CHONDROITIN SULFATE SODIUM

PYROGEN FREE

PRODUCT PROFILE

SYNTEX S.A.
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Brief introduction

Chondroitin Sulfate from mammalians contains 4-Chondroitin Sulfate (or CS-A) with minor amounts of a 6-Chondroitin Sulfate (or CS-C). Both of them are macromolecules made by alternate sequences of D-glucuronate and N-Acetyl Glucosamine 4-0 Sulfate (or 6-0 Sulfate) respectively.
Pyrogen free CS is a white or ivory white powder, hygroscopic, soluble in water, almost insoluble in most organic solvents.

Compendia References:
Chondroitin Sulfate is well described, as is, in USP and EP. The pyrogen free Chondroitin sulfate presents tighter specifications about total plate count, pathogens and endotoxin that are stated by Syntex S.A. taking as references other APIs for injection.

Uses
Pyrogen free CS sodium is a well-known therapeutic agent used in Human and Veterinary Medicine.
In Human medicine, it is widely used in eye drops and intra-ocular injections. Intramuscular and intra-articulation administration is another recognized use of pyrogen-free CS sodium salt.
Uses in Veterinary Medicines include articulation pathologies in racing horses and joint disorders in pets, being the parenteral administration well-indicated both for pets and sport horses.
Novel uses in urinary pathologies are under examination. Preliminary trials of instilled CS, show improvements symptoms of interstitial cystitis (1).
CS is also reported to inhibit urinary stone formations (2). There is a range of ways in which CS could impact urinary stone formation including inhibition of mineral nucleation and easing excretion of partially mineralized forms (1) (3).
There is another pyrogen free CS with a low proteins level that it is used in Medical Devices registered in Europe.

Production
Bovine cattle (from which CS is obtained) fulfill the requirements for the health of animals suitable for human consumption. Such animals are exclusively born and growth in Argentina (BSE-free status)
Syntex S.A. produces pyrogen free CS Sodium at full industrial scale from its own CS.

Some comments about viral and inmunotoxical inactivation in Syntex pyrogen- free CS

Producers of therapeutically biological products must demonstrate that they are not introducing disease-causing agents into patients.
Three kind of biological risk could be mentioned:

a) Viral origin risk
b) Inmunotoxical risk
c) Pyrogenic response

So, some comment could be done regarding these three items. Of course, elimination of microbial organism (bacteria) is performed as state of the art and will not be commented.
Possible presence of viral agents and inmunotoxical profile of pyrogen free CS, including inactivation processes is commented as follow:

Viral Inactivation:

Conventional viruses and other adventitious agents such prions ("slow viruses") is one of the main focus in inactivation steps performed in the production of a biopharmaceutical, such us CS pyrogen –free grade.
Certainly, BSE, (bovine spongiform encephalophaty, mad cow disease) are neurological diseases caused by an agent called "prion". These diseases include Creutzfeld-Jakob disease in humans and scrapie in sheeps. One particular BSE is of a particular concern for producers of biological products: BSE agent has now been shown to be transmissible to sheep by direct parenteral injection (4) so indicating that concern about the use of bovine tissues in the production of biopharmaceuticals is valid.
For this reason and according to EMEA/410/01 Rev 2 (5) Syntex S.A. introduce the following actions:

- Control of animal sources (geographical origin exclusive Argentina),
- Control of the procedures in slaughterhouses to avoid cross contamination with another high risk bovine tissues
- Validation of inactivation steps included as routine in the production method of Syntex pyrogen free CS. This means the treatment in well-controlled conditions with alkali (6). For this reason, Syntex S.A. has validated viral inactivation steps, for both prions (BSE) (7) and conventional viruses (8) in qualified virological institutes of international renown. In this line, Syntex S.A. has received the corresponding "Certificate of Suitability" from EDQM (9)

Inmunotoxical Inactivation:

Inmunotoxical effects after administration via parenteral route of a biopharmaceutical product could be due to different reasons, for instance:

- Alergy, sensibilization
- Antigenicity

Antigenicity is a very serious problem which causes pain, inflammation and make red-hot in application site, papule, swall-non-supurative eruption. First step in manufacturing process of Syntex pyrogen free CS is washing of starting bovine connective tissues with hot-boiling water by prolongued period of time.
Inactivation and denaturation of native proteins,phospholipids and other antigen molecules (including hemoglobin traces) is achieved in this first step.
Alkaline treatment also operates for elimination / demolition of antigenic residual protein remaining from prevoious steps, hot water washing aperation, proteolitic digestion and massive elimination of low molecular weight peptides, which are currently wasted (together with allergens, if any).

Pyrogenic response inactivation:

Demolition and elimination of endotoxin (bacterial) is achieved by the same alkaline process above mentioned. Carefully done non-aggressive treatment for pyrogen elimination follows to alkaline processyielding a pyrogen-free CS.

Specifications

EP or USP specifications for CS oral grade plus endotoxin and bacterial control

Packaging

1 – 5 – 25 kg in double polyethylene bags in lined drums.

References

(1) Lauder, R; Complementary Therapies in Medicine (2009); 17, 56-62

(2) Khan, SR; Kok, DJ; Front Biosci (2004) 9:1450-82

(3) Gohel, MD et al; Carbohydr. Res (2007), 342:79-86

(4) Houston, F et al; Lancet (2000); 9234:999-1000

(5) Note for guidance on minimizing the risk of transmitting Animal spong. Encephalop. EMEA/410/01 Rev. 2

(6) Guidelines from Ministerio della Sanita 100/CSS/1.1.4/985 (6 Jul 1991) Roma, It.

(7) "Validation of GAG manufacture procedure to remove unconventional slow viruses in golden syrian hmsters treated by intracerebral route" – Ricerca Biomedica Antoine Marxer, RBM Exo 910287 (Issued 14 june 93)

(8) "Chondroitin Sulfate produced by Syntex S.A.: Evaluation of viral safety level associated with manufacturing process" – INTA – Protocole 26 / 2003

(9) EDQM – Certificate of Suitability R1-CEP2006-179 Rev 00, to Syntex S.A.