

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

Chondroitin Sulfate

(structum)

UK/W/007/pdWS/001

Rapporteur:	UK
Date of the Final report (Day 120):	02.09.2009
Date of finalisation of PAR	14.09.2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	See section V
INN (or common name) of the active substance(s):	Chondroitin sulphate
MAH:	See section V
Currently approved Indication(s)	Symptomatic treatment of osteoarthritis
Pharmaco-therapeutic group (ATC Code):	Drugs for treatment of osteoarthritis
Pharmaceutical form(s) and strength(s):	Hard capsules 250mg, 500mg

INDEX

I. Executive summary and recommendation

II. Recommendation

III. Introduction

IV. Scientific discussion

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

IV.2 Non-clinical aspects

1. Introduction

2. Discussion of non clinical aspects

IV.3 Clinical aspects

1. Introduction

2. Clinical overview

3. Clinical studies

4. Discussion of clinical aspects

III. Members States' overall conclusion and recommendation

IV. Additional clarifications requested

V. Medicinal products and Marketing Authorisation holders involved

I EXECUTIVE SUMMARY

Chondroitin is a mixture of high molecular weight glycosaminoglycans and disaccharide polymers composed of equimolar amounts of D-glucuronic acid, D-acetylgalactosamine and sulphates in 10–30 disaccharide units. (Glycosaminoglycans are the substances in which collagen fibres are embedded in cartilage.)

On the basis of *in vitro* studies, the following action mechanisms may be attributed to CS:

- Stimulation of high-molecular weight proteoglycan and hyaluronic acid synthesis,
- Inhibition of the main enzymes involved in destruction of the cartilaginous matrix: metalloproteinases (collagenases, stromelysin) and aggrecanases (ADAMTS4 and ADAMTS5),
- Inhibition of pro-inflammatory factor secretion (TNF- α , IL-6, IL-1, PGE2, NO).

These action mechanisms are thought to explain and support the observed clinical activity as a symptomatic slow-acting drug for osteoarthritis with pain improvement and enhancement function.

Chondroitin has been licensed in the following European countries for the symptomatic treatment of osteoarthritis: France, Luxembourg, Portugal, Poland, Bulgaria, Hungary, Romania and Czech Republic.

The data package submitted by one MAH under article 45 of the Paediatric Regulation comprises 2 clinical studies conducted in children submitted as clinical expert reports. It is noted that these studies have been performed by the MAH. After request from the assessor the MAH also submitted a brief description of the product including the current marketing authorisation status in EU/EEA and the currently approved SmPCs (translated in English) from the following countries: France, Portugal, Poland, Bulgaria, Hungary, Romania and Czech Republic.

The Company's view regarding the need for any change to the European SmPC texts as a consequence of the data presented is not provided.

II RECOMMENDATION

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

The currently approved indication is osteoarthritis, a disease characterized by joint degeneration of the articular cartilage, mainly associated with aging. Extensive review of the literature doesn't reveal evidence of the prevalence of primary osteoarthritis in the paediatric population (0-18 years). The presented data is insufficient to support a variation application to extend the use of chondroitin sulphate to the paediatric population.

It is therefore recommended that the SmPC of chondroitin sulphate containing products across the EU should contain the following statement:

4.2 Posology and method of administration

Use in children:

There is no evidence to support the use of chondroitin sulphate in children 0 to 18 years. Use of chondroitin sulphate in children is therefore not recommended.

III INTRODUCTION

On 5 May 2009, a MAH submitted 2 completed paediatric studies for chondroitin sulphate, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

After request from the assessor, the MAH also submitted on 7 July 2009 a brief description of the product including the current marketing authorisation status in EU/EEA and the currently approved SmPCs (translated in English) from the following countries: France, Portugal, Poland, Bulgaria, Hungary, Romania and Czech Republic.

IV SCIENTIFIC DISCUSSION

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

Chondroitin sulphate (CS) is an ingredient found commonly in dietary supplements used as an alternative medicine to treat osteoarthritis. It is also approved and regulated as a symptomatic slow-acting drug for this disease (SYSADOA) in Europe and some other countries. It is commonly found in products in combination with glucosamine. In a review of the current literature, CS has shown an inconsistent yet overall positive efficacy in decreasing osteoarthritic pain and improving joint function. Most of the clinical trials on CS as an individual supplement suggest a therapeutic value but fall short of proving a role for its independent use. Most trials found the safety of these compounds to be equal to that of placebo.

I.2 Non-clinical aspects

1. Introduction

Non-clinical studies have not been provided or summarized by the MAH on chondroitin sulphate. 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 of non clinical aspects

The benefit of chondroitin sulphate in patients with osteoarthritis is likely to be the result of a number of effects including its anti-inflammatory activity, the stimulation of the synthesis of proteoglycans and hyaluronic acid, and the decrease in catabolic activity of chondrocytes inhibiting the synthesis of proteolytic enzymes, nitric oxide and other substances that contribute to damage cartilage matrix and cause death of articular chondrocytes. A review of the literature conducted by the assessor has revealed that recently, new mechanisms of action have been described. It would have been interesting to investigate if these effects of chondroitin sulphate are confirmed on immature juvenile cartilage.

I.3 Clinical aspects

1. Introduction

The MAH submitted the following 2 completed paediatric studies expert reports:

- A. Etienne M. Structum capsules: Treatment of bone demineralization in children.
- B. Francillon J. Structum capsules: Fracture consolidation

The MAH states that these studies were conducted in 1971-1972 and the clinical expert reports are the only documents that could be provided for these studies.

Assessor's Comment

It is noted that the MAH has provided the clinical expert reports of the 2 clinical trials admitting that they contain limited data only. In addition there is no introduction of the authors of these clinical reports. No further information is provided regarding the clinical settings of these studies. The use of chondroitin in osteoporosis and bone healing after fractures is investigated but there is no evidence of the rationale for the research hypothesis. The definition of paediatric osteoporosis used in these studies is very loose and no validated methods of laboratory investigation (i.e. DEXA z-score) have been utilized to confirm the diagnosis or to review the treatment outcomes. Similarly the clinical outcome of bone healing after fracture is influenced by many parameters such as type of injury and method of treatment that have not been taken into account in these studies. In terms of safety, no major issues were noted with the use of chondroitin in these studies. However the number of patients was overall very small and overall these studies confirm a short term safety profile of chondroitin sulphate which is already well documented.

2. Clinical overview

No clinical overview in relation to implications for paediatric use of chondroitin sulphate based on the findings of these studies is provided by the MAH.

3. Clinical studies

Etienne M. Structum capsules: Treatment of bone demineralization in children

➤ **Methods**

- Objective

Investigate the effect of chondroitin sulphate for bone demineralization in children.

- Study design

Not identified.

- Study population /Sample size

A variable cohort of patients with osteoporosis was identified and distinguished in 4 categories:

A. Immobilization osteoporosis (n=10)

B. Prevention of immobilization osteoporosis (n=11)

C. Retarded consolidation (n=3)

D. Osteoporosis related to a disorder in intestinal calcium absorption (patients with gluten intolerance) (n=2)

Additionally 1 case of vitamin sensitive rickets was also included. In total 27 children were included in the study (13 boys and 14 girls) with a mean age 7.5 years (range 6months to 14 years).

- Treatments

The treatment per age group was as follows:

2 capsules (500mg) daily up to 1 year of age

3 capsules (750mg) daily from 1 year to 5 years of age

3-6 capsules (750-1500 mg) daily over 5 years of age

Total duration of the study was 1594 days and the mean duration 59 days.

- Study criteria

Not clearly mentioned. The author concludes that "*The clinical criteria were poor and related not to osteoporosis but injury or surgery which provided the rationale for treatment. Consolidation duration was a good assessment criterion*". It is also mentioned that the radiological criteria included 2 radiological examinations for each patient at a mean interval of 2 months. These examinations determined the degree of possible demineralization and callus quality. The laboratory criteria included phosphorus and calcium investigations at unspecified intervals

through treatment. Safety and acceptability were also monitored but no specific parameters are mentioned.

- Statistical Methods
Not specified.

➤ **Results**

Overall the author of the report concluded that the drug under investigation was considered “*to be very useful treatment for bone demineralization in children since it is a physiological treatment that is very well tolerated and non-toxic*”.

- Efficacy results

The results in the different osteoporosis group are summarized by the author of the report below:

- **Treatment of immobilization osteoporosis (10 cases)**

- . 2 very good results
- . 2 good results
- . 5 fairly good results
- . 1 poor result

- **Prevention of immobilization osteoporosis (11 cases)**

- . 10 good results
- . 1 poor result

- **Retarded consolidation (3 cases)**

- . 2 very good results
- . 1 poor result

Satisfactory results were also obtained in osteoporosis of digestive etiology (2 cases)

- . 1 very good result
- . 1 fairly good result

Lastly, in rickets (1 case), the result was fairly good.

Overall, out of 27 cases studied, the following results were obtained:

- 17 very good and good results
- 7 fairly good results
- 3 poor results

- Safety results

No adverse reactions were thought to be related to treatment with chondroitin sulphate. Vomiting was observed in 2 cases but it was thought to be related to the effect of general anaesthesia.

- Laboratory results
A slight increase in the blood calcium, alkaline phosphatase and urinary calcium was observed. However it was concluded that none of the changes appeared to be significant.

Assessor's Comment

This report does not contain vital 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. Osteoporosis due to post fracture immobilization is a problem almost exclusively in adults. Transient demineralization has been noted in adolescents with femur fractures but there is no evidence justifying the need of treatment. In the assessor's opinion, this is a very limited study which does not offer robust evidence on the effect of chondroitin sulphate in paediatric osteoporotic patients.

Francillon J. Structum capsules: Fracture consolidation

➤ **Methods**

- Objective
Investigate the effect of chondroitin sulphate in fractures or their sequelae
- Study design
Not identified.
- Study population /Sample size
27 patients were included in the study aged 16 to 70 years (mean age 39 years). 8 were women and 19 were men and they were divided according to their initial diagnosis into the following groups:

- arm fractures	7 cases
of which 5 post-traumatic sequelae of the hands	
- sequelae of spinal fractures	2 cases
- femur fractures	8 cases
- fractures of the leg and instep	10 cases
of which 2 cases of post-traumatic osteoporosis	
- Treatments
The patients received 4 capsules of chondroitin sulphate daily (1000mg) for 30 to 90 days (mean 48 days).
- Assessment criteria
The author of the report concludes that it is very difficult to define quantitative criteria to investigate the effects of chondroitin on callus formation and fracture healing. Therefore the assessment of the treatment effect was restricted to the consolidation times using clinical or radiological criteria. Safety and adverse events were also monitored but no specific parameters are mentioned.
- Statistical Methods
Not specified

➤ **Results**

Overall the author of the report concluded that a positive effect of the treatment with chondroitin was demonstrated regarding the fracture consolidation and facilitation of the callus formation. Additionally it was thought that pain in post-traumatic osteoporosis was significantly alleviated.

- **Efficacy results**

Overall for 27 cases the results were reported as follows:

very good result	good result	moderate result	nil result
5	17	1	4

2 failures in fractured limbs that were treated surgically consisted patients with pseudarthrosis with fistula and one case with a low-grade infection. The results in 7 out of the 10 cases of post-traumatic osteoporosis and pain of the hand were found to be good.

- **Safety results**

The safety of chondroitin was excellent in all patients of this study.

Assessor's Comment

This is a very old study conducted in adolescents and adults patients with fractures of the limbs or the spine. The author has not provided detailed information regarding the paediatric cohort in this study as the results are presented as a total. There is no clear information regarding the rationale of the treatment with chondroitin sulphate and the efficacy outcomes are very vague.

In the assessor's opinion, this is a very limited study which does not offer robust evidence on the effect of chondroitin sulphate in paediatric fracture patients.

4. Discussion on clinical aspects

In the literature chondroitin sulphate has shown inconsistent efficacy in decreasing osteoarthritic 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. By definition 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 chondroitin sulphate can be made.

V MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The currently approved indication is osteoarthritis, a disease characterized by joint degeneration of the articular cartilage, mainly associated with aging. Extensive review of the literature doesn't reveal evidence of the prevalence of primary osteoarthritis in the paediatric population (0-18 years). The presented data is insufficient to support a variation application to extend the use of chondroitin sulphate to the paediatric population.

➤ Recommendation

It is recommended that the SmPC contains the following statement:

4.2 Posology and method of administration

Use in children:

There is no evidence to support the use of chondroitin sulphate in children 0 to 18 years.
Use of chondroitin sulphate in children is therefore not recommended.

VI ADDITIONAL CLARIFICATIONS REQUESTED

No additional data have been requested.

VII MEDICINAL PRODUCTS AND MARKETING AUTORISATION HOLDERS INVOLVED

STRUCTUM Hard capsules 250mg, 500mg MAH: Pierre Fabre Medicament.