



Nuffield Health Brighton Hospital
Warren Road, Woodingdean, Brighton BN2 6DX
(T) 01273 621 144
(F) 01273 690 670
(E) info@andrewyelland.com
www.andrewyelland.com

Macrolane™ VRF

General procedure information

MACROLANE VRF is a NASHA™ gel for volume restoration and contouring of body surfaces.

What is NASHA™?

Stabilized, non-animal hyaluronic acid (NASHA) is unique to Q-MED. Naturally-occurring hyaluronic acid (HA) undergoes a process where less than one percent is stabilized to form a permanent three-dimensional HA network without damaging the original chemical structure.

This stabilization process produces a biologically degradable NASHA gel that carries minimal risk of allergic reaction or transmission of infectious substances and enables a longer durability.

What does VRF stand for?

VRF stands for Volume Restoration Factor. The VRF gives guidance to physicians on selecting a MACROLANE VRF product according to the fill volume required.

This is a tissue tailored concept for body aesthetics to meet the needs of individual patients.

What is the difference between MACROLANE VRF and RESTYLANE®?

MACROLANE VRF is a thicker gel used for body aesthetics rather than facial aesthetics. It therefore creates greater volume with a slower absorption.

Why was MACROLANE VRF developed?

For decades, plastic surgeons have injected endogenous fat and other products to restore volume in areas of the body.

Such procedures can be time-consuming, unpredictable and involve long recovery periods due to bruising and swelling.

As both experience and confidence in the efficacy and safety of NASHA have grown, there has been increasing interest in the development of NASHA-based products for volumetric restoration in other areas of the body.

MACROLANE VRF is the first hyaluronic acid product developed for this purpose — naturally restoring or adding volume to the body, providing instant, long-lasting results without invasive surgery and the associated downtime time or risks.

How is MACROLANE VRF used?

Macrolane has been specifically developed for volume restoration and contouring of body surfaces.

Macrolane VRF is used specifically in areas such as

- concavities caused by liposuction
- trauma and surgical scars
- buttock shaping
- calves
- breast shaping

For what indications is MACROLANE VRF approved for use?

MACROLANE VRF is currently approved for volume restoration and contouring of body surfaces including the breast.

How is the treatment performed?

General anaesthesia is not required and the procedure can be carried out in a clean 'office' environment similar to minor surgery, only requiring between 30 and 90 minutes depending on the site and quantity of gel injected.

Who can use MACROLANE VRF?

All procedures are carried out by surgeons who have similar experience to fat injections or similar. However, the purchase of MACROLANE VRF is restricted to those surgeons who have undergone specific MACROLANE VRF training for either body contouring or breast shaping, as provided by Q-MED. Following completion of the training, surgeons will be issued with a certificate, allowing them to practise treatment appropriately.

How long does MACROLANE VRF last?

MACROLANE VRF is intended to last for 12-18 months.⁷ Each individual treatment programme will include a yearly top-up as required to maintain patient expectation.

Have there been any clinical trials with MACROLANE VRF?

There have been two pilot studies of MACROLANE to date, both involving the original formulation of MACROLANE that has since been refined and enhanced to become MACROLANE VRF. The first was a small study of the use of MACROLANE in augmentation of the female breast. A high level of improvement (97 percent improvement at 3 months) and high level of patient satisfaction (95 percent satisfaction at 3 months) was reported.

The use of MACROLANE in patients with concave body deformities has also been researched. Patients with asymmetry following liposuction, surgical scars or post-traumatic fat atrophy were all treated with MACROLANE. More than 80 percent of patients reported improvements at 3 months and persistent improvement was seen at 12 months.

A study in Japan involving 1100 patients who underwent breast augmentation with NASHA gels demonstrated the safety and efficacy of NASHA.¹¹ The authors reported non-surgical mammary augmentation with NASHA to be an easy and minimally invasive procedure, demonstrating favourable results.

Are there more clinical trials planned?

Q-MED is investing in ongoing clinical studies both globally and in the UK to specifically evaluate the safety, efficacy and new injection techniques of MACROLANE VRF.

Was the safety of MACROLANE VRF assessed in clinical trials?

The safety of Q-MED products is always monitored in clinical trials. In the two pilot studies described above, there were no reports of serious adverse events. Mild and transient injection site pain, six-week inflammatory symptoms and some capsular formation were reported in the breast augmentation study. All these events resolved without medical intervention and no clinical or radiological alterations of the breast occurred.

In the second study, the majority of adverse events were reported on the day of injection and were of mild to moderate intensity. There were some reports of fever, but all were resolved within one week, either spontaneously or after treatment with antibiotics or non-steroidal anti-inflammatory drugs (NSAIDS).

In the breast augmentation study in Japan, there were few adverse events reported. In 1100 patients who underwent mammary augmentation with NASHA, there was one reported case of a subcutaneous mass or lump which was subsequently aspirated, two reported cases of infection and no reports of allergic reaction.

What are the benefits of MACROLANE VRF to patients?

Market research has shown there to be a significant number of women who would like to adjust the shape of their body in a natural, non-permanent way that does not involve the use of implants or body fat in a major surgical procedure. Many women are also very hesitant about undergoing general anaesthesia or being left with a scar. With MACROLANE VRF, the procedure is short and requires only local anaesthetic and minimal time away from work or after-work activities.



Nuffield Health Brighton Hospital
Warren Road, Woodingdean, Brighton BN2 6DX
(T) 01273 621 144
(F) 01273 690 670
(E) info@andrewyelland.com
www.andrewyelland.com

When and how will Q-Med officially launch MACROLANE VRF?

MACROLANE VRF is currently available to selectively trained plastic and aesthetic surgeons; however, the launch of MACROLANE VRF is planned for IMCAS (International Master Course on Ageing Skin) in January 2008.

What will a treatment with MACROLANE VRF cost?

The consumer: The treatment cost is dependant on the experience of the surgeon and the demographic area.

The physician: The cost of MACROLANE VRF is dependant on the amount of product used per treatment session. Surgeons should discuss this in more detail with a Q-MED representative.

Are there risks involved with MACROLANE VRF?

There are risks with all medical procedures. MACROLANE VRF is produced using NASHA technology which has been used in more than 7 million treatments in 70 countries worldwide with excellent results and minimal adverse effects.

Can Macrolane cause breast cancer?

Macrolane™ VRF 20/30 are NASHA™ gels and as such consist of stabilized hyaluronic acid (20 mg /ml gel, i.e. ca. 2 % vol /vol) and 98 % water. Due to the only very slight (< 1%) stabilization of the hyaluronic acid in the NASHA gels, the hyaluronic acid therein is practically the same as naturally occurring hyaluronic acid present in joints and tissues in the human body. Therefore the NASHA implants are fully biocompatible and recognized by natural hyaluronic acid degrading enzymes (such as hyaluronidases).

The onset of cancer, including breast cancer, is a long sequentially occurring multi-step process, involving both endogenous (changes in our genetic material) and exogenous factors (for example our life-style).

The steps a normal cell has to pass through to become a cancer cell are:

Initiation (for example through mutation of our genetic material (DNA) induced by ionizing radiation or by the action of toxic chemicals in the environment, and /or through altered cell to cell communication mechanisms which controls cell division and proliferation).

Promotion, the second step, whereby the cells containing mutated genetic material are stimulated for cell division and proliferation, thus passing the damage to newly formed cells. Also a process of selection favouring the mutated cells is active during this step. The promotion step leads to the formation of benign tumours. The latter are considered as a pre-step for the formation of malign tumours (cancer).

Progression, involving the transformation of benign tumours into malignancy (cancer). This step involves additional mutations, activation of oncogenes and immunosuppression which acting concurrently lead to the formation of a tumour and the onset of metastasis.

The hyaluronic acid molecules in the gel network of Macrolane VRF and all the NASHA gels are large polymeric chains ($M_w > 1$ million Daltons) similar to the natural hyaluronic acid polymers present in the skin to give structure and volume. These large polymers are not capable to induce mutations in the genetic material and therefore can not and do not initiate the cancer process. If the contrary were true then we would all suffer of cancer in the skin and other organs, since hyaluronic acid is ubiquitously present in the body.

If we consider hyaluronic acid/NASHA gels/Macrolane VRF gels alone the hyaluronic acid present in the gels cannot mutate/ change the genetic material in cells; no initiation means no promotion and no progression. This means: no cancer.

Can cancer develop after Macrolane injection?

The amount of hyaluronic acid injected through the Macrolane VRF treatment is extremely small (2 % of the implanted volume) compared with the natural concentration of hyaluronic acid in the skin. Besides, the hyaluronic acid molecules present in the NASHA gels are bound to each other and confined to the gel network and therefore not available to exert any biological activity. In order to participate in any biological process, including cancer, the hyaluronic acid molecules would have to leave the gel network in substantial amounts.

The degradation process of the NASHA gels is very slow (several months) compared to the degradation rate of natural hyaluronic acid polymers present in the skin (half-life: 16 h in the dermis) or in the circulation (half-life: 3 – 4 minutes). Therefore, the very small amount of free hyaluronic acid leaving the gel network every day due to the gel degradation process, would be diluted by several orders of magnitude by the amount of hyaluronic acid naturally present in the skin and thereafter subjected to biodegradation and turn-over.

Even if some hyaluronic acid molecules freed from the NASHA gel network would survive the dilution effect described above, they would have to compete with millions of naturally occurring hyaluronic acid molecules present in the skin, for migration through the extracellular matrix, attachment to hyaluronic acid receptors (for example CD44) present on the cellular membranes to exert any biological effect.

Considering the whole picture involved in the cancer process, the amount of hyaluronic acid injected through the implants, the amount of hyaluronic acid present in the skin, and the turn-over rate of hyaluronic acid in skin, the probability of the participation of hyaluronic acid molecules originating from NASHA gels/Macrolane VRF gels in the development of breast cancer or any other is practically non-existent.

This conclusion is based on an exhaustive review of the pertinent literature prior to the preparation of a Risk Analysis on the Use of NASHA implants for the augmentation of the female breast (Q-Med's internal document), which was submitted to the Notified Body (KEMA, The Netherlands) for approval and to be granted the CE-label.



Nuffield Health Brighton Hospital
Warren Road, Woodingdean, Brighton BN2 6DX
(T) 01273 621 144
(F) 01273 690 670
(E) info@andrewyelland.com
www.andrewyelland.com

If cancer develops after the injection of the gel implants it would be caused by factors other than the Macrolane VRF treatment.

How important is MACROLANE VRF to Q-Med?

Q-MED sees a definite role for a minimally invasive and safe product such as MACROLANE VRF for those women and men who are resistant to undergoing a surgical procedure under general anaesthesia.

When will MACROLANE VRF be approved for breast enhancement?

Today Macrolane VRF is approved for volume restoration and contouring of body surfaces including breast shaping in both men and women.

Are Q-MED products already being used for breast enhancement?

Yes, many physicians see advantages of using Macrolane for breast shaping as opposed to more invasive techniques.