



LOW MOLECULAR WEIGHT CHONDROITIN SULFATE TRIETHANOLAMINE SALT

PRODUCT PROFILE

MARCH 2010



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Description

Low molecular weight chondroitin sulphate is obtained by chemical depolymerization from natural CS (U.S. Patent N° 4.977.250 and European Patent N° 268.885) radical fragmentation.

The resultant product is subjected to sequences of ion exchange in order to remove the Na⁺ ion and replace it by the equivalent weight in triethanolamine, thus obtaining the triethanolamine salt of the depolymerised product.

Introduction

Chondroitin Sulfate is a natural mucopolysaccharide present in the cartilaginous tissue where it performs mechanical functions due to its capacity to regulate water distribution. The cartilage, subjected to an inflammatory recession (either a traumatic one or due to other etiology) suffers diverse alterations such as loss of CS and degradation of hyaluronic acid and collagen from the cartilaginous matrix caused by a severe attack mediated by the presence of free radicals, among other reasons.

The restitution of the lost CS, not only provides a solution to the mechanical problem but also completes the recovering by inhibiting the degrading proteolytic activity of collagen and stimulating its synthesis.

The main obstacle to a local administration of the product via dermis (topical use) is the hydrophilia of the natural compound and certainly, its high molecular weight. Both CS properties restrain cutaneous absorption.

Therefore, Syntex developed a low molecular weight and low hydrophilic chondroitin sulphate in order to get a natural anti arthritic therapy.

Development Purpose

1. To obtain a CS topical form of administration therapeutically useful in the field of arthritis.
2. The election of the cation replacing Na⁺ was made in order to fulfil two necessities at the same time: the first one, to facilitate the lipophilicity of the polysaccharide molecule replacing sodium by a suitable organic base. Among those of a particularly low toxicity, those organic bases contained in cosmetic or pharmaceutical creams were preferred.
The second necessity to be covered, essential in antiarthritic products, was that the oligosaccharide molecule be associated with a chemical group being a strong scavenger of free radicals, particularly HO[•] main responsible of the fragmentation of the hyaluronic acid and articular chondroitin sulphate in inflammatory processes. This was achieved using the organic base Triethanolamine which complies with both former mentioned criteria, that is, low toxicity (cosmetic use), lipophilicity and an excellent free radicals scavenger, particularly HO[•]



Proof of efficacy

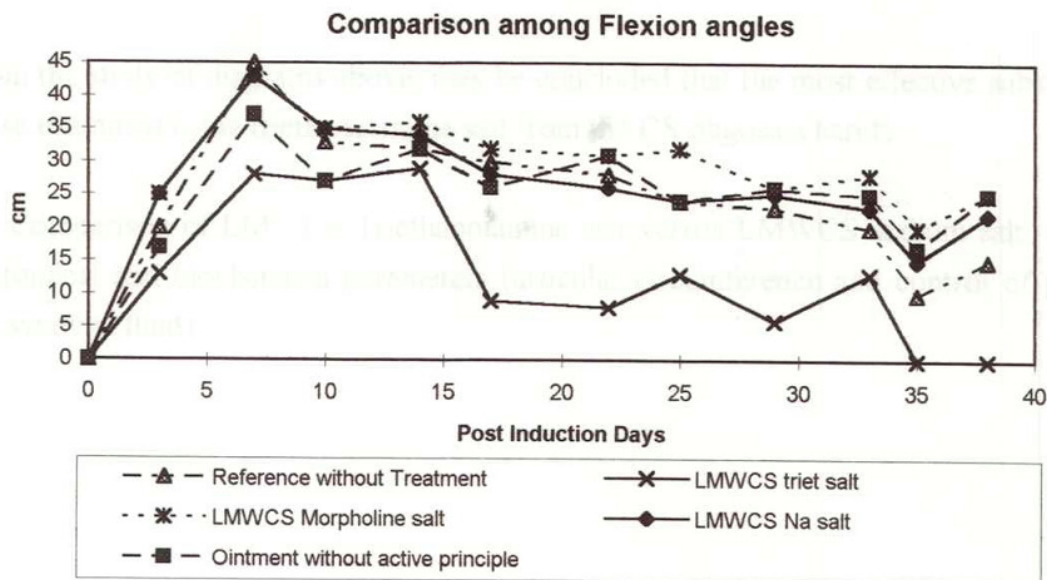
Comparison versus low molecular weight chondroitin sulphate sodium salt (LMWCSNa)

The product was subjected to pharmacological tests performed by veterinarian doctors in Syntex farm located in Ayacucho (Province of Buenos Aires, Argentina).

Strong and large mammals were used, that is, healthy horses serologically and sanitarily controlled in which a model of aseptic arthritis in the knee was experimentally developed. (Videla Dorna et al, XII Jornadas de actualización técnico-científica, Asociación Argentina de Veterinaria Equina, Buenos Aires, Junio de 1994) (Congress of scientific technical actualization, Argentine Association of Equine Veterinary, Buenos Aires, June 1994)

- a) A study of a series of organic-base salts, triethanolamine among them, applied as a cream in the previously mentioned aseptic arthritis model, versus the depolymerized chondroitin sulphate sodium salt (LMWCS sodium salt)
The results obtained are shown as follows:

Fig.1





The product was also assayed in Department of Surgery and Clinical Medicine, Faculty of Veterinary Sciences, University of Buenos Aires (Scipione, H. et al; "Efficacy of topical use of LMWCS-TEA in induced arthritis in equines"; World Equine Veterinary Association, 7th World Congress, Sorrento, Napoles, 5/7 Oct 2001)

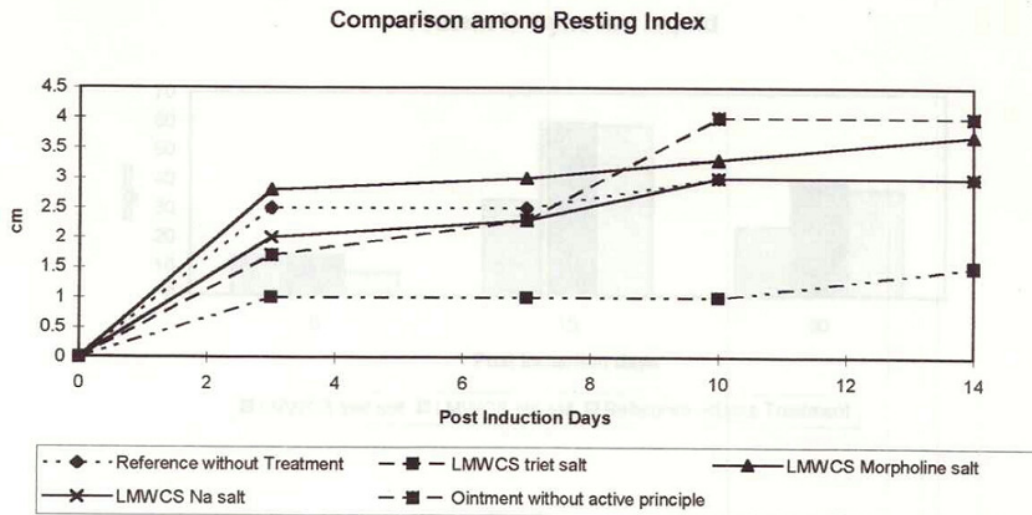


Fig. 2

From the study of the diagrams above, it may be concluded that the most effective substance from those examined is the triethanolamine salt from the CS oligosaccharide.

b) Comparison of LMWCS Triethanolamine salt versus LMWCS sodium salt. Control of anatomical and biochemical parameters (articular circumference and control of proteins in the synovial fluid).

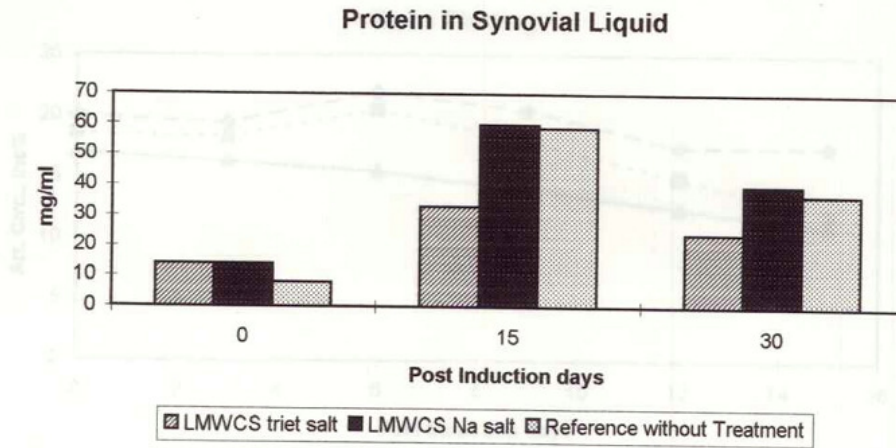


Fig.3

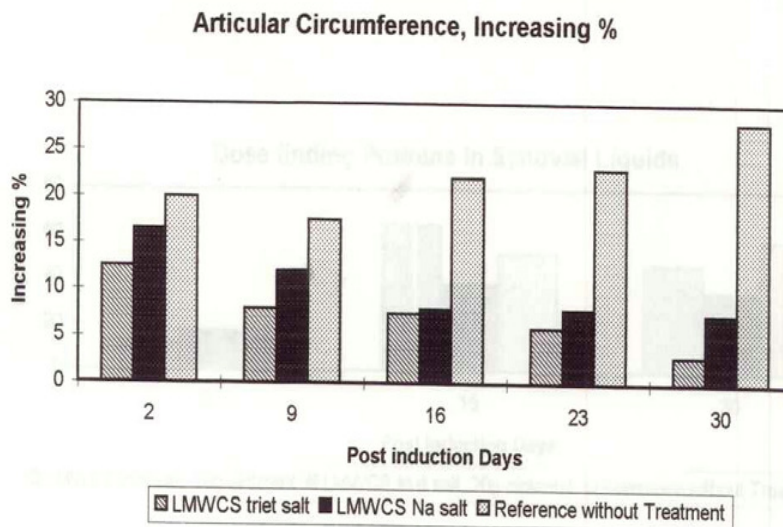


Fig.4

c) Dose finding. The suggested dose to be administered is 20gr a day of an ointment containing a 5% of active product, applied in the articulation to be treated.

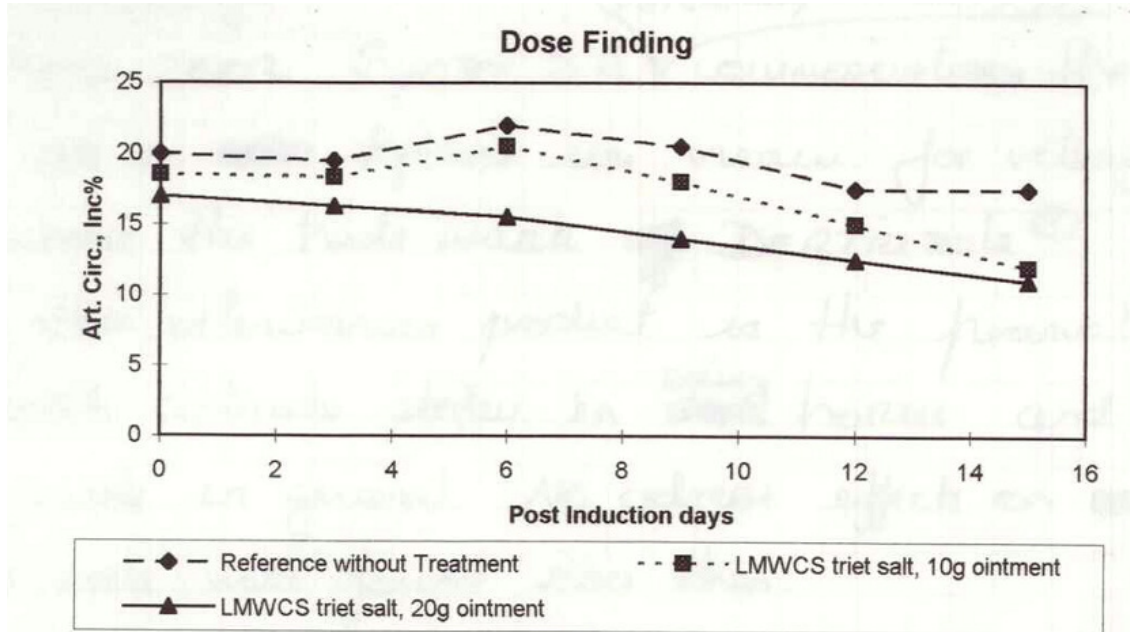


Fig. 5

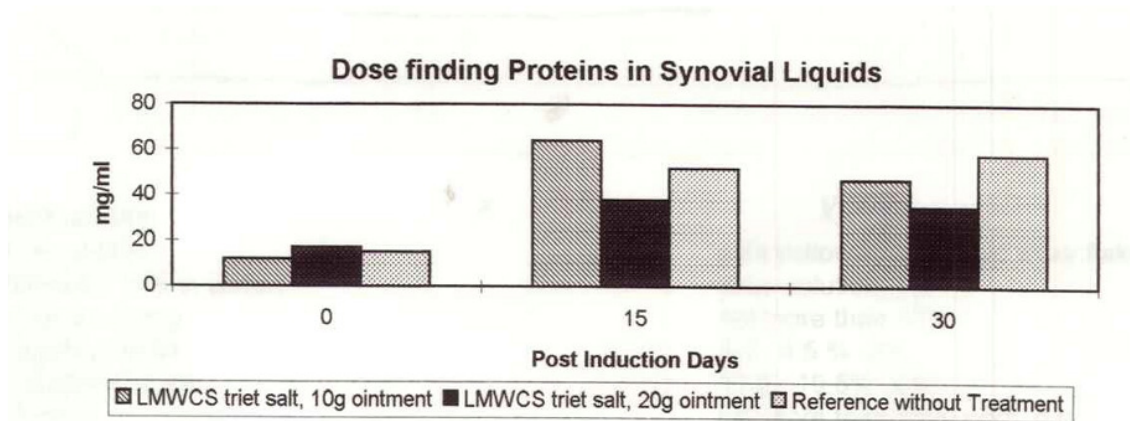


Fig.6



Marketing

Since 2002 Syntex S.A. Veterinary Division commercializes the product as a topical use cream for veterinary uses under the trademark Dertrisoletm. The focus of this veterinarian product is the preservation of articular health status in racing horses and sports animals in general. No adverse effects on treated animals were found since then.

Syntex presenta la 3ra generación de
Glicosaminoglicanos Sulfatados
con actividad antiartrósica.

"Oligosacáridos de Condrotín Sulfato
Salificados con Trietanolamina"



Va más allá de la piel, actuando
efectivamente sobre la articulación



VENTA LIBRE EN VETERINARIAS

SYNTEX S.A.
Industria Bioquímica & Farmacéutica



Specifications

Appearance:	pale yellow, very hygroscopic waxy flakes
Solubility (5% in water):	clear solution
Loss on drying:	not more than 10%
Organic Sulfur:	3.0 – 4.5% d.b.
Hexuronic acids:	13.5 – 19.5% d.b.
Sodium:	not more than 3000 ppm d.b.
Specific optical rotation:	-10° / -20° d.b.
pH (5% solution)	4.0 – 6.0
Triethanolamine:	38.0 -50.0% d.b.
Heavy Metals:	not more than 30 ppm

Weight-average molecular weight (\bar{M}_w)
(Size-Exclusion Chromatography): 4500 – 6500 Da

Packaging

1 – 5kg net weight polyethylene-lined drums.

Final notes

- Studies of acute and chronic toxicity were not performed, although considering the broad use and innocuity of the components used, undesirable side-effects should not be expected.
- Tests on human beings have not been performed to date.
- The information presented herein is based on the best data available and is believed to be correct. However, nothing stated in the bulletin should be taken as a warranty, expressed or implicit regarding the accuracy of the information on the use of the product; nor shall anything contained herein be intended to constitute a permission or recommendation to practice any invention covered by a patent owned by Syntex S.A., without a license from the owner of the patent.