

Safety and Toxicological Studies Regarding AQUAMID®

a report by

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Polyacrylamide hydrogel (PAAG) is an atoxic, stable, non-resorbable sterile watery gel for injection into the soft tissues. It consists of 2.5% cross-linked polyacrylamide and non-pyrogenic water. Due to its unique characteristics, the gel is highly biocompatible.

PAAG has been used in plastic and aesthetic surgery in the former Soviet Union for more than 10 years. The total number of patients treated with PAAG is approximately 30,000 and another 30,000 patients have since been injected with AQUAMID® during the last two years.

There is comprehensive data regarding the safety of the gel including pre-clinical as well as clinical studies. In order to obtain a CE Mark for facial corrections, a retrospective clinical study on safety following facial corrections has been conducted. The purpose of the study was to evaluate the safety and long-term aesthetic results of facial corrections performed with PAAG. The study was carried out in Kiev by Danish plastic surgeons.¹

A prospective European multicentre study was also conducted to evaluate the safety and long-term aesthetic results of facial corrections performed with AQUAMID® in 15 centres in six countries, (Germany, the Netherlands, Italy, Spain, Sweden and Denmark).

The effect has been rated by 93% of the 247 patients included in the study as either being good or very good, as judged by both patient and investigator. The injections of AQUAMID® were found to be very well tolerated.

Clinical laboratory evaluations showed that all results from the blood and urine samples taken show no significant change between the results after one year and those of the pre-inclusion tests. All values fall between the acceptable normal range. There were also no significant changes in the average blood

pressure and heart beat rate of the patients after day 0, day 28, month 3, 6 and 12 of the study.² The results of this study was presented at IPRAS 2003: the 13th International Congress of the International Confederation for Plastic, Reconstructive and Aesthetic Surgery, on the 10–15 August 2003, in Sydney, Australia. A publication containing the results is currently in preparation.

Two post marketing surveillance studies were also carried out, one in France and one in Brazil. In France, 68 patients in five different centres were followed for one year. The results show that the patients evaluated were either satisfied or very satisfied with the results after one year.³ A publication is in progress. A new protocol has been written up to continue the study so as to follow as many of these patients as possible over the next five years.

In Brazil, 130 patients were followed in 13 centres throughout the country for six months. The results of this study are still being processed. A further study, including 10 HIV patients in Brazil, is also currently being undertaken to examine the efficacy of AQUAMID® in filling the soft tissue left by lipodystrophy in the cheek area. Lipodystrophy is a common side effect experienced by patients on HIV medication such as antiretroviral therapies (HAART) and other protease inhibitor drug therapies.

Polyacrylamide is widely used in biomedical research as well as in industry. Polyacrylamide gel has already been used for decades in the preparation of soft contact lenses. In biomedical research, polyacrylamides serve as tissue implant materials, tissue models, body fluid models, detectors of penicillin antibodies and as carriers of hormones and drugs in animal studies.

In the US, most of the polyacrylamides are used in water and wastewater treatment as a thickening and suspending agent. In lesser amounts, polyacrylamide is used in sugar clarification and

1. A Rosetzsky and M Bildsøe, "Integrated Clinical/Statistical Report", CON-FACE 01 dated 13 September 2000.

2. K R Rytting, Meddoc A/S, "Clinical study report dated 29 January 2003".

3. A Jonasen and M Bildsøe, "Integrated Clinical/Statistical Report", CON-FACE 02 dated February 2003.



drug production.⁴ Another branch extensively using polyacrylamides is the aesthetic industry.⁵

An extensive interest in polyacrylamides originated because of their use in groundwater clearance. Obviously, chemicals used for groundwater treatment have to be non-toxic to exclude possible hazards to humans or animals.

Comprehensive toxicology studies of polyacrylamides show that polyacrylamide is non-toxic to humans as well as animals.⁶ Thus, a long-term feeding study (two years) in dogs and rats with polyacrylamides revealed that there were no specific toxic effects on animals. D J King and R R Noss from the University of Massachusetts summarise in their review numerous articles reporting toxicology studies with polyacrylamides.⁷ They came to the conclusion that polyacrylamides are non-toxic when used in the limited range. It is generally believed that the main toxicological concern with polyacrylamide is its acrylamide monomer content.⁸

The content of monomer in AQUAMID® is below 0.0064µg/ml according to the Certificate of Analysis from Nycomed A/S. Thus, by implantation of the AQUAMID®, the single dose of monomer is lower than the exposure to drinking water in one or two days.⁹

The stability as well as toxicity of the PAAG has been investigated extensively in the former Soviet Union during the past 10 years. Some investigations were performed also in Norway and the US. The stability

of the gel was assessed by various methods, for example exposure of the gel to enzymes, bacteria, oxidising agents, etc.^{10,11} All studies revealed that PAAG is a stable, practically non-degradable product.

In vitro experiments concerning cytotoxicity were performed on cell cultures as well as on human blood cells. No cytotoxic effects were detected after incubation for 24, 48 hours and 10–12 days with PAAG.^{10,12} In addition, no impact on human blood cells were observed after incubation with 5% PAAG for 24 hours.¹³

In vivo studies were performed on various species including rats, mice, rabbits and dogs. In BALB/c mice, PAAG had no mutagenic effects assessed by micronuclei test.¹⁴ Subchronic toxicology studies in rats revealed no effects on blood and liver biochemistry, and no inflammatory processes were observed.¹⁵ After 6–8 weeks of PAAG injection (S.C.) in rabbits, no physiological and histological changes were observed.¹⁶ Also, liver and spleen were not affected by PAAG implantation, indicating that PAAG is not degraded and is not migrating in the organism.

No carcinogenic effects were seen 18 months after implantation of PAAG (i.m.) assayed by immunodetection of organospecific tumour-associated antigens.¹⁷

Histology carried out on different tissues of various animals as well as humans after longer time of incubation (six months, three years) showed that the gel inter-grows with thin inter-layers of

4. D D McCollister, C L Hake, S E Sadek and V K Rowe, "Toxicological investigations of polyacrylamides", *Toxicol. Applied Pharmacol.*, vol 7 (1965), pp. 639–651.
5. *Final report of the safety assessment of polyacrylamide*, J. Amer. College of Toxicology, vol 10 (1991), pp. 193–203.
6. E A Smith and F W Oehme, "Acrylamide and polyacrylamide: A review of production, use, environmental fate and neurotoxicity", *Rev. Environ. Health*, vol 9 (1991), pp. 215–228.
7. D J King and R R Noss, "Toxicity of polyacrylamide and acrylamide monomer", *Rev. Environ. Health*, vol 8 (1989), pp. 3–44.
8. E Silvestro and A M Desmarais, "Toxicity of chemical compounds used for enhanced oil recovery", final report. Contract No. DOE/BC/10014-5. United States Department of Energy. Bartersville, OK, September 1980.
9. E J Conway, et al., "Assessment of the need for, and character of limitations on acrylamide and its compounds", US Environmental Protection Agency Contract No.68-01-4308. USEPA, Office of toxic substances, Washington DC, 1979.
10. K Bertheussen, "Report from biological test of Royamid in cell cultures", 1998.
11. Y V Rul and V A Kovanskaya, "Medicobiological assessment of hydrogel PAAG "Interfall"".
12. V M Cherednichenko, "Results of study interaction process between hydrophylic gel (PAA) "Interfall" and tissues of organisms of experimental animals while implanting", 1993.
13. G Kogut, "Investigation concerning hemolytic activity of preparation "Interfall"".
14. N A Galatenko, "Assessment of cytogenotoxic (mutagenous), cytotoxic and cytostatic activity of the acrylamide and commercial samples of polyacrylamide hydrogel PAAG "Interfall" by means of a micronuclear test", 1995.
15. N I Tsvilikhovskiy and S D Melnichuk, "Study of principal biochemical and cytological indices of blood of rats in two weeks after intraperitoneal injection of polyacrylamide gel", 1994.
16. J Sosa, A Wayne Smith and I T Jackson, "The use of Royamid (polyacrylamide) in soft tissue augmentation: an experimental assessment", Abstract submitted to The European Association of Plastic Surgery, Amsterdam, 1997.
17. N L Novichenko, "Determination of a potential carcinogenic activity of polyacrylamide gel by methods of immunodetection of organospecific tumour-associated antigens", 1992.

connective tissue and elastic fibres. No fibrous capsules were observed, neither dystrophic nor necrotic changes, chronic inflammation, local allergic reactions, haemodynamic disturbances, carcinogenic effects or calcium salt deposits. No gel was found in lymphatic nodes.¹⁸⁻²⁰

Since the 1980s, a hydrogel consisting of 5% polyacrylamide and 95% water, developed and manufactured in the Ukraine, has been used in aesthetic/plastic surgery. Most of the patients treated with PAAG have undergone breast augmentation and/or facial corrections. In 1996, a retrospective clinical study was performed by a group of Danish/Ukrainian surgeons on 175 patients who were selected randomly from a list of 390 patients who had undergone mammoplasty before 1 July 1994 at the clinic in Kiev.²¹

The tolerability of the injections, assessed by side effects and the results of the laboratory investigations, showed that the injection sessions were well tolerated and only few side effects (2%) were observed. These adverse effects occurred

mostly due to the wrong technique of injections and could be corrected or they were judged to be unrelated to the gel injection. The overall aesthetic results assessed by surgeons and patients themselves were very good.

A paper has recently been published on the long-term toxicological study in human tissue, where histology samples were taken from women who had PAAG implanted for a mean period of 3.9 years. Results showed no calcification and that the pseudoepithelial layer around the gel is thin compared with reactions to other foreign bodies, which indicated that polyacrylamide gel is well tolerated by the human body.²²

Polyacrylamides have already been used in biomedical applications, for example soft lenses and in the aesthetics industry for decades. Review of the scientific literature indicates that polyacrylamides are non-toxic when used in accordance with the existing guidelines. Toxicology studies performed with PAAG also showed that this product is non-toxic and is well tolerated by the human body. ■

18. N A Galatenko, "Results of study interaction process between hydrophylic gel (PAAG) "Interfall" and tissues of organs of experimental animals while implanting", 1993.

19. N A Galatenko, "Toxicological estimation of hydrogel PAAG "Interfall" as an implant", 1992.

20. N N Grigorieva and I Ischenko, "Structural-functional characteristics of organs and tissues under injection of polyacrylamide gel "Interfall" in clinic and experiment", 1991

21. K R Rytting, J Schiøtz and A Jørgensen, "Clinical study report dated 3 January 1998".

22. L H Christensen, V B Breiting, A Aasted, A Jørgensen and I Kebuladze, "Long term effects of polyacrylamide hydrogel (PAAG, Interfall/Contura SA) in human breast tissue", *Plast. Reconstr. Surg.*, 111 (2003), p. 1,883.
