
Aquamid[®] for Facial Augmentation

White paper

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Aquamid is a patented polyacrylamide hydrogel that has been shown to offer distinct advantages over other injectable soft tissue fillers used for aesthetic enhancement and reconstructive procedures. Aquamid looks and feels like normal subcutaneous tissue, making it ideal for facial contouring. It provides volume to deeper wrinkles and folds, sunken cheeks, and thin lips. The gel is not biodegradable, making augmentation long lasting.

Since the CE mark was granted in 2001 in Europe, more than 300,000 syringes of Aquamid have been injected by physicians in more than 40 countries globally.

What is Aquamid?

Aquamid is an injectable, transparent, colorless, polyacrylamide hydrogel that stays soft and looks and feels like a natural part of the tissue. When injected subcutaneously, Aquamid acts as a tissue substitute, occupying extracellular space and augmenting skin and underlying tissue depleted due to aging.

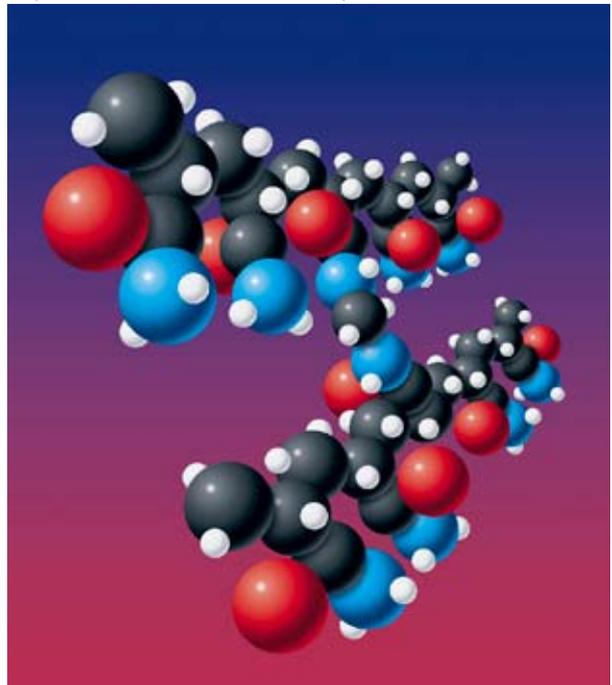
Produced using Contura's proprietary hydrogel technology, Aquamid is composed of 97.5% non-pyrogenic water and 2.5% cross-linked polyacrylamide (Fig. 1), which results in a unique combination of elasticity, viscosity, and stability, tailored especially for soft-tissue enhancement. Polyacrylamide vary substantially in their properties, and Aquamid contains the highest water content and least dry matter of any polyacrylamide gel used for soft tissue augmentation.

Effect of Aquamid in Tissue

Because Aquamid is hydrophilic, its water component is in dynamic equilibrium with the surrounding tissue,^{1,2} while the cross-linked polymer backbone ensures stability of the gel. Aquamid maintains its size and shape and does not migrate within the tissue after injection due to its large molecular size, high cohesive properties^{1,3,4} and the fact that there is vessel in-growth from surrounding tissue.⁵ (Fig. 2) Polyacrylamide gel is fully resistant to biodegradation,⁶⁻⁸ as has been demonstrated in several histology studies, even as long as 10 years after injection.^{5,9-11} (Fig. 3)

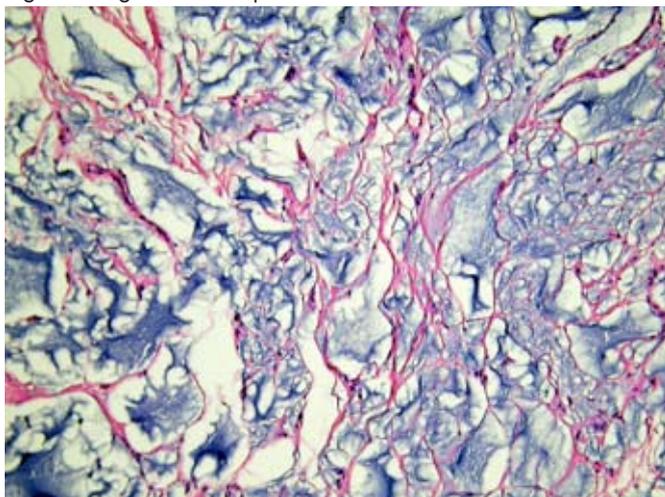
The hydrogel is homogeneous, containing no microparticles or microspheres. Aquamid's filling effect relies

Fig. 1: Chemical structure of Aquamid



A model of the chemical structure of Aquamid (polyacrylamide hydrogel) reveals cross-links created by covalent bonds and polymer backbone that, together, form a highly stable and large molecule.

Fig. 2: Integration of Aquamid in host tissue



In-growth of connective tissue in Aquamid 14 months after injection is apparent by the presence of fine, fibrous strands of connective tissue (pink) throughout the hydrogel (blue).

re-injection, with the increased risk of bruising, infection, itching, hematoma, and other possible effects that may occur with each injection.

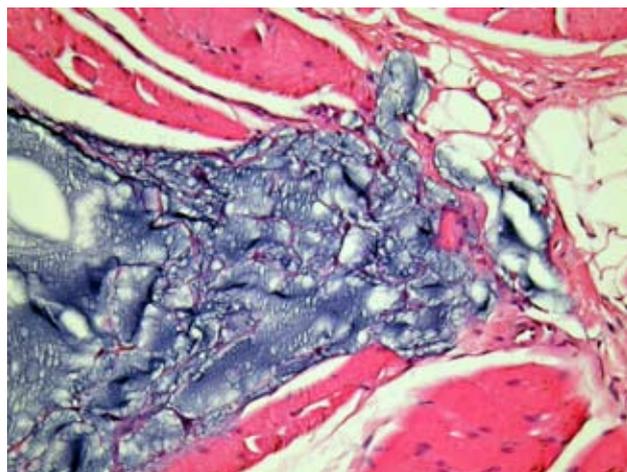
Aquamid does not migrate, but can be moved slightly along natural boundaries within the tissue, if pressure is placed directly on the injected area prior to the establishment of a sufficient vessel-bearing network. The ability to move Aquamid in this way lasts for about only 48 hours.

Injection of any foreign substance into the body will elicit a foreign-body response, but because Aquamid is hydrophilic and without micro particles, this response is mild. Biopsies have shown a weak reaction at six months and little to no reaction within 24 months after the injection.^{1, 8, 10-12} Unlike some products derived from animal sources, Aquamid contains no animal protein and thus avoids the need for skin testing or the risk of allergic reactions.¹³

After Aquamid is injected, macrophages enter the gel, and a vessel-bearing network starts to form in which collagen-producing fibroblasts gradually replace the macrophages.¹ The polymer backbone of Aquamid is cross-linked with covalent bonds, thus creating

exclusively on adding volume from the gel itself, unlike other tissue fillers (e.g. particle-based fillers or silicone) that often depend on an excessive foreign-body response to achieve the desired effect.^{3, 5, 11} For these other fillers, the full effect is not apparent for several weeks, so the aesthetic result is difficult to predict. In addition, superimposed inflammation can increase the likelihood of firm nodule formation and tissue hardening. Aquamid provides an aesthetic effect by the injected volume only, and the result is immediate with no need for return office visits, once the desired aesthetic effect is achieved. As Aquamid is not resorbed, there is no need for periodic

Fig. 3: Aquamid in human tissue four years after injection into the chin



Histologic evaluation of Aquamid injected into the chin four years previously shows no sign of degradation and is well integrated with surrounding tissue, as evidenced by the presence of fine strands of tissue (pink) throughout the Aquamid hydrogel (blue).

a very large molecule with infinite molecular

size. This is thought to prevent phagocytosis by macrophages and therefore also active migration. Microscopic examination of tissue augmented with Aquamid up to eight years previously has shown that the vessel network is unchanged and that the gel substitutes for the extracellular tissue matrix.^{5,9} It is postulated that the high water-exchange capacity of Aquamid prevents formation of a biofilm, which may explain why late inflammatory nodules are not seen after injection with Aquamid but are seen with fillers like silicone gel and combination gels (particle-based fillers).^{10, 11} Granuloma formation, hardness, and calcification without infection have not been reported for Aquamid.^{1, 10, 14} (Figure 4).

Injection Technique

Good injection technique is essential not only for optimal aesthetic results, but also to minimize the risk of infection, which can occur with injection of any soft-tissue filler. Strict aseptic procedure must be followed to avoid contamination. It is also important to ensure that patients are appropriate candidates and not affected by a condition that may increase risk of infection or otherwise negatively affect outcome.

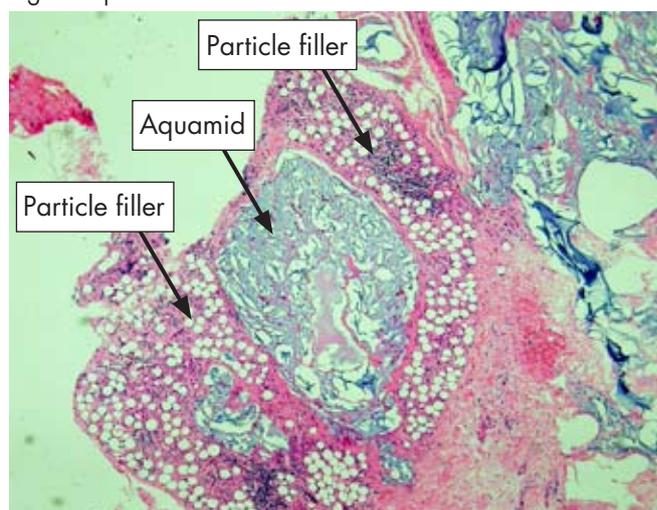
Aquamid must be injected subcutaneously – never intra-dermally – always injecting the gel while withdrawing the needle, following a retrograde linear tracing injection technique. Because the injected gel volume does not decrease after injection and is difficult to remove after injection, overcorrection must be avoided. The gel can be removed by aspiration or through fine incision by applying pressure to the tissue within the first months after injection. It cannot, however, be removed completely.

Aesthetic Results with Aquamid

Physician and patient satisfaction with the aesthetic outcome achieved with Aquamid is as important as being assured of its safety and biocompatibility. More than 1000 patients treated with Aquamid (or a precursor formulation in use prior to 2000, when the formulation and manufacturing process were further developed by Contura) have been evaluated in more than 10 clinical studies conducted in Europe, Australia, and Latin America.^{9-12, 14-21} Overall, in studies evaluating the aesthetic effect of Aquamid in facial soft-tissue enhancement, both investigators and patients have judged the aesthetic outcome positively.^{3, 14-16}

In a pilot study of 59 patients, 56 of whom were treated with Aquamid for aesthetic correction, 100% were satisfied with the result at the nine-month follow up.³ Breiting et al. evaluated 104 patients who underwent

Fig.4: Aquamid vs. Particle Filler



Particle filler elicits an inflammatory response and fibrosis, whereas Aquamid allows formation of a fine, fibrous network, with no inflammation or fibrosis.

facial enhancement with polyacrylamide hydrogel a few months to as long as nine years previously.

Ninety-nine percent of the investigators assessed treatment outcome as being good (21%) or very good (78%), with 1% assessing outcome as unsuccessful.¹⁵ All patients (100%) assessed treatment outcome as good (22%) or very good (78%). Their positive experience was affirmed with 89% of patients indicating they would accept injection of polyacrylamide hydrogel if undergoing another facial correction.

In the first prospective clinical trial of Aquamid in facial soft-tissue enhancement, 251 patients were initially enrolled (Table 1). At each assessment period (28 days, 3, 6, 12, 24, 36, 48, and 60 months post injection), both investigators and patients rated their assessment of the aesthetic results with Aquamid in the two highest categories of the rating scales given to them.^{14, 16, 27, 28} In these assessments, investigators rated more than 90% of the results as good or very good. During the same time period, more than 90% of patients judged the results to be satisfactory or very satisfactory.

Table 1: Five year clinical study follow-up data

	1 year	2 year	4 year	5 year
Number of patients	228	101	81	116
Patient satisfaction	93%	91%	>90%	>90%
Investigator assessment	97%	92%	>90%	>90%

Summary of evaluation of the long-term aesthetic results of facial cosmetic treatments with Aquamid.^{14, 16, 27, 28}

Several studies have explored the value of Aquamid in the correction of facial lipoatrophy in patients with HIV-associated lipoatrophy.^{12, 17-19} In each of these studies, Aquamid was judged as providing effective and aesthetically satisfying facial contour correction, and also was seen as significantly improving quality of life due to the psychological and social benefits associated with improved facial appearance. In a study of 138 patients comparing Aquamid with autologous fat and polyactic acid, a much smaller proportion of patients in the Aquamid group than in the autologous fat and polyactic acid groups (8% vs. 88% and 85%, respectively) required a new round of injections 48 weeks after the initial procedure. This finding led investigators to suggest a significant potential cost saving with Aquamid.¹⁹ The lack of significant side effects at the 24-month follow-up among 31 HIV-infected patients treated with Aquamid was noted as a significant positive finding by another investigator. Aquamid provided a minimally invasive, effective, long-lasting facial contour correction that significantly improved the quality of life in human immunodeficiency virus-infected patients.¹⁷

Safety Profile

Polyacrylamide has a long history of use in medical products and in the purification of foods. It is used in the production of soft contact lenses and intraocular lenses,^{1, 22} as an ingredient for microencapsulated gelspheres used in drug delivery,²³⁻²⁵ in food-packaging products,⁶ and as a flocculating agent in

sedimentation and water purification.^{6, 26} Polyacrylamide gel is also used in the clarification of beet and cane sugar juices.⁶

The effects of Aquamid have been investigated in vitro and in vivo, as well as in clinical studies. The in vitro and in vivo studies found that Aquamid was well tolerated, with no systemic or local complications.^{1, 4} No inflammatory reaction was noted, and a minimal foreign body reaction was revealed. In addition, these studies found no change in consistency or volume of the polyacrylamide hydrogel over time. Testing for presence of acrylamide monomer (a starting ingredient in the polymerization process) identified a very low concentration of acrylamide monomer, providing a large margin of safety. Based on a 10-ml Aquamid implant* in a 30-year old adult, the average lifetime daily dose was calculated to be 10,000 times lower than the worldwide acceptable daily dose of acrylamide. ^{Data on file}

In clinical studies, the majority of adverse events (AEs) occurring with Aquamid were transient local reactions that typically resolved spontaneously within one to two weeks. Effects seen within the first day or two after injection included slight redness, transit swelling, hematoma formation, itching and moderate pain within the treatment area.^{3, 11, 16} These findings were confirmed in a clinical study with 5-year follow-up.²⁸

Infections in connection with the injection procedure occur with any tissue filler. There is an early risk of infection with Aquamid until the fibrous network has formed. These infections can result when bacteria that are typically non-pathogenic as part of the normal skin flora become pathogenic in an anaerobic environment. Because bacterial growth within the gel is slow, symptoms of infection, such as tingling, redness and swelling, do not usually appear until one to two weeks after injection. These infections respond to antibiotic treatment, whereas corticosteroids and large doses of NSAIDs must not be used, as they aggravate the condition by masking infection symptoms and lowering immune response.¹⁰

While Contura has encouraged reporting of any adverse events that may be related to Aquamid injection, there has been a very low incidence (<0.1%) of spontaneously reported adverse events based on 300,000 injections. Of the 40,000 individuals who received Aquamid injections between May of 2001 (when Aquamid received its first approval) and September of 2003, there were 55 who reported adverse events. In Christensen's analysis of these reports, she found that for AEs presenting as nodules or swellings later than one week and less than one year after injection, treatment with a broad-spectrum antibiotic was effective in resolving the problem.¹⁰ Apart from infections erroneously treated with steroids, large doses of NSAIDs or weak antibiotics, no long-term adverse reactions have been reported with Aquamid. In contrast, long-term adverse events have been seen with silicone gel and combination gels.¹¹

* Approximately 2 ml of Aquamid are injected for a typical aesthetic correction

Ongoing Clinical Evaluations

The five-year follow up data on 116 patients injected with Aquamid in Europe has been presented at the American Society of Aesthetic Plastic Surgery (ASAPS) annual meeting in May of 2008.²⁸ Data on the experience of patients 12 and 24 months after the first injection were published in 2005 and 2006 in *Plastic and Reconstructive Surgery*.^{14, 16}

In the United States, Aquamid is currently being evaluated in a double-blind, multicenter trial comparing the effectiveness of Aquamid with that of Restylane® for the aesthetic treatment of facial wrinkles/folds. This trial, evaluating 315 patients at 13 different centers, includes both plastic surgeons and dermatologists as investigators. Data from this study will be submitted to support the PMA application for Aquamid.

About Contura

Contura is a medical technology company based in Denmark that develops and commercializes soft tissue fillers. Contura's products – Aquamid® for facial contouring and Bulkamid® for the treatment of female urinary incontinence – are manufactured using the company's patented polyacrylamide technology, which enables optimization of the hydrogel's visco-elastic properties for specific medical indications. Both Aquamid and Bulkamid are on the market in a number of countries outside of the United States. Aquamid is sold through a network of local distributors in 40 countries. Ethicon Inc., a Johnson & Johnson company, holds the exclusive worldwide distribution rights for Bulkamid.

Clinical trials evaluating Aquamid and Bulkamid are ongoing in the United States. Data from these trials will be used to support PMA applications for these products.

Contura's products are developed, manufactured and tested in Denmark in compliance with the European regulatory requirements for medical devices.

www.contura.com

www.aquamid.com

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