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# Injectable Polyethylene Glycol Gel as Dermal Filler: 01 Year Clinical and Ultrasound Follow-Up

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## Abstract

Facial alterations that occur with aging are result of combined effects of soft tissue atrophy with loss of facial volume, gravitational factor and decrease of elastic tissue. In order to minimize these alterations, minimally invasive procedures such as cutaneous filling have been gaining space in clinical practice. In 2008, Scientech Corporation - Italia introduced hydrogel of polyethylene glycol (PEG) REMAKE® as cutaneous filler. This prospective study was developed to prove the effectiveness, safety and durability over the 12 months after the application of PEG hydrogel, commercialized under the name of REMAKE®. 40 female volunteers were included, between 30 and 60 years, with signs of malar region volume loss between 2 and 3 (Raspaldo's classification) and Nasogenian furrow accentuation, with score between 2 and 3 (Day and collaborators' classification). No patient had carried out procedures of temporary filling for 1 year or permanent filling at any time. Objective parameters always show the scale of the improvement and an evaluation was selected through ultrasound exams and surface scan for evaluation of size and depth of wrinkles improvement. Evaluations by the US were carried out for 30, 120 and 360 days of product use, in a pilot group of 18 patients randomly selected to measure the product in the application plan and numerically assess alterations of volume (absorption/migration). Its durability of up to 01 year after application is proved when no significant reduction.

**Keywords:** Facial fillers; Aesthetic procedures; Polyethylene glycol

## Introduction

Facial changes that come with age are the result of the combined effects of soft tissue atrophy and loss of facial volume, gravitational factor and reduction of elastic tissue with presence of skin flaccidity, formation of rhytides, loss of muscle tone and progressive bone resorption [1-3]. These changes are potentiated by tobaccoism, more exposure to sun, nutritional factors, among others.

The face subcutaneous tissue is formed by individual fat compartments that can gain or lose volume in different times of life, with different speeds [4]. A young face is characterized by a gradual transition among these compartments. The change in the face contour during aging originates, partially, in the alterations occurring in these compartments, due to volume loss or gain or even a repositioning of these compartments, causing atrophies (lipoatrophies) or hypertrophies ("buccula") and rhytides. That explains why the different face areas age differently [4].

In order to minimize the different facial dystrophies, the minimally invasive procedures – like dermal fillers [1-3] have been gaining ground in the medical practice, both for its practicality and for the high safety level of the products when correctly applied.

The restoration of facial volume with fillers is indicated in facial aging treatment, as well as in facial traumas, acne scars, genetic lipoatrophies or lipoatrophies associated to antiretroviral treatment in Acquired Immunodeficiency Syndrome [1-3].

The procedure is ambulatory, minimally invasive, well tolerated by patients, once it can be made with previous use of topic anesthetic or blocking of sensory nerves. The level of correction is predictable and results are immediate [1-3].

In 2008, Scientech Corporation – Italy, introduced the polyethylene glycol hydrogel (PEG) REMAKE®, as a dermal filler [5]. Reticulate PEG hydrogels are hydrophilic polymeric networks that absorb over 1,000 times its dry weight in water and are employed to restore soft tissues (tissue engineering), for presenting similarities with these tissues physical properties [6-8]. It is biocompatible [5], stable and degraded by hydrolysis of ester bonds, depending on the temperature and pH [5-7].

Its use is indicated for restoration of soft tissues, restoration of facial and hands volume, depressed and distensible scars, correction of deep grooves and rhytides [5].

The hydrogel is composed of 4% PEG and 96% of and non-pyrogenic water. It is a synthetic, colorless and homogeneous gel, non-mutagenic and fully degraded, in 24 months in average, after its implantation [5].

This prospective study was developed to prove its efficacy, safety and durability in the 12 months following application of PEG hydrogel, commercialized as REMAKE®.

## Ethical Aspects

The study protocol and the free and informed consent, as well as the whole safety dossier of the product assessed was approved by São Francisco University ethics committee for research under number 481618, as indicated by the system "Plataforma Brasil" maintained by the National Health Agency, Brazilian responsible federal agency.

## Material and Method

The study included 40 volunteers (women) between 30 and 60 years old, with signs of volume loss in malar region, between 2 and 3, according to Raspaldo [3] clinical classification and nasolabial fold accentuation, with score between 2 and 3, according to clinical classification by Day and collaborators [9]. None of the patients had gone under temporary dermal filler procedures for 1 year or permanent dermal filler at any moment. Patients with diseases in the connective tissue, uncontrolled, chronic pathologies, autoimmune disease or using immunobiologicals were not included in this study.

The product REMAKE® was applied after skin antisepsis and local anesthesia with topic cream anesthetic, 30 minutes before the procedure associated to the injection of an anesthetic wheal (lidocain without vasoconstrictor agent) in the skin to introduce the micro-cannula or anesthetic blocking of infraorbital nerve. The application was made in subcutaneous plan, with the micro-cannula (model SOFTFIL 18G x 70) at 1 cm from the labial commissure, by means a punctiform orifice carried out with 18G needle, in cheek zygomatic and medial esthetic sub-units (orbital and medial lateral fat of the cheek), and in the nasolabial fold, below the skin. The method for injection of REMAKE® product was performed in "bolus" and/or through threading technique, both being ambulatory procedures.

Then the patient was advised to make cold compresses in the first 24-48 hours and to avoid touching the area, and also not to take medications with anticoagulant effect.

All patients were instructed to return for visits in the following intervals: 07 (seven) days (V3), 15 (fifteen) days (V4), 30 (thirty) days (V5), 120 (one hundred and twenty) days (V6), and 360 (three hundred and sixty) days. During the visits, clinical subjective assessments were carried out, according to Narins [10] 5-point global improvement scale. Photographic assessments were performed starting from photos standardized by 2 dermatologists with 10 or more years of experience in the technique; ultrasound assessments, intended to assess the product position and volume and cutaneous relief, with ultrasound equipment (model Mysono U6 with 12 MHz transductor); and, finally, assessments of cutaneous micro-relief were performed using the optical equipment Primos Lite (GFMesstechnik GmbH), in order to assess cutaneous relief (fine and deep wrinkles and grooves).

The investigator physician who applied the product was instructed to classify the degree of difficulty found to perform the procedure in each patient, in a scale from 01-10, and also whether it was observed the presence of lumps after application; in case of a positive answer, describe the measures taken to reduce them.

The patients were also inquired, soon after the procedure, about the degree of discomfort/pain during the procedure, in a 0-10 scale.

A PATIENT JOURNAL was provided to patients on the application day, where they recorded how were their first 7 days following the application and whether any medications was used during this period.

## Results

| Global Aesthetic Improvement | Visit 3 (7d) | | Visit 4 (15d) | | Visit 5 (30d) | | Visit 6 (120d) | | Visit 8 (360d) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Inv 1 | Inv 2 | Inv 1 | Inv 2 | Inv 1 | Inv 2 | Inv 1 | Inv 2 | Inv 1 | Inv 2 |
| 1=Very much improved | 28 | 26 | 30 | 29 | 24 | 24 | 18 | 17 | 3 | 2 |
| 2=Moderately improved | 4 | 6 | 8 | 9 | 7 | 8 | 15 | 16 | 15 | 7 |
| 3=Somewhat improved | 7 | 8 | 1 | 1 | 6 | 5 | 1 | 1 | 8 | 7 |
| 4=No change | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 13 |
| 5=Worse | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| N | 40 | 40 | 39 | 39 | 37 | 37 | 34 | 34 | 30 | 30 |
| Average | 1.53 | 1.55 | 1.26 | 1.28 | 1.51 | 1.49 | 1.5 | 1.53 | 2.43 | 3.13 |
| Wilcoxon* | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.001 |

**Table 1:** Showing Inv. (investigator); N (population sample). *Confidence interval - 95%.

## Discussion

Polyethylene glycol (PEG) is a polymer composed of repeated units of ethylene glycol with different molecular weights, and distinct purposes [6]. It has several chemical properties, which makes it useful in different areas, like biotechnology and medicine [6,7]. In medicine, it is topically used in cosmetics, suppositories, and for oral use in laxatives and tablets. It is also injectable in solutions for restoration of cartilaginous tissue [11] and subcutaneous tissue [12], due to its innocuousness and biodegradability [13].

## Photographic assessment

PEG hydrogel degradation occurs by means of hydrolysis of sterile connections [5,6,8]. This process is initiated by the action of some non-specific enzymes released by macrophages and fibroblasts of the tissue circumjacent to the hydrogel, like esterases, oxidases and reductases, which are eliminated through the lymphatic system. The PEG hydrogel degradation process is not toxic, since it does not release any toxic residue (residual monomers) or free radicals [5-7].


**Figure 1:** Showing Photographic assessment in visits 03 (7 days); V4 (15 days) V5 (30 days); V6 (120 days) and V8 (360 days).

In the last 30 years, synthetic forms of skin fillers have been developed and used to correct disorders in orthopedics, rheumatology and ophthalmology areas. More recently, in the last decade, they have been used in urology for vesicoureteral reflux and in dermatology and plastic surgery for aesthetic filling or face repair [14,15].

Like other several works found in the indexed literature, the subjective parameter was used to observe improvement in treated facial areas by means of photographic observations by two observers, of pre and post treatment situations and the averages of marks assigned by investigators in all experimental intervals were statistically assessed (Wilcoxon test), as show in Table 1. A statistically significant improvement ($p<0.001$) was observed in Global Aesthetic Improvement item for all experimental intervals, based on the assessment by both investigators. A statistically significant improvement ($p<0.05$, Wilcoxon) was observed in the assessment of zigomatic region volume loss starting from visit 03, in 07 days, which was kept in all experimental intervals based on both investigators' assessment. A statistically significant improvement was observed ($p<0.001$, Wilcoxon) in Wrinkles intensity item starting from visit 03, in 07 days, which was maintained in all experimental intervals based on both investigators' assessment, as reported in works.

| Ultrasound | Area ($cm^2$) | | | Length (cm) | | |
|---|---|---|---|---|---|---|
| | V5(30d) | V6(120d) | V8(360d) | V5(30d) | V6(120d) | V8(360d) |
| Average | 0.22 | 0.19 | 0.16 | 2.71 | 2.67 | 2.3 |
| Variation | - | -11% | -25% | - | -1% | -15% |
| Student T Test | - | 0.448 | 0.116 | - | 0.907 | 0.208 |

**Table 2:** Average of measures obtained in initial visit, at 30 days (v5) 120 days (v6) and 360 days (v8).

However, objective parameters always show the improvement magnitude and the assessment was selected by ultrasound exams and superficial scan to assess wrinkles size and depth improvement.

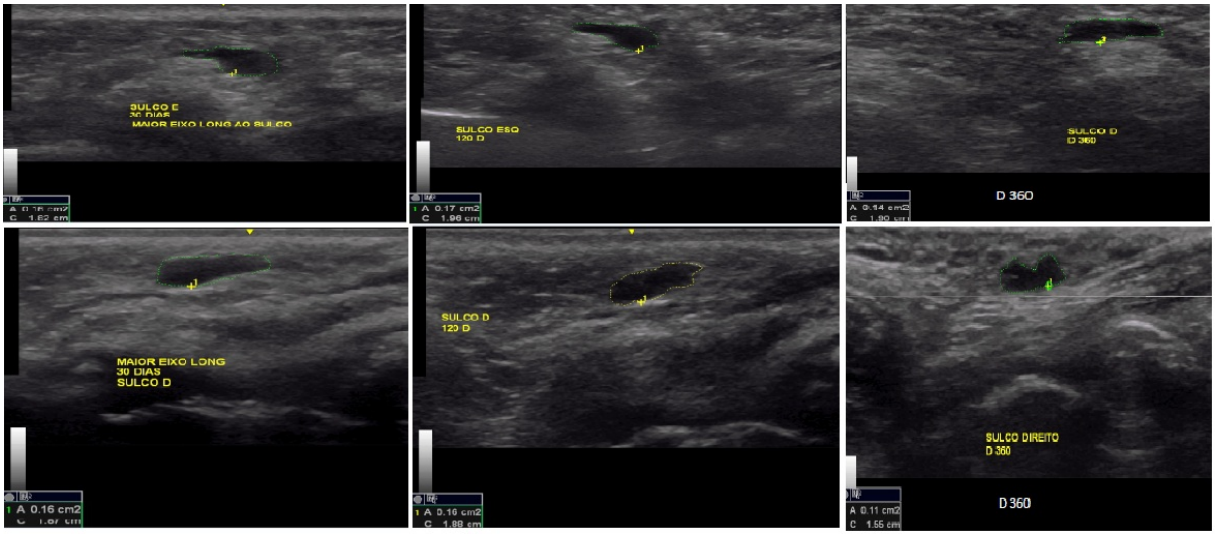
From the 40 patients included, 30 concluded the study. No adverse effect resulting from the product application or permanence was observed in visits. No patient reported any adverse effect during the study period.

The product was considered easy or very easy to apply in 100% of the patients. The presence of lumps was observed in 3 patients, which fully receded with hand massage, performed during the intervention.

With regard to pain or discomfort during application, from the 40 patients assessed, 25 (62.5%) reported total absence of any symptom; 10 patients reported almost no discomfort or pain (25%) and 4 patients (10%) reported light pain/discomfort; 1 (2.5%) reported moderate discomfort.

## Ultrasound

The assessments were performed at 30, 120 and 360 days of use, in a pilot group of 18 patients randomly selected, to measure the product in the application plan, and numerically assess volume alterations (absorption/migration) (Table 2).




**Figures 2 and 3:** Ultrasound assessment in visits v5 (30 days) and V6 (120 days) in two patients assessed (n=18). The maintenance of the product in the application location during the 30 day period is observed (Left Groove / 30 days / larger axis / Left Groove / 120 days / Left Groove / 360 days / Right Groove / 30 days / larger axis / Right Groove/120 days / Right Groove/360 days).

The ultrasound showed to be an appropriate tool to assess the product behavior in vivo, since it allows its localization and measurement, in addition to being a painless and non-invasive method [16-27].

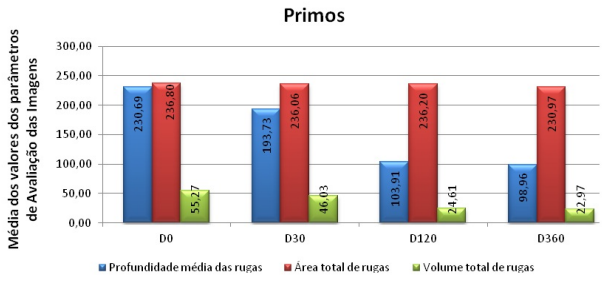



**Figure 4:** Assessment of cutaneous relief parameters with Primos ® equipment: lower averages mean smaller relief.

Its durability in up to 01 year after application is demonstrated because no significant reduction in the volume deposited in the procedure location was observed. The application was also comfortable to the physician, being assessed as easy or very easy to the physician with experience in micro-cannula technique (volumizing) or needle (groove filling). It was observed that both area and length occupied by the product have suffered a slight reduction, with no statistically significant differences. So, we can conclude that the product remains practically unchanged at the location after 120 and 360 days. Figure 2 and 3 illustrates the images collected in the different times.

The absence of nodular or granulomatous formations or any undesirable effect sign on the implant region confirms its high biocompatibility.

## Assessment of cutaneous relief with Primos equipment

The cutaneous relief parameters assessed were: wrinkles average depth, total area, and total volume were measured by Primos equipment in $mm^2$. Averages reduction means improvement of parameters (skin with lower relief), as shown in Figure 4.

The use of this type of scanner helps to measure alterations observed on skin relief, the degree of correction with PEG hydrogel can be quantified and the result maintenance after the procedure.

A progressive reduction in wrinkles average depth, total area and total volume was observed in the assessment intervals: after 30, 120 and 360 days, and this reduction is statistically significant ($p<0.05$) for average depth and total volume of wrinkles after 120 and 360 days.

The PEG hydrogel 4% assessed in the present study showed a tolerance profile compatible with other filling products, like hyaluronic acid [16], both in the immediate post procedure and throughout the 360 days of assessment; however its use is shown to be more versatile, since the same product can be applied on different plans [15,16]. Its

permanence in the application location has shown very low level of absorption, keeping significant clinical improvement [17].

The instrumental assessments employed in this work (ultrasound and Primos®) showed to be appropriate for assessing more precisely and sensitively the presence of the filler, as well as the duration and correlation with clinical efficacy.

## Conclusion

The PEG hydrogel 4% (REMAKE®) was well tolerated and efficient in the improvement of aging signs associated to loss of volume and presence of facial rhytides, showing significang duration in up to 01 year after one single application.

In the ultrasound assessment, the presence of the product was kept without significant losses, thus keeping its clinical effect.

The PEG hydrogel 4% (REMAKE®) has also shown to be safe for use; no reaction was observe dor referred to on occurrences of adverse effects or even discomfort feeling after 360 days from the filler application, and no migration was detected in the ultrasound assessment. The level of satisfaction of patients was kept during the period analyzed.

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