigating doctors rated the therapeutic results as 'good' in 58.7% of the patients and 'sufficient' in 36%. Insufficient results were reported in 5.3% of the patients and it was mainly of patients who did not respond to any treatment. The major action of glucosamine was observed on pain at rest and on standing and limited passive movement. The efficacy rating of treatment was differently distributed according to the different localization of the arthrosis, with the better results in shoulder and elbow patients. No influence of the sex or age of patients was observed. Obesity was related to a significant shift from good to sufficient results similarly gastro-intestinal disorders and their treatment or the treatment with diuretics shifted from good to sufficient the overall rating of efficacy. The reporting symptoms after the end of treatment are presented in the figure below.

Changes in the sum of symptom scores after the end of treatment and without maintenance: mean (\pm S.E.M.) scores



- **Safety results**
Tolerability was evaluated in all 1208 patients and was rated as 'complete' in 1041 patients (86%) and in 30(2.5%) was defined as insufficient. Among these patients, treatment was discontinued in 28. The prevalence of limited tolerability appeared to be strongly associated with the presence of concomitant diseases or treatments. Overall 186 complaints were recorded from 146 patients and they are presented below.

Symptom	No. of complaints	% of total treated patients
Digestive		
Epigastric pain/tenderness	42	3.48
Heartburn	33	2.73
Diarrhoea	30	2.48
Nausea	14	1.16
Dyspepsia	12	0.99
Vomiting	10	0.83
Constipation	8	0.66
Gastric heaviness	6	0.50
Anorexia	3	0.25
Abdominal pain	3	0.25
Meteorism	2	0.17
Non-digestive		
Drowsiness	10	0.83
Skin reactions	4	0.33
Headache	4	0.33
Somnolence	2	0.17
Insomnia	1	0.08
Oedema	1	0.08
Tachycardia	1	0.08

Assessor's Comment

This is an extensive study conducted in a large number of arthrosis patients; however the open design of the study limits the validity of the reported positive effects of glucosamine in the treated population. It is noted that the diagnosis of all the paediatric patients that participated in this study was arthrosis of the vertebral column, a rather atypical condition that is usually associated with underlying alignment conditions of the spine or rheumatologic diseases. No further information is provided regarding this paediatric cohort. The assessment criteria are not very clearly presented and the author has not provided detailed information regarding the paediatric cohort in this study as the results are presented as a total. A control group of patients with the condition was not available and the efficacy outcomes should be reviewed with caution. In the assessor's opinion, this study offers no evidence on the effect of glucosamine sulphate in paediatric patients.

A multicenter clinical trial on the efficacy and tolerability of glucosamine sulphate (DONA) in the treatment of osteoarthritis.

Rovati L.C. et al Confidential report 1989

➤ **Methods**

- Objective
Investigate the efficacy and tolerability of glucosamine sulphate in the treatment of osteoarthritis.
- Study design
Open non controlled multicentre study of 3 parallel treatment groups of 6 weeks duration.

- Study population /Sample size
1283 patients affected by osteoarthritis at various joint locations were included in the study (33% males and 67% females). The mean age was 57 years (range 16-87 years) with 80% of the patients were aged above 45 years.

- Treatment

The different treatment groups were as follows:

- 1) 500mg glucosamine sulphate 3 times daily orally for 6 weeks
- 2) One IM injection of 400mg glucosamine sulphate 2 times a week for 6 weeks
- 3) One IM injection of 400mg glucosamine sulphate 2 times a week for 3 weeks and concomitantly 500mg glucosamine sulphate 3 times daily orally for 6 weeks

- Assessment criteria

The following evaluation criteria were used:

- Articular pain. Pain at rest, tenderness and pain at movement were scored according to the following scale:

1 = none 2 = mild 3 = severe 4 = incapacitating

- Articular swelling. It was scored according to the following scale:

1 = none 2 = mild 3 = evident 4 = deforming

- Movement limitation. The limitation of active and passive movements were each scored according to the following scale:

1 = none 2 = of 25% 3 = between 25% and 50% 4 = more than 50%

- Morning stiffness. It was expressed in minutes, according to the information received from the patients following the specific question

- Overall judgement of efficacy. At the end of treatment, the investigators and patients were asked to rate the efficacy of the therapy with glucosamine sulphate according to the following scale:

1 = disappearance of symptoms 2 = definite improvement

3 = improvement 4 = unchanged 5 = worsening

- Statistical Methods

Methods of descriptive statistics were used to analyse patients' characteristics and the results of the study. The results before and after treatment on the evaluation criteria of efficacy such as pain, swelling and movement limitation, were analysed and compared by the Wilcoxon matched-pairs signed-ranks test. The duration of morning stiffness before and after treatment was analysed and compared by the student's t test for matched-pairs results.

➤ Results

- Efficacy results

All symptoms taken into consideration improved after 6 weeks treatment. The improvement of each symptom was statistically significant as determined by the appropriate tests. The same results were evident and comparable for each dosage

schedule. Of the entire study population, 40% of patients experienced a 'definite improvement', about 30% an 'improvement' and about 20% disappearance of symptoms'. Only 6-8% did not report any improvement. These results were comparable for all treatment groups.

- **Safety results**

Of the whole study population, 50 patients experienced adverse events (3.9%). The reported adverse events were classified as 'mild and transient' in most cases. The distribution of the AE was 3.9% with oral treatment, 2.4% at the IM treatment group and 5.2% after the combination of administrations. The prevalence between treatment schedules was not statistically significant. No serious AE was reported. About 80% of the AEs were upper gastrointestinal complains and local AEs of no clinical significance after IM injection occurred in only 6 cases (1.1%).

Assessor's Comment

This study mainly focuses on the efficacy of glucosamine in adult osteoarthritic patients. The number of the adolescent patients (16-18 years) participating in the study is not defined and the results are presented as a whole. Osteoarthritis is a disease that is mainly associating with aging and therefore is not applicable to the adolescent population.

In the assessor's opinion, this study offers no evidence on the effect of glucosamine sulphate in paediatric patients.

4. Discussion on clinical aspects

In the literature glucosamine has shown inconsistent efficacy in decreasing osteoarthretic pain and improving joint function. Osteoarthritis, the most common type of joint disease, is a degenerative disorder that results from the degradation of articular cartilage in the synovial joints. Although it is clear that the condition affects primarily adults, in the paediatric population there are a number of conditions in which the articular cartilage undergoes significant structural and biochemical breakdown such as idiopathic chondrolysis of the hip, juvenile rheumatoid arthritis, osteochondritis dissecans and chondromalacia patellae. Prolonged immobilization and incongruity of joints in adolescences with cerebral palsy have been associated with cartilage degenerative changes and pain. Trauma of the joints at a young age and conditions such as slipped capital femoral epiphysis or Perthes alter the mechanic loading and decrease the tensile strength of the joint cartilage.

If a true chondroprotective mechanism was proven, there could theoretically be a therapeutic benefit in paediatric conditions associated with articular cartilage degeneration. However the drug fails to prove efficacy even for the adult indication and therefore any speculation of significant paediatric benefit is unlikely. In the literature, there is no published data for the use of this drug in paediatric conditions associated with structural or biochemical deficit of the articular cartilage, that eventually lead to degenerative joint changes.

In the submitted studies, these issues are not been addressed and therefore no valid conclusions for the paediatric use of glucosamine can be made.

5. PSUR

The post marketing experience with the licensed glucosamine sulphate product is summarized in the Periodic Safety Up-date Reports (PSURs) submitted by the MAH, containing the safety data reported globally for the period since 20November 2003 to 31 March 2008.

During this review period, regarding the patients' exposure to products containing glucosamine an estimated 6,355,997patients/months was obtained for the oral route and 194,252 patients/month for the parenteral route. The MAH confirms that one phase II clinical study is in active stage during the period covered in this PSUR.

In the sixth PSUR submitted by the MAH covering the period from 1st July 2007 to 31st March 2008 a total of 162 spontaneous case safety reports were received. Of these 17 cases were regarded as serious unlisted and 1 as serious listed. The other 144 were non-serious reports. None of these safety reports included events in paediatric patients (0-18 years). Among the cases regarded as serious unlisted, a patient who developed acute pancreatitis is included as well as 22 patients in which glucosamine was considered to interact with the concomitant use of warfarin. In most currently approved SmPCs a warning for patients concomitantly in treatment with warfarin or other anticoagulant in general is detailed in section 4.5. Over all the MAH concludes that this information remains in accord with the previous reference safety information and that the risk-benefit ratio of glucosamine remains unchanged as favourable.

Assessor’s Comment

The data provided in this safety review confirm that glucosamine is generally well tolerated. No unexpected ADRs have been identified. The assessor agrees that the data presented in the PSUR reports do not include any safety concerns relevant to the paediatric population.

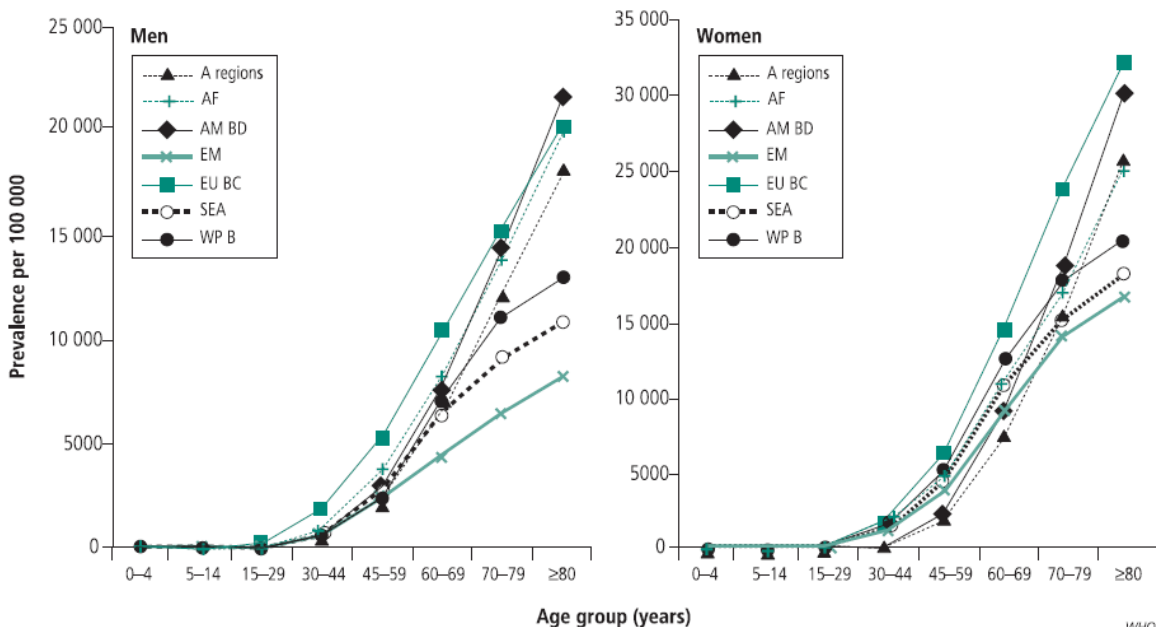
6. Additional reference

The following published article is submitted as under article 45 of the Paediatric Regulation by the MAH as supporting literature reference:

Woolf A.D., Pflieger B. **Burden of major musculoskeletal conditions.** Bulletin of the World Health Organisation 2003; 81 (9): 646-656

This paper describes the burden of four major musculoskeletal conditions: osteoarthritis, rheumatoid arthritis, osteoporosis, and low back pain. All the data presented on osteoarthritis are relevant to the adult population as the overall prevalence of the disease is summarized below

Fig. 1. **Prevalence of osteoarthritis of the knee, by age group, sex, and region, 2000** (16). A regions = developed countries in North America, Western Europe, Japan, Australia, and New Zealand. AF = countries in sub-Saharan Africa. AM BD = developing countries in the Americas. EM = countries in the Eastern Mediterranean and North African regions. EU BC = developing countries in Europe. SEA = countries in South-east Asia. WP B = countries in the Western Pacific region



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III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ **Overall conclusion**

The presented data are considered to be insufficient to support a variation application to extend the use of chondroitin sulphate to the paediatric population.

➤ **Recommendation**

It is recommended that for consistency between glucosamine containing products (as sulphate and hydrochloride) across the EU, it is recommended that all SmPCs and PLs contain the following statement:

4.2 Posology and method of administration

Children and adolescents:

Glucosamine should not be used in children and adolescents below the age of 18 years (see 4.4).

4.4 Special warning and precaution for use

Glucosamine should not be used in children and adolescents under the age of 18 years since safety and efficacy have not been established.

IV. ADDITIONAL CLARIFICATIONS REQUESTED

No additional data have been requested