

Product Information Bulletin



Safety and toxicology of PROTASAN™ UP chitosans

PROTASAN™ ultrapure chitosans are manufactured in accordance with cGMP guidelines (Code of Federal Regulations, Title 21, Part 210 and 211), NS-EN ISO 9001:2000 (Quality Management System) and ISO 13485:2003 (Medical Device Directive) standards. Ultrapure – UP – implies that the products contain low levels of residual endotoxin. The current specification is <500 EU/g for the PROTASAN UP G 113 and <100 EU/g for the other PROTASAN UP CI and UP G salts, and PROTASAN UP Base products. PROTASAN™ chitosans are ideal for a wide variety of pharmaceutical, biomedical, biotechnology and tissue engineering applications. The safety and toxicology profile of the ultrapure PROTASAN™ products are described in Drug Master Files submitted to the US FDA. The table below is meant to serve as a summary over some of the studies performed and the conclusions drawn from them.

Report number	Title	Animal species	Chitosan products	Concentration	Conclusion
ALG-95-001	Effect of chitosan salts on cell survival of V-79 and 3T3 cells cultured in vitro	In vitro cell culture 3T3 mouse fibroblasts V79 Chinese hamster	PROTASAN UP G 213 (84 mPas) PROTASAN UP CL 113 (12 mPas)	0-1 mg/ml 24 hr exposure	Little or no effect at up to 1 mg/ml. Reduction in cell survival by 15% (CL) and 35% (G) at 5 mg/ml.
658/525	Single dose toxicity study by the intraperitoneal route	Mouse	PROTASAN UP G 213 (84 mPas)	100, 250, 500 mg/kg	No mortality. No abnormal clinical signs, normal weight increase.
658/526	Single dose toxicity study by the intraperitoneal route	Rat	PROTASAN UP G 213 (84 mPas)	100, 250, 500 mg/kg	No mortality. No abnormal clinical signs, normal weight increase.
658/527	Single dose toxicity study by the intraperitoneal route	Mouse	PROTASAN UP CL 113 (12 mPas)	100, 250, 500 mg/kg	No mortality. No abnormal clinical signs, normal weight increase.
658/528	Single dose toxicity study by the intraperitoneal route	Rat	PROTASAN UP CL 113 (12 mPas)	100, 250, 500 mg/kg	No mortality. No abnormal clinical signs, normal weight increase.
658/539	13 week oral (gavage) toxicity study	Rat	PROTASAN UP G 213 (91 mPas)	100, 300, 600 mg/kg	No treatment related deaths. No differences in body weight nor food consumption. No abnormal clinical signs, normal weight increase.
658/540	7 day intranasal tolerance	Rat	PROTASAN UP G 213 (91 mPas)	0.5 and 1 mg admin. x 3 per day	No mortality during study. Treated animals have some increase in mucus production, no clear dose-effect seen. No abnormal clinical signs, normal weight increase.
658/538	Single dose toxicity study by the intravenous route	Rat	PROTASAN UP G 213 (91 mPas)	25 mg/kg	No mortality was observed. Subdued behaviour up to 30 minutes after injection. Treated animals lost weight between days 1 and 2, thereafter weight gains similar to control.

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Report number	Title	Animal species	Chitosan products	Concentration	Conclusion
658/543	Single dose toxicity study by the intravenous route	Rat	PROTASAN UP G 113 (2.8 mPas)	20, 50, 100 mg/kg in preliminary, 25 mg/kg in main study	No mortality at 20 or 25 mg/kg, 2/2 and 1/2 deaths at 50 and 100 mg/kg, resp. Lower body weight on day 1-2, same as control after.
658/557	Single dose toxicity study by the intravenous route	Rat	PROTASAN UP CL 113 (5 mPas)	25, 50, 100 mg/kg in preliminary, 50 mg/kg in main study	No mortality at 25 and 50 mg/kg in preliminary study. Mortality was 1/10 treated animals in main study at 50 mg/kg.
658/541	Sensitizing potential in the guinea pig. Magnusson & Kligman test (GPMT)	Guinea pig	PROTASAN UP G 213 (91 mPas)	1 mg/kg intradermal, 60 mg/ml topical occlusive induction. 60 mg/ml topical challenge	No mortality observed. Body weight not influenced. Induction: moderate irritation at injection site. After challenge no sign of delayed hypersensitivity.
658/556	Sensitizing potential in the guinea pig. Magnusson & Kligman test (GPMT)	Guinea pig	PROTASAN UP CL 113, (5 mPas)	0.5 mg/ml intradermal, 60 mg/ml topical occlusive induction. 60 mg/ml topical challenge	No mortality. No influence on body weight. Signs of irritation were noted during induction. No delayed hypersensitivity in test animals.
658/542	Evaluation of the potential to induce immediate hypersensitivity: induced anaphylactic shock	Guinea pig	PROTASAN UP G 213 (91 mPas)	10 mg/kg subcutaneous induction, 20 mg/kg intravenous challenge	No mortality observed. Body weight similar in all groups. Cyanosis noted in 5 treated animals within 1 hr of challenge, cleared by 4 hr.
10396	Bacterial reverse mutation test	Plate incorporation	PROTASAN UP G 213 (75 mPas)	≤5000 mg	No significant increase in numbers of revertants. 5000 µg/plate toxic to TA98 and TA 1537 (± activation).
507340	Acute dermal irritation test	Rabbits	PROTASAN UP B 80/20 and 80/500	0.5 g	No edema or erythema. Non-irritant.
507356	Local lymph node assay (hypersensitivity)	Mouse	PROTASAN UP B 80/20 and 80/500	1, 2.5, 5% 0.5, 1, 2%	No adverse clinical signs. No Simulation Index over 3 = no sensitizing effect.

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The information contained in this bulletin is intended to be general in nature. Techniques and data pertaining to specific uses for NovaMatrix/FMC products and new developments will be published periodically in the form of supplemental application bulletins. Our technical staff is ready to offer assistance in the use of NovaMatrix/FMC products.

Regulatory Status

PROTASAN™ chitosan chloride meets the standards set forth in the European Pharmacopoeia (EP 1774). PROTASAN™ chitosan products satisfy ASTM F 2103 for use in tissue engineered medical products (TEMPS). PROTASAN™ chitosan products are manufactured in compliance with current Good Manufacturing Practice and described in a DMF submitted to the US FDA.

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