SUMMARY OF THE MEDICAL DEVICE: MIGSPRAY

Code name: MIGSPRAY

Batch code: MIG

Indication: Osmotic liquid bandage to clean the nasal mucosa for preventive treatment of migraine.

Introduction: Bandages are necessary to protect any damaged surface of the body. They are used as a physical barrier to keep environmental contaminants out and to minimize contaminants on the damaged surface. Almost all the currently available bandages are made up of cotton or polymeric substances which are flexible but solid. Therefore, such bandages remain on the surface without being in direct contact with the injured surface and cannot be applied on the hidden body orifices such as the mouth & nasal cavities, genital orifices, surface of eyes or deep wounds. Such cavities are often humid and exudate liquid where a liquid bandage cannot remain long-lastingly on these surfaces.

It is well known that the nasal mucosa is the most sensitive and delicate organ in our body. It is highly vascularized and a key organ manifesting multiple internal physio-pathological interactions occurring in the body. This is the reason why nasal swabs are used to detect the presence of different disease related indicators (ex. Viruses, cytokine - proteins, enzymes). Nasal mucosa being highly sensitive, rich in multiple types of cellular receptors, and vascularized, this organ is commonly affected by physiological changes in the body.

Migraine is the 2nd most debilitating chronic medical illness in the world affecting nearly 11% world population, creating a significant socio-economic burden on the society.

The cellular and molecular mechanisms of migraine pathogenesis are not fully explained yet but now it is widely accepted that migraine headache is the result of the chain of neuro-vascular events triggered by the endogenous and exogenous factors which lead to the activation of trigemino-vascular system. The trigeminal nerve is the largest cranial nerve, having a large sensory route possessing peripheral and sensory processes. The peripheral processes divide in three sensory branches: ophthalmic, maxillary and mandibular in the nasal area. The activation of trigemino-vascular system causes release of various vasodilators, especially calcitonin gene-related peptide (CGRP) that dilate blood vessels and produce an inflammatory response causing pain. During the migraine attacks, a decreased level of the neurotransmitter serotonin and

increased levels of CGRP are observed. Triptans, the most commonly used antimigraine drug, act on trigemino-vascular system to antagonise and to bring down the elevated serum levels of key protein CGRP. Currently CGRP receptor antagonists, olcegepant and telcagepant are under consideration for antimigraine therapeutics. CGRP triggers neurogenic inflammation of the meninges during the migraine attack causes pain by the activation of the trigeminal nerve terminals. The release of neuropeptides in trigeminal nerve ending which provides the sensory stimulation of nasal cavity and sinuses, causes a number of changes in nasal mucosa such as runny nose, nasal congestion, and a feeling of fullness on face, linked to the vasodilation, vascular damage and release of CGRP mediated nasal inflammation[1]. The release of neuropeptides on nasal mucosa causes mast cell degranulation and the release of other pro-inflammatory proteins such as IL-6, IL-12, and tumor necrosis factor α (TNF-α), TSLP (Thymus stromal LymphoProtein) which produce nasal mucosa inflammation and further leakage of CGRP on the nasal mucosa due to cellular and vascular damages [2]. In the absence of any preventive and safe migraine therapy, current research is strongly directed to find a CGRP receptor antagonist peptide formulated for nasal administration to treat migraine [3]. A few clinical trials have also been conducted by associating CGRP and pro-inflammatory cytokine inhibitors but were not launched because of unknown reasons[4].

These research efforts demonstrated that inhibiting CGRP protein receptors or the protein on the nasal surface may constitute an important mechanism of preventing or treating migraine. Most of this research is directed to block CGRP receptors but blocking a receptor with a systemic anti-CGRP drug may have multiple side effects as these receptors are also present in other organs and their other physiological functions in the body are still not clearly defined. Therefore, blocking CGRP directly receptors or proteins directly may have poor benefit/risk ratio. Its also difficult to find a drug which can block specifically CGRP proteins on the nasal mucosa. Moreover, blocking CGRP alone may not prove useful as neurogenic inflammation also involve the release of multiple cerebral and nasal pro-inflammatory cytokines which may continue the inflammatory cycle. Nasal inflammation damages nasal mucosa cells, allowing free systemic entry/exit of these proteins which may lead to prolonging migraine duration[5].

Therefore, an ideal treatment should not only minimize circulating levels of CGRP but should also reduce inflammation by reducing or eliminating proinflammatory cytokines. Such a drug / device / treatment should be long-lasting (4-6h) and should not have any undesired effects which is the main drawback of many anti-migraine treatments.

We envisaged applying a device on the nasal mucosa which can attract and trap continuously the proteins present on the nasal surface. Cleaning the nasal mucosa continuously of the contaminants (pro-inflammatory cytokines, CGRP, dead cells, cellular debris, other small free-floating particles) should help reducing circulating concentrations of these proteins and thereby their consequences[1,6]. Such a device should act topically without any interactions with the underlying cells and without ant interaction with the CGRP or other receptors to avoid any side-effect.

MIGSPRAY is a viscous liquid which forms a bandage-like layer (film) on any biological surface, such as the nasal mucosa. It contains Aqua, Glycerol, Solagum AX, Migcyanidin: association of extracts of *Salix alba*, *Curcuma longa*, *Vitis vinifera*, *Mentha piperita* and *Tanacetum parthenium*; and potassium sorbate + sodium benzoate + citric acid as stabilizers.

Glycerol is a highly osmotic "cell friendly" solution which is totally safe, highly osmotic, and vegetable by-product, commonly used in food, in pharmaceutical products and in cosmetic industry. Glycerol provides osmotic cleaning properties to the film solution by generating an osmotic outward liquid flow from the inner parts of the nasal tissues, thereby detaching and draining surface contaminants. Unfortunately, this osmotic flow equally dilutes glycerol and reduced rapidly its osmotic cleaning power. Therefore, to provide better resistance and longer duration of the film, a very small quantity (<0.80%, much below the concentration which may have any cellular effects) of selected food grade specific tannin rich whole plant extracts is added in the preparation.

Tannins are very big & inert polymeric molecules having capacity to bind with specific proteins &/or macromolecules. Their binding with glycerol forms a polymeric mesh, which can resist mechanical pressure and can remain on any live surface for 4-6h as a liquid protective and cleaning bandage. The concentration of each ingredient is adjusted in such a way that there are no free glycerol or tannin molecules remain in the film. Other plant extracts which are not bound to glycerol get expelled through the biological liquid flow generated by the osmotic action of glycerol.

The film acts in the same way as a cotton/polymer protective bandage with the exception that it is liquid, can be applied on the hidden body cavities, and is capable of cleaning the surface through osmotic activity to remove surface contaminants.

The glycerol stable film is further rendered absorbent by adding a small amount of some food grade jellifying agents called Solagum, which is an association of Acacia gum & Xanthan gums.

These gums swells when in contact with hypotonic liquid flow and renders the film jellifying & absorbent.

As plant polymers are big molecules, after glycerol binding, a few sites may remain free to bind to some other proteins or macromolecules but this reaction takes place exclusively in the polymeric glycerol film placed on the nasal mucosa surface, without any interaction with the underlying live cellular structures. Therefore, the glycerol binding polymers were further selected based on their capacity to bind with the incoming protein particles from the nasal mucosa, such as CGRP and pro-inflammatory cytokines.

Up to the time the polymeric film remains on the nasal mucosa, osmosis continues which forms a liquid film between the film and the nasal surface. Therefore, the mode of action of Migspray is mechanical, topical and comparable to a cotton/polymer bandage used to protect damaged surfaces against infections.

Once the nasal mucosa is protected and cleaned of all contaminants, an ideal environment is created which should also allow nasal mucosa cell growth to reconstitute the natural nasal barrier. In vitro cell growth experiments prove that a broken cell monolayer can totally repair within 24h if they have optimal cell growth environment. Intact nasal barrier helps natural defense to minimize systemic entry of any undesired particle.

The mode of action of the device is exclusively mechanical and similar to a polymer protective bandage that it is liquid, can be applied on the nasal cavity, is capable of cleaning the surface through osmotic activity, and is capable of absorbing or trapping any contaminant.

Presentation: 15 ml spray containing a transparent viscous bandage forming liquid (approx. 125 sprays).

Functions of ingredients: Glycerol as a cell friendly osmotic liquid to introduce osmotic, mechanical cleaning properties in MIGSPRAY.

Solagum: film forming and film jellifying agent.

Unpurified plant extracts: Tannins bind to glycerol and Solagum to render the film flexible & resistant to the mechanical pressures for a prolonged action.

Preservatives: Help improve product in-use stability.

Mode of action: When sprayed on the nasal mucosa, MIGSPRAY forms a slightly osmotic, resistant, flexible, and absorbent barrier film, like a transparent bandage on the nasal mucosa. The positive, glycerol induced, osmotic pressure of the film attracts hypotonic liquid from the inner parts of the mucosa, thereby detaching and absorbing the free-proteins and other contaminants present on the surface. These particles are then trapped in the film. Cleaning the nasal surface equally prepares a favorable ground for nasal mucosa repair and self-defense.

MIGSPRAY acts mechanically on the nasal surface without being absorbed in the body, is not very irritant and acts rapidly. Clinical results show noticeable preventive effects on migraine, thereby improving quality of life.

Performance: The performance of VITROBIO medical devices is claimed by its hypertonic and protective barrier forming bandage structure. (1) The film is formed immediately after product application (2) Osmotic nature of the film attracts hypotonic liquid from the inner parts of the tissue which helps to detach & drain free floating surface impurities (3) Solagum reacts with outflowing hypotonic liquid, swells and forms a thick absorbent & semi-permeable film (4) the detached impurities including CGRP, pro-inflammatory cytokines, and other free floating protein molecules are captured in the absorbent film (5) small un-trapped particles may drain out of the film with the osmotic liquid flow (6) when any tissue is clean and free of contaminants & chemicals, cells start growing immediately to repair damaged tissue as a natural physiological healing process (7) an intact mucosal barrier does not allow systemic entry of nasal surface contaminants (8) all interactions takes place in the film, on the live biological surface without affecting underlying cells.

This performance of the barrier film justifies the use of MIGSPRAY to reduce the frequency and intensity of migraine attacks.

The main function of the liquid filmogen bandage is just to remain on the surface & to clean the nasal mucosa of all free-floating contaminants. All interactions occur in the osmotic bandage without any interference with any cellular functions.

This liquid filmogen bandage meets regulatory requirements to be classified as a medical device as multiple scientific studies prove exclusively topical mode of action of MIGSPRAY without any interactions with the underlying cellular structures.

The key studies include: (1) Selection of filmogen ingredients, (2) Choice of the glycerol & jellifying ingredient concentrations used, (3) Osmotic potential of different concentrations of glycerol, (4) absence of cytotoxic potential of plant extracts used & concentrations selected, (5) Proof of resistance of the film to mechanical pressures, (6) Proof of 100% glycerol binding with plant extracts and absence of free glycerol &/or plant tannins in the film, (7) Filmogen properties of finished formulations, (8) Absence of any cytotoxicity of finished formulations, (9) Protein molecule trapping affinity of free sites of glycerol polymeric filmogen bandage, (10) Clinical study proving safety and the efficacy of the product, & (11) Regulatory studies defining product's *in vitro, in vivo* toxicities, mutagenic potential, long-term stability, in-use stability, long-term repeated dose oral toxicity (GLP, 28-days, repeated applications) with no effect on hematological, blood-biochemical, urinary, organ weights, glycerol-related, & cellular (histopathological) parameters proving safety and exclusively topical mode of action of the barrier filmogen liquid bandage.

All the studies conducted prove total safety and exclusively topical mode of action of MIGSPRAY, justifying its registration as a medical device.

Stability: Current 24-months (36 month in progress).

Directions for use: The product is only for topical use in the nasal cavity. For symptomatic treatment, apply 2-3 sprays in each nostril, 3-4 times a day. MIGSPRAY may also be used as a preventive measure by applying 2-3 sprays in each nostril, 5-15 minutes before expecting a migraine attack.

Patients above 12 having no known allergy to any of the ingredients can use the product.

Other product details:

Type of product: A Class I Medical Device in EU. Made in France. (Class IIa in 2021-2022, all dossiers available).

Justification to classify the product as a Class I Medical Device: As per the Directive 2001/83/EC, To be considered as a Medicinal product, a product shall meet the following 2 criteria: (1) having properties for treating or preventing disease in human beings; (2) may be used in or administered to human beings with view to restore, correct, modify physiological

function by exerting a pharmacological, immunological, or metabolic action, or to make a medical diagnosis.

MIGSPRAY meets Medical Device regulations as per the EU Directive 93/42/EEC. MIGSPRAY does not exert any pharmacological, immunological, or metabolic action, or make a medical diagnosis, therefore it is not classified as a medicinal product.

Clinical trial: Showing efficacy and total safety of MIGSPRAY (n=269).

Authorized claims: For the prevention of migraine.

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