



ELLANSÉ® SAFETY
A POLYCAPROLACTONE-BASED
COLLAGEN STIMULATOR

SAFETY DATA REPORT
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Regenerate Beauty through
Collagen Stimulation



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1. INTRODUCTION

ELLANSÉ[®], an injectable product used in aesthetics, belongs to a new generation of collagen stimulators that provides immediate and sustained correction by volumization through biostimulation, with long-lasting effects of different durations from 1 to 4 years* and high degree of patient satisfaction.

Sub-dermal implantation of ELLANSÉ[®] in the face is indicated for lasting correction of facial wrinkles and ageing signs or any facial age-related conditions.

ELLANSÉ[®] is made of carboxymethyl cellulose, the component which provides the immediate effect, and of polycaprolactone which provides the sustained effect.

The development of ELLANSÉ[®] started in 2006 at Aqtis in Utrecht (The Netherlands), a Sinclair Pharmaceuticals company since 2014, as an innovative bioresorbable product. The CE mark was obtained in 2009, the KFDA registration in 2013 in South Korea, the TGA in Australia, etc. Today, ELLANSÉ[®] is a global brand, registered and launched in many of the world leading markets.

The present report is aimed at providing information to support the safety of ELLANSÉ[®] and defining its safety profile as a bioresorbable medical device safely used in humans in aesthetics. The available literature on polycaprolactone, its main component, is considerable since thousands of publications have been dedicated to this polymer. Thus the present report is not intended to be an exhaustive overview but a summary, emphasizing various aspects of safety evaluation to provide a body of evidence of ELLANSÉ[®] safety.

From a general point of view, the safety of a drug or a medical device has to be viewed from the product components to the finished product administered in humans: the characteristics of the components, their inherent quality, and the quality of production, all contribute to the safety of the finished product, which is also largely based on its biocompatibility, biodegradability ... Various tests, studies, or adverse events reporting systems provide results which all together support the safety of the finished product.

Safety of dermal fillers and collagen stimulators, as well as that of aesthetic procedures, is mandatory. Severe side effects are fortunately rare and often due to inappropriate selection of subjects, injection errors such as injection in wrong area, wrong depth of injection, excessive volume injected, etc. Management of potential severe complications has to be handled in the best possible way and optimal options to treat complications have to be permanently searched for.

* *Expected longevity in-vivo based on extrapolation of clinical data from S and M and accepted PCL degradation behaviour.*

2. ELLANSÉ® SAFETY

ELLANSÉ® is a Class III medical device, a classification described in the Medical Device Guidance document of the European Commission (Medical Device classification as a 'risk based' system "The classification of medical devices is a 'risk based' system based on the vulnerability of the human body taking account of the potential risks associated with the device" directive 93/42/EEC).

ELLANSÉ® obtained the CE Mark in 2009 and the approval of Authorities in many countries since then, including the KFDA and TGA, on the basis of all submitted and reviewed safety information and data.

ELLANSÉ® safety documentation is based both on the findings of a number of investigations and the outcomes of its clinical use and the experience of physicians since its introduction on the market. ELLANSÉ® has been marketed for more than 5 years, and its worldwide use in daily medical practice since then reinforces the knowledge of its safety.

The present summary will consider ELLANSÉ® safety from its components, carboxymethyl cellulose and polycaprolactone characteristics, overall medical uses, their quality and safety, the finished product safety data gathered from experimental and clinical studies, pharmacovigilance regular follow-up and surveys according to the regulations.

2.1. ELLANSÉ® PRODUCT COMPONENTS SAFETY

ELLANSÉ® contains compounds with well-established and documented safety and performance characteristics.

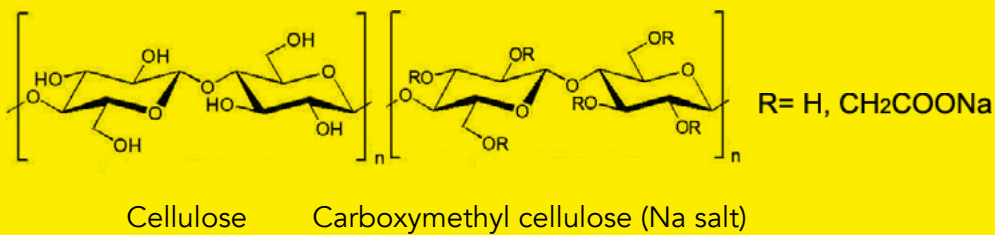
- Carboxymethyl cellulose (CMC) forms the basis of the gel carrier with PBS (Phosphate Buffered Saline) and glycerin representing 70% by volume.
PBS is the solvent medium and glycerin enhances CMC solubility
- Polycaprolactone (PCL) microspheres represent 30% by volume

Both CMC and PCL have been respectively classified by the FDA as Generally Recognized As Safe (GRAS) substances and approved by the FDA as safe to use in medical devices in humans.

2.1.1 Carboxymethyl cellulose (CMC)

Main characteristics

The CMC-based gel represents 70% by volume in ELLANSÉ® composition. CMC, a polysaccharide is a well-known cellulose derivative with carboxymethyl groups (-CH₂-COOH) bound to some of the hydroxyl groups of the glucopyranose monomers that make up the cellulose backbone.



Cellulose is the most abundant naturally occurring polymer of glucose, found as the main constituent of plants and natural fibers such as cotton and linen. Among the cellulose ethers, only NaCMC is a polyelectrolyte, and thus a 'smart' cellulose derivative which shows sensitivity to pH and ionic strength (Sannino et al, 2009). "Smart" materials based on cellulose inherit its unique properties, such as strong mechanical strength, and biocompatibility, thus studies on "smart" materials based on cellulose have bloomed during the last decade (Qiu & Hu, 2013). This shows that CMC not only continues to be widely used but it is at the center of new product developments supporting its biocompatibility.

Properties and uses

Carboxymethyl cellulose is one of the most important cellulose derivatives having wide applications; this polymer is used as a thickener and/or emulsifying agent in many fields in the food, pharmaceutical and cosmetic industries due to its non-toxicity. It is a pharmaceutical excipient used in the formulation of many drugs.

It is extensively used in injectable products containing dexamethasone such as Decadron and Dalalone and applied in drug delivery formulations for the release of drugs such as nifedipine (Barbucci et al, 2004; Pal et al, 2006) and as components of therapies for preventing postsurgical adhesions (e.g. Genzyme's Septrafilm) (Ito et al, 2007; Lee et al, 2005).

CMC is hygroscopic forming a gel with water and this property, to absorb water, is of particular interest in cosmetics; CMC can produce tissue filling already in its native state.

CMC in the composition of ELLANSÉ® exerts filling capacity creating immediate volume after injection.

CMC in ELLANSÉ® is therefore a non-toxic, naturally occurring, cellulose derivative used in a number of applications which provides the immediate volumizing effect seen with ELLANSÉ®.

Safety

The safety of CMC is therefore supported by its large use in the food, pharmaceutical and cosmetic industries but also, and specifically with respect to its use as aesthetic products and indications, in the composition of dermal fillers and volumizers such as Radiesse®, Erelle®, Laresse® and Sculptra® as a gel carrier and/or through its filling function.

CMC is classified as a GRAS (Generally Recognized As Safe) substance in food additives by the FDA:

“Sodium carboxymethyl cellulose is listed in FDA 21 CFR 182 as generally recognized as Safe (GRAS), Section 182.1745.” Glycerin and PBS entering in the composition of the CMC gel are listed in 21 CFR 182; GRAS section 182.1320 and 182.6285 respectively.

It is a non-animal nor human or bacterial but a plant origin substance; it is non-cross linked avoiding the use of cross-linking reticulating agent and the potential related toxicity.

The available literature shows that CMC is an inert substance extremely safe, non-allergenic, and free of mutagenic or carcinogenic potential. (McElligott & Hurst, 1968). It has been tested in many toxicological studies in various animal species, evaluating acute, chronic and carcinogenic potential evidencing its safety (WHO Food additives series).

Some studies underline a bactericidal effect within the tissues, thus making the substance absolutely safe (Keipert & Voigt, 1979).

In the aesthetic field recent clinical studies have evaluated the efficacy and safety of BDDE cross-linked CMC hydrogel in soft tissue augmentation. From the Leonardis clinical study it is concluded that CMC « proves to be an ideal agent for soft tissue augmentation with regard to safety and ease of application. It did not cause infection, extrusion, migration, or adverse reactions in the patients who have been followed for two years » (Leonardis et al, 2010). Furthermore the follow-up study at 3 years in 350 patients has confirmed the safety (Leonardis & Palange, 2015).

The CMC carrier is gradually absorbed over a period of around 4 to 6 weeks.

Taken together all these findings and the wide use of carboxymethyl cellulose (CMC) in different products, in different application fields are in favour of its safety in humans and of its safety as a component of ELLANSÉ®, providing an immediate filling effect.

2.1.2 Polycaprolactone (PCL)

Polycaprolactone is a polymer which is part of the fascinating history of polymers that started at the beginning of the 1900's with the synthesis of PCL by the Carothers group. This gave rise to a number of major biomedical applications offering great perspectives for the future. PCL is used either alone or as copolymer with other polymers enlarging the applications of PCL. The natural and synthetic polymers have been the object of a great development in aesthetics; it is the case for polylactic acid (SCULPTRA®) and polycaprolactone (ELLANSÉ®) which are also the components of threads used to treat facial laxity.

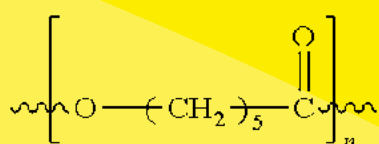
PCL products are used in a number of applications and exist under various forms: microspheres, nanoparticles, films, fibres, micelles, scaffolds etc.

Polycaprolactone is the component of ELLANSÉ® that provides its long lasting volumizing effect via collagen stimulation. In ELLANSÉ® composition, PCL is present as microspheres and represents 30% in volume. It is a synthetic biocompatible and bioresorbable polymer widely used for several decades and FDA approved in several medical devices.

Main characteristics

Polycaprolactone is an aliphatic polyester belonging to the poly- α -hydroxy acid group and belongs to the same chemical group than polylactic acid, polyglycolic acid.

PCL is a polymer made of a chain of a repeated single unit sequence; its chemical formula is given below. The length of the chain (n) defining the molecular weight of the polymer is of particular importance in the case of the ELLANSÉ® product line to characterize and differentiate the various products: ELLANSÉ®-S; ELLANSÉ®-M ; ELLANSÉ®-L and ELLANSÉ®-E, having duration of action of 1, 2, 3 and 4 years respectively*.



PolyCaprolactone

PCL is a semi-crystalline polymer having glass transition temperature of -60° and a low melting point ranging from 59° to 64° depending on its crystalline nature. PCL can be blended with other polymers such as poly-L-lactic acid, polylactic-co-glycolic acid to control permeability of the delivery systems and to modify the biodegradation that can be enhanced with the copolymers, depending on the targeted indication. This enlarges considerably its use and provides further support for its safety.

It is synthesised by the ring opening polymerization of the cycle monomer of ϵ -caprolactone by the use of catalysts such as stannous octoate, with well standardized synthesis and production processes.



* Expected longevity in-vivo based on extrapolation of clinical data from S and M and accepted PCL degradation behaviour.

A large scope of medical uses

The numerous advantages and wide array of functions that can be related to polymeric systems have stimulated scientists and physicians to use polymers in a large range of applications. The most developed polymers in biomedical field are the poly hydroxy acids, including polylactide (PLA), polyglycolide (PGA) and polycaprolactone (PCL).

These polymers were originally employed as resorbable sutures (Albertsson & Varma, 2003) and their application in the biomedical arena has grown up to include drug delivery systems (Breitenbach et al, 2000), tissue regeneration scaffolds (Agrawal & Ray, 2001; Hutmacher, 2000) and others such as fixation devices in surgery (An et al, 2000), etc.

Polycaprolactone is one of the most widely used polymers because of its biocompatibility, bioresorbability, and mechanical properties.

The description of some of the numerous medical applications of PCL that will be given hereafter is intended to support the safety of PCL in its development and use in humans.

ELLANSÉ® is the only aesthetic injectable made of polycaprolactone, conferring its originality and uniqueness; it has been available on the market since 2009.

However, it is one of the earliest polymers synthesized in the early 1930s. Its interesting physicochemical properties have stimulated extensive research into its numerous applications in the biomedical field. A few examples are presented to illustrate its large use, in drug delivery systems, sutures, biomaterials in prosthetics, tissue engineering etc.

Drug-delivery devices for controlled release: «During the resorbable-polymer-boom of the 1970s and 1980s polycaprolactone due to its high permeability to many drugs, excellent biocompatibility and ability to be fully excreted from the body, was widely used in drug delivery devices, most suitable for long term delivery given its slow biodegradation. Much research has been focused on degradable polymer microspheres for drug delivery. The advantage of microspheres is that they can be injected or ingested, they can be tailored for desired release profiles and in some cases can even provide organ-targeted release» (Woodruff & Hutmacher, 2010). The importance of microspheres will be discussed later in this report to show its contribution in the mechanism of action of ELLANSÉ®.

Various drugs have been encapsulated in PCL microspheres for their effective delivery of various drugs such as:

Anticancer drugs

- Taxol (Dordunoo et al, 1995)
- Colchicine, (Das et al, 2000)

Anti-inflammatory agents

- Sulfasalazine:bethamethasone
- Ibuprofen, (Carreras et al, 2013)

- Ketoprofen, (Giunchedi et al, 1994)
- Indomethacin, (Bodmeier & Chen, 1989)

Anti-hypertensive drugs: nifedipine and propranolol (Perez et al, 2000)

PCL microspheres containing cyclosporine (Aberturas et al, 2002) and chlorpromazine (Chang et al, 1986) were also intensively studied.

PCL can be used as a vaccine carrier as it has good permeability to proteins, degrades slowly and does not generate an acidic environment which can adversely affect the antigenicity of the vaccine (Jameela et al, 1997).

Contraceptive devices: Among the drug release systems developed on the basis of PCL one has been particularly investigated and contributed to the important information on PCL safety (Ma et al, 2006). It is the biodegradable delivery system, Capronor[®] the composition of which is made of PCL containing levonorgestrel. It was extensively studied from a toxicological point of view, providing data on chronic toxicity -90 days toxicity study in rats, 2 years toxicity study in rats and dogs-, on mutagenicity by the Ames test.

In the 2 year toxicity study in rats, PCL capsules (Mn 66,000) were implanted on the back of a rat. Results showed that the molecular weight decreased to 15,000 without changes of the implant and a thin layer of connective tissue was observed around the capsules. At 30 months there was a further decrease of the molecular weight to 8,000; then the capsule were becoming fragile and broke. This shows that during the degradation process the molecular weight progressively decreases with time and that degradation is achieved when the molecular weight reaches a given molecular weight.

This study not only provides toxicological information but also makes the link with the degradation kinetics evaluated at the same time.

In the dog study the evaluated parameters namely hematology, serum biochemistry, urine analysis, organ weight and histopathological examination showed no toxicity of the PCL capsule.

Two clinical studies using the Capronor[®] delivery system, have been conducted showing no side effects beyond the usual ones associated with minidoses of a progestogen. Even if the development of this product was not pursued, the experimental and clinical data collected document its safety including that of PCL.

Sutures: Sutures are the most widely used materials in wound closure; they are in general made of natural or synthetic absorbable or non-absorbable polymers.

Synthetic absorbable polymers and especially the aliphatic polyesters, of which PCL is one, are used for sutures presenting the advantage of reproducible degradability inside a biological

environment. Sutures made of polyhydroxy esters such as dextran made of polyglycolide PGA, developed and commercialized since 1970 by Davis and Gek and Vicryl® from polyglycolide -poly lactide PLGA co-polymer PCL copolymer with polyglycolide is the composition of the well-known monofilament suture Monocryl®, largely used in several surgery fields for many years (Middleton & Tipton, 2000). Data obtained from these studies show that absorption is complete, between the 91st and 119th days of implantation, with slight or minimal tissue reaction (Bezwada et al, 1995) reinforcing the safety profile of PCL.

Implants and fixation devices in surgery: Aliphatic polyesters have been used for the design of internal fixation device. (Kulkarni et al, 1971).

PCL was studied for application as a resorbable composite implant for craniofacial repair.

Filling material in dentistry: PCL is used as a synthetic polymer-based root canal filling material as part of the composite of Resilon™.

Tissue engineering: scaffold fabrication: PCL has been extensively used in 3D-scaffold-based tissue engineering to promote the repair and regeneration of tissues in the presence of cells. PCL has found a great interest since the birth time of this new field during the 1900s and 2000s, given its superior rheological and viscoelastic properties over other resorbable polymers (Woodruff & Hutmacher, 2010).

These are few of the numerous biomedical applications of polycaprolactone but sufficient to realize that this polymer has been used worldwide for years in humans in numerous fields and continues to be used safely and effectively.

It is interesting to shortly present some perspectives that PCL opens in the medical field making this polymer continue to be a key player in the future.

Medical perspectives: Polycaprolactone a key player in the future

A 3D-print PCL device in tracheobronchomalacia in human

Polycaprolactone has contributed to save lives:

It is wise to report the recent and extraordinary discovery and medical use of a groundbreaking 3D-printed device designed in 2013 at the Michigan University which saved a baby's life; the baby was suffering from tracheobronchomalacia; he stopped breathing and was turning blue.

«A bioresorbable splint has been created and used for first time at the University, where doctors implanted the device in an infant and stopped this life-threatening condition. The material used, polycaprolactone is a nice choice for this. It takes about two to three years for the trachea to remodel and grow into a healthy state, and that's about how long this material will take to dissolve into the body» says the discoverer.

Effect in tetralogy of Fallot in human

With the same type of device made of polycaprolactone the American specialists saved another baby's life end of 2014. The baby has a condition called tetralogy of Fallot with absent pulmonary valve, which can put tremendous pressure on the airways. Researchers create and implant a tracheal splint made from a biopolymer called polycaprolactone.

Effect on the meniscus in animal

"A 3D-printed implant or scaffold for regeneration of the meniscus-in animal.

"With a similar concept than that described in the case of tracheobronchomalacia management, a group of researchers at the Columbia University have devised a way to replace the knee's protective lining, the meniscus, using a personalized 3D-printed implant, or scaffold, infused with human growth factors that prompt the body to regenerate the lining on its own. The therapy, successfully tested in sheep, could provide the first effective and long-lasting repair of damaged menisci, which occur in millions of Americans each year and can lead to debilitating arthritis.

The scaffold, infused with two recombinant human proteins is made of polycaprolactone, a biodegradable polymer that is also used to make surgical sutures".

A scaffold to repair heart birth defect in human

Researchers have created a new type of biodegradable scaffold to repair the hearts of infants with birth defects, the polymer used is polycaprolactone.

A bioabsorbable polymer for artificial gastric wall in animal

Researchers in Japan have developed a groundbreaking material that can repair and regenerate the gastric wall without deforming the stomach or disrupting GI function. The material, an implanted bioabsorbable polymer (BAP) patch, has been shown to preserve normal GI function after GI surgery in animal models. The BAP patch is composed of a 50:50 copolymer of polylactic acid and polycaprolactone reinforced with polyglycolic acid fibers.

To summarize, these futurist biomedical applications of PCL, taken as examples, several being still at an experimental stage, encourage high level research on this polymer and obviously permanently continue to release information for a better knowledge of its characteristics and behavior when implanted in humans. Last but not least this research on PCL use will open the way to tremendous important medical discoveries. This research brings strong further support for the safe use of polycaprolactone in humans.

Safety

In order to guarantee the safety and performance of medical devices, various tests described in international guidelines have to be carried out. These tests are performed according to ISO standards 10993 relating to the biocompatibility of medical devices. Medical devices have to comply with those requirements.

Indeed, the biological safety of a biodegradable medical implant device contacting tissue and tissue fluid and a contact duration longer than 30 days has to be evaluated by means of several tests: cytotoxicity, genotoxicity, sensitization, irritation, acute systemic toxicity, pyrogenicity, carcinogenicity, sub-chronic and chronic toxicity, implantation, biodegradation.

Polycaprolactone has been tested in different experimental conditions in most of these tests:

Cytotoxicity and biocompatibility:

- PCL was found to be nontoxic in a study investigating pure PCL and chitin short fiber reinforced PCL (Duan et al, 2006).
- An in vitro study evaluating the toxicity of the degradation products of six polymers including PCL, ϵ -hydroxycaproic acid, the degradation product of PCL was shown non-toxic (Taylor et al, 1994).

Cytocompatibility:

- PCL films were tested in vitro on L929 mouse fibroblasts; there was good adhesion, growth, viability, morphology and mitochondrial activity of cells on the PCL films (Serrano et al, 2004).

Sensitization, pyrogenicity, acute systemic toxicity:

- PCL was shown to be non-sensitizing, non-pyrogenic and no acute toxicity was detected (Duan et al, 2006).

Sub-acute, sub-chronic and chronic toxicity:

- PCL cylinders tested during an eight week study do not show local or systemic toxic effects (Rutledge et al, 2003).

Safety, biocompatibility, biodegradability and bioresorbability are the main factors that must be considered before selection of materials to be used in a product, whatever the field of application, including aesthetics which addresses healthy subjects.

PCL is biocompatible

As described above PCL biocompatibility has been demonstrated in several recommended tests in particular on fibroblasts; however, its very wide use in various forms in the numerous biomedical applications brings very strong additional basis for its biocompatibility when implanted or injected in humans.

PCL is biodegradable

In vitro degradation

PCL microparticles degradation was evaluated in vitro in PBS at 37°C and PH 7.4 with and without lipase and compared to PCL films. It appears that the surface area has no important influence on the degradation rate and that PCL degrades homogeneously in vitro; the degradation is quicker in presence of lipase; with lipase the surface of PCL microparticles present channels and pores while there is no change without lipase of the surface that remain smooth (Chen et al, 2000). PCL films (Mn180,000 Da) in the same conditions followed for 2 years, showed a slow and gradual decrease in Mn with a loss of 70% to 50,000 Da in 60 weeks. Mass loss start (0.4%) was detected at 2 years.

In vivo degradation

The biodegradable property of polycaprolactone was first identified in 1973. PCL is degraded by hydrolysis via a bulk degradation, an internal process « occurring when water penetrates the entire polymer bulk, causing hydrolysis through the entire polymer matrix »; it means that the up-take of water is faster than the rate of hydrolysis.

PCL is bioresorbable

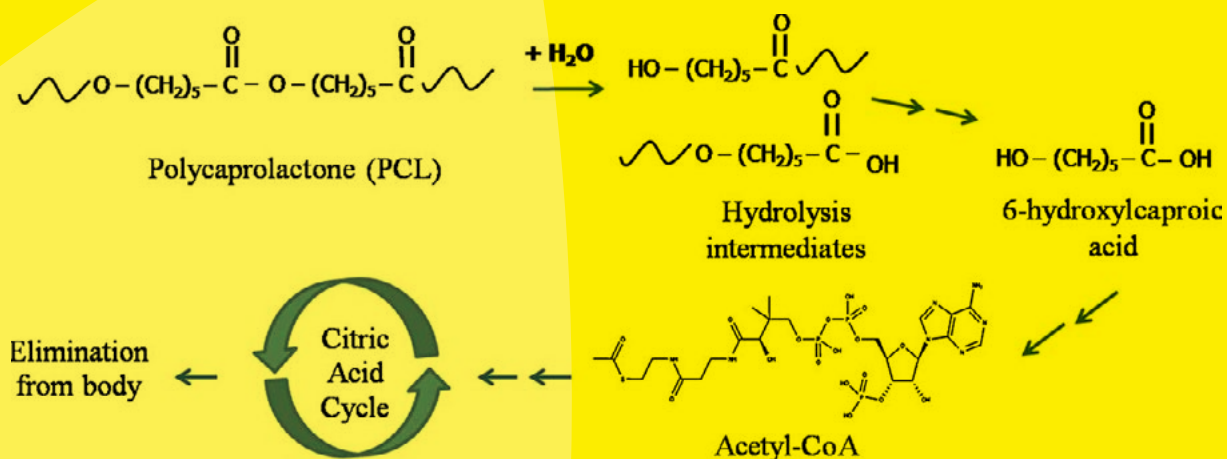
The hydrolytic bioresorption of PCL occurs in two phases (Pitt et al, 1981; Pitt, 1990; Woodward et al, 1985; Chen et al, 2000), **first a non-enzymatic hydrolytic cleavage of the ester linkages**. This first phase shows a **controlled, predictable, first-order, linear bioresorption pattern, where the average length of the polymer chain (molecular weight Mn) in the microspheres continuously decreases with time (t) via chain scission according to the kinetic law** (k = the average rate constant for chain scission).

$$M_n = M_{n,0} \times e^{-kt}$$

So water permeability into the formulation is the rate limiting step for this non enzymatic fragmentation. **In this first phase the mass and volume of the implant remains intact. The shape of the implant remains also unchanged.** This is the basis of the Sustained Performance of the entire ELLANSÉ® product line.

The short second phase starts at a **specific chain length** that has been determined to correspond to chain molecular weight of around 3,000 Da to 5,000 Da allowing the small fragments to diffuse through the polymeric matrix; it is characterized by the onset of controlled and predictable total mass loss via bioresorption of the microspheres and excretion through the normal metabolic pathways.

The first phase is tunable; the length of the second is identical for the entire ELLANSÉ® range. This phase is characterized by a decrease in the rate of chain scission and the onset of mass loss.



From Lam CX et al, 2008

Several research teams have particularly contributed to the understanding of the **PCL degradation mechanism evidencing, as previously described, in a first step, the bulk hydrolysis process of the ester linkages, accompanied by a molecular weight decrease with time according to the kinetic law.** Pitt found a k value of $3 \times 10^{-3} \text{day}^{-1}$ for PCL with a molecular weight of 51,000 Da, meaning that the M_n decrease to 5,000 Da occurs in about 112 weeks.

Implantation of low molecular weight ^3H labeled PCL (M_n 3,000 Da) has allowed for the study of the second phase of the degradation with the demonstration of the complete PCL excretion by urine and feces in about 150 days and no residual radioactivity in blood and organs (Ma et al, 2006; Sun et al, 2006). This second phase was also studied by other research teams by using low molecular weight implants (M_n 3,000 Da) ^{14}C and ^3H labeled PCL powder. It was shown that the absorption of PCL is rapid about 50% radioactivity being excreted in 60 days. At the level of the implant site, only 9% of radioactivity was found at 120 days. As expected the only metabolites detected were ϵ -hydroxy caproic acid and water (Pitt et al, 1981; Pitt, 1990; Woodward et al, 1985).

PCL is totally bioresorbable

As shown PCL is not only biodegradable but it is totally bioresorbable, as the final degradation process leads to the **elimination of the non-toxic degradation by-products, CO_2 and H_2O from the body**; indeed bioresorbables are polymeric materials and devices which show bulk degradation and further resorb in vivo, with total elimination and no residual side effects (Middleton & Tipton, 2000; Gunatillake & Adhikari, 2003; Hutmacher et al, 1996).

Biocompatibility, bioresorbability with predictable and controlled bioresorption are major features of PCL microspheres contributing to the safety of ELLANSÉ®.

2.2 ELLANSÉ® FINISHED PRODUCT SAFETY

The ELLANSÉ® final product is a sterile non pyrogenic white gel made of polycaprolactone microspheres presented in a ready-to-use syringe of 1ml.

All the ELLANSÉ® products ELLANSÉ® -S, -M, -L and -E are made of unique totally smooth and spherical shaped PCL microspheres, homogeneously suspended in a tailor-made aqueous CMC gel carrier. The only difference between the four products is their duration of action of 1, 2, 3 and 4 years* respectively corresponding to their longevity, which can be controlled and tuned; this is achieved by using different initial chain lengths (or chain molecular weights) which define the bioresorption time of the PCL microspheres as described above.

ELLANSÉ® obtained the CE Mark, attesting of conformity with the European directive requirements 93/42/EEC, modified by 2007/47/EC, the classification based on a « risk-based » system.

Quality and characteristics

ELLANSÉ® is manufactured in Utrecht in the Netherlands at a site that complies with specific Good Manufacturing Practices.

ELLANSÉ® is subject to strict quality control from the raw materials to the finished product which is released in compliance with the product specifications; the tests are performed on all the batches and the microspheres shape and size measured.

The CE Mark, KFDA, TGA and other national regulatory Authorities' approvals bring a confirmation of the quality of the production of the ELLANSÉ® products -S; -M; -L and -E. The approvals and launches in around 70 countries support its safety in the approved indication in human, in aesthetics.

ELLANSÉ® experimental safety

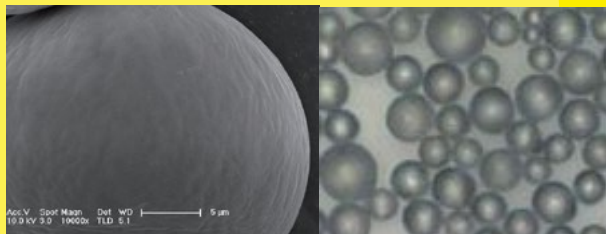
In the course of the CE Mark regulatory process, ELLANSÉ® was evaluated according to ISO 10993 standards. Safety was evaluated through in vitro and in vivo biocompatibility and toxicity tests such as cytotoxicity, intra-cutaneous irritation (by intra dermal injection in rabbits), sensitization (in guinea pig – maximization method), acute systemic toxicity (in mice by intraperitoneal route), sub-chronic toxicity (28 days toxicity in Sprague Dawley rats), genotoxicity (Ames test by direct contact), local tolerance (2 weeks after intra dermal injection in rabbits), degradation and pyrogenicity.

Degradation of the four ELLANSÉ® products in PBS at 37° and PH 7.4 was tested and results were shown to be consistent with published data.

** Expected longevity in-vivo based on extrapolation of clinical data from S and M and accepted PCL degradation behaviour.*

In the selected experimental conditions, ELLANSÉ® was considered non-toxic, non-mutagenic, non-pyrogenic, and biocompatible.

Biocompatibility of the device depends upon the composition of the biodegradable microspheres but also on their shape, surface structure, particle size. ELLANSÉ® microspheres with smooth and regular surface, spherical shape, size of 25-50 μm contribute to the product biocompatibility.



SEM&light microscope pictures of smooth and spherical shaped PCL microspheres

These microspheres' characteristics also explain the regular distribution of the collagen layer around them, forming a scaffold with minimal inflammatory reaction (Laeschke, 2004).

The mechanism of action has been investigated in animals using ELLANSÉ®-S and-M, injected as a bolus on the back of rabbits. Biopsies were taken at different times post injection and examined for the presence of PCL microspheres and for the production of collagen. With ELLANSÉ®-M collagen III and collagen I were identified at 9 months and mostly collagen type-I at 21 months; microparticles were present at 21 months. For ELLANSÉ®-S at 9 months the microspheres were no longer visible (Nicolau & Marijnissen-Hofsté, 2013).

ELLANSÉ® Clinical safety from clinical studies

Regarding the mechanism of action, the stimulatory effect of ELLANSÉ®-M on collagen stimulation was studied in human biopsies taken after injection at the temple area in patients willing to undergo temple lifting surgery; at 13 months' the presence of collagen was evidenced confirming in human for the first time the mechanism of action of ELLANSÉ® on collagen stimulation. As expected microspheres were still visible in histology (Kim & van Abel, 2015).

Moreover, relevant information regarding safety is generated from clinical studies evaluating both efficacy and safety.

The clinical studies conducted on ELLANSÉ® have evaluated both its efficacy and safety. In the present report, safety data are emphasized.

Moers-Carpi MM et al, 2013

The first study which corresponds to the first administration of ELLANSÉ® in humans is a prospective, randomized, controlled study evaluating the efficacy, safety, satisfaction, longevity of ELLANSÉ®-S versus ELLANSÉ®-M for correction of nasolabial folds. It was performed in a

European medical clinic in Munich Germany by Dr Moers-carpi a renowned dermatologist. 40 patients were included and followed at different times post injection, 3, 6, 9, 12, 15, 18 and 24 months. « At 12 months, the efficacy outcomes on Wrinkle Severity Rating Scale (WSRS) and Global Aesthetic Improvement Scale (GAIS) of ELLANSÉ®-S and ELLANSÉ®-M were consistently maintained with sustained improvement in 90% and 91.4 % of patients respectively. At 24 months, ELLANSÉ®-M was found to be more effective than ELLANSÉ®-S with respect to GAIS and WSRS, showing sustained improvement for the entire 2-years' study period. » Patient satisfaction was high for both products (Moers-Carpi & Sherwood, 2013).

This study showed that ELLANSÉ®-S and ELLANSÉ®-M have sustained efficacy with ELLANSÉ®-M demonstrating longer-lasting effect than Ellansé-S, providing the proof of concept of the longer duration of action of ELLANSÉ®-M versus ELLANSÉ®-S.

Regarding safety, « no serious events were reported at any time points. Reported injection-related immediate adverse events such as edema in majority mild or moderate and ecchymosis all resolved without intervention. No nodules, granulomas or other complications were reported. ELLANSÉ®-S and ELLANSÉ®-M are both considered to be safe and well tolerated » (Moers-Carpi & Sherwood, 2013).

This study complies with the requirements of the Health Authorities to evaluate efficacy and safety of dermal fillers on long term given the risk of delayed adverse events.

ELLANSÉ® safety was followed in this study for 24 months. Long term safety of ELLANSÉ® was evidenced up to 2 years (Moers-Carpi & Sherwood, 2013).

Galadari H et al, 2015

The second study is a randomized, prospective, blinded, split face, single center study comparing polycaprolactone to hyaluronic acid for the treatment of nasolabial folds; the study conducted by H Galadari enrolled 40 subjects treated in split face with ELLANSÉ®-S on one side and Perlane on the other side. Efficacy and safety were assessed at 1, 3, 6, 9 and 12 months post treatment using the Wrinkle Severity Rating Scale (WSRS) and the Global Aesthetic Improvement Scale (GAIS). GAIS results show that ELLANSÉ® has greater aesthetic improvements in the treatment of NLFs over the NASHA filler at 6, 9 and 12 months after initial treatment. The highest significant improvements were noted at 9 and 12 months. The same results were observed at 6, 9 and 12 months after initial treatment using the WSRS (Galadari et al, 2015).

The study showed that ELLANSÉ®-S has prolonged aesthetic effect over hyaluronic acid (NaSHA).

Regarding safety « treatment was well tolerated for all patients for both ELLANSÉ® and NASHA. Following initial treatment related mild adverse events were noted which all resolved without intervention. No adverse events were reported at 1, 3, 6, 9 and 12 months post treatment (Galadari et al, 2015).

Taken together the authors consider the studies results to show ELLANSÉ® to be safe and well tolerated.

ELLANSÉ® safety from Post Marketing Surveillance (PMS)

Reactions such as redness, oedema following dermal filler injection are mostly temporary and can be affected by numerous external factors injection technique, injection site, number of injections, depth of injection etc...and factors specific to the subject such as personal intolerance, medical history and previous treatment.

The French Agency (ANSM) has listed the side effects that can occur following treatment with dermal fillers:

- Immediate side effects (1day - 15days): haematoma, erythema, oedema estimated duration 8 days
- Semi-delayed side effects (15days - 3months): infection (relating to conditions of asepsis), necrosis, non-specific inflammation estimated duration 1-6 months
- Delayed (3-24 months): allergy, erythema, pigmentation estimated duration 1-12 months
- Delayed (rare) side effects (> 3 months – x years): Granuloma X months - permanent

Based on available data up to 2012 ANSM estimated that side effects affect between 0.1 and 1% of injected persons.

Given their invasive characteristics and the considerable scatter of subjects undergoing aesthetic procedures injectable wrinkle filler must be traced back during each injection in the same way as medical devices, as stated in Decree No. 2006-1497 and Order dated of 2007, January, 26th.

Thus a person receiving an injection must be told of the characteristics of the injected product and the circumstances of the injection (clinician, location, treatment plan, and injection site).

Vigilance system seeks to prevent the recurrence of incidents and the risk of serious adverse events involving medical devices. With this in mind, it is important that healthcare professionals, that are legally obliged to do so, report these serious adverse events to the manufacturer such that appropriate preventive or corrective measures can be taken.

In line with this, the FDA stated that “as in any medical procedure, there are risks involved with the use of soft tissue fillers. That is why it is important to understand their limits and possible risks”.

Any soft tissue filler can cause long-term side effects, permanent side effects, or both. However, most side effects associated with soft tissue fillers happen shortly after injection and most resolve within less than two weeks:

- bruising, - redness, - swelling, - pain, - tenderness, - itching, - rash.

In some cases side effects may appear weeks, months or years after injection.

Less common side effects include:

- raised bumps in or under the skin (nodules or granulomas) that may need to be surgically removed
- infection
- open or draining wounds
- a sore at the injection site
- allergic reaction
- necrosis (tissue death).

The following rare side effects have also been reported to FDA:

- severe allergic reaction (anaphylactic shock) that requires immediate emergency medical assistance
- migration / movement of filler material from the site of injection-leakage or rupture of the filler material at the injection site or through the skin (which may result from tissue reaction or infection)
- formation of permanent hard nodules in the face or hand
- vision abnormalities, including blindness
- stroke
- injury to the blood supply
- damage to the skin or the lips.

ELLANSÉ® Safety - Adverse events PMS

ELLANSÉ® obtained the CE Mark and was launched in 2009. It is presently introduced in 52 countries with more than 300,000 syringes sold in the 6 years since the first launch.

A vigilance system is in place, that ensures close follow up and reporting of adverse events.

From a review of Adverse Events from launch to December 2015, the following can be confirmed.

There are 155 cases for 323726 syringes sold which gives an adverse event rate of 0.048% or 1 adverse event per 2089 syringes.

Adverse Event Rate by failure modes is as follows:

Adverse Event Rate

Edema/Swelling: 0.017%

Lumps/Nodules: 0.016%

Inflammation/Infection: 0.002%

Several of the cases are related to the injection procedure itself, such as oedema cases that disappear spontaneously or after a few days following the administration of oral corticoids. The nodules or indurations appear generally to be linked to technical errors, such as too superficial injections. These types of side effects reported with ELLANSÉ® are in line with those cited by the Authorities and those already published. No trend of a specific side effect has been reported.

Physicians' training is also necessary; recommendations in particular on the injection techniques, the volume injected in different areas have to be strictly followed and where not to inject (i.e. the lips, glabella and eyelids).

Detailed information on the contraindications, warnings, precautions and direction for use are given in the Instruction for Use (IFU). Several publications also provide recommendations to avoid complications with dermal fillers (Sherman, 2009).

Regarding management of adverse events for dermal fillers in general, numerous publications have described the modalities of complications' treatment (Bailey et al, 2011; Lemperle et al, 2009; Ozturk et al, 2013). For nodules treatment, the use of corticoids is often proposed injected in very small volumes strictly within the nodules, 0.01 ml to 0.05 ml depending on the volume to be treated. Treatment has to be continued until inflammation has disappeared.

For prevention of nodules in the case of ELLANSÉ®, avoid large volumes, no bolus should be more than 0.2 to 0.4ml; inject slowly; do not inject within muscles, lips and eyelids; do not inject in the superficial layers of the skin nor in the same area where permanent fillers have been previously injected for precaution.

3. DISCUSSION

ELLANSÉ® used in aesthetics has two main components, carboxymethyl cellulose and polycaprolactone microspheres respectively classified as Generally Recognized As Safe (GRAS) substances and approved by the FDA for use in many medical devices. Both are well known products found in the composition of many biomedical products used in humans for many years and therefore their safety has been widely investigated. In a recent review on fillers Carruthers wrote that both components of ELLANSÉ® have a long history of safety in the medical and pharmaceutical industries and that clinical safety and efficacy assessed in a 2-year prospective, randomized study, has demonstrated excellent results when used in the nasolabial folds, with no serious adverse effects (Carruthers et al, 2015).

ELLANSÉ® is a biocompatible, biodegradable and bioresorbable product presented in sterile non pyrogenic gel in a ready to use syringe. It does not contain any animal, bacterial or human components meaning no allergic test is needed prior to injection. It has been submitted to all the tests according to ISO standards required by Health Authorities and its safety has been demonstrated in clinical trials and post marketing surveillance during the 5 years since its launch. A strict adverse event follow-up and reporting is in place allowing evaluation of the evolution of side effects on a regular basis and the Adverse Event rate calculated. Up to now no ELLANSÉ® specific side effects have been reported; the profile is in line with that described for other fillers.

Nevertheless precaution of use has to be respected as well as all recommendations regarding the selection of the subjects, their medical history, the area to be treated, techniques of injection, injected volume and depth of injection as well as conditions of the environment, so as to avoid side effects. The training of physicians is essential regarding anatomy, product characteristics and mechanism of action integrating the fact that ELLANSÉ® is a collagen stimulator but also injection techniques and practice.

The knowledge of the safety profile of ELLANSÉ® will benefit further from the extensive fundamental research on PCL which is being conducted in the best research centers for various applications, as well as from the clinical experience that will accumulate with its further use in aesthetics worldwide.

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