

F. ADVERSE EVENTS

During the two studies that have been conducted with *Derma Veil* (2001-2003 & 2002-2005) several adverse events occurred caused by trauma to the tissues by the puncture of the needle during application of anesthesia or the implant. The most frequent adverse reactions registered in the participants were erythema and ecchymosis. Also there were several cases of edema and hematoma as well as some bleeding.

During both studies none of the participants showed serious reactions, or secondary complications of any nature neither during the investigation's treatment sessions, nor afterwards during the close to two year's observation periods of each study.

Participants expressed various levels of pain caused by the injection of anesthesia and the implant, as well as due to the sensation of the implant's presence. In every case, an ice compress was applied to the participants for a few minutes to diminish blood flow. Afterwards topical anesthesia (*Anestop – Pro-Medic*) was applied to diminish pain due to the needle's puncture when applying local anesthesia (*Xylocaine, 2% lidocaine – Astra Zeneca*) to neutralize in turn the pain of the injection to infiltrate the product.

1. *Del Prado Protocol TAG-194/01:*

Study performed with 30* participants from the 3rd of May 2001 through the 22 of June 2002 with a final review and addendum on the 12 of June 2003.

a. Biological symptoms:

Participants:	5		12			9				4					30
Session:	1 st	2 nd	1 st	2 nd	3 rd	1 st	2 nd	3 rd	4 th	1 st	2 nd	3 rd	4 th	5 th	-
• Bruising/redness **	5	5	12	12	12	9	9	9	9	4	4	4	4	4	102
• Edema:															
- Mild	2	1	2	1	1	-	2	-	2	1	-	-	1	-	13
- Moderate	-	-	2	1	1	-	-	1	2	2	1	3	2	1	16
- Major	-	-	-	-	-	2	1	-	-	-	3	1	-	-	7
• Hematoma															
- Mild	-	-	-	-	-	-	-	-	1	-	-	-	1	-	2
- Moderate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
- Major	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
• Other ***	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Totals:	7	6	16	14	14	11	12	10	14	7	8	8	8	5	140

* Safety data were collected *a posteriori* for 29 of the patients at 25 months from the start of the Study.

** Ecchymosis/erythema.

*** Secondary reactions; papules, nodules, granuloma, Complications; necrosis, infection.

b. Pain symptoms (Local anesthesia was applied to all participants):

Session:	1st	2nd	3rd	4th	5th
Participants:	30	30	25	13	4

• **Pain due to implant injection:**

- None	26	28	25	12	4
- Moderate	4*	2*	-	1*	-
- Painful	-	-	-	-	-

• **Pain due to implant:**

- None	21	24	20	12	3
- Moderate	9	6	5	1	1
- Painful	-	-	-	-	-

* Due to the insertion of needle when applying anesthesia.

2. Government Controlled Protocol TAG-099/02:

Study performed with 30 * participants from the 24th of September 2002 through the 15 of February 2003 with a final review and addendum on the 19 of September 2005.

a. Biological symptoms:

	Participants:	30	30	23	14	Total
	Session:	1 st	2 nd	3 rd	4 th	
a. Ecchymosis/erythema		28	30	19	12	89
• Edema						
- Mild		2	3	4	1	10
- Moderate		5	3	2	2	12
- Major		2	1	-	-	3
• Hematoma						
- Mild		2	1	3	1	7
- Moderate		3	2	1	-	6
- Major		-	-	-	-	-
• Other **		-	-	-	-	-
Totals:		42	40	29	16	127

* Safety data were collected *a posteriori* for 26 of the patients at approximately 34 months from the last session.

**Secondary reactions; papules, nodules, granuloma, Complications; necrosis, infection.

b. Pain symptoms (Local anesthesia was applied to all participants):

<i>Session:</i>	1st	2nd	3rd	4th
<i>Participants:</i>	30	30	23	14
• Pain due to anesthesia injection:				
- None:	27	29	22	14
- Moderate:	2	1	-	-
- Painful:	1	-	1	-
• Pain due to implant injection:				
- None:	27	30	22	14
- Moderate:	3	-	1	-
- Painful:	-	-	-	-
• Pain due to Implant: *				
- None:	2	20	18	9
- Moderate:	17 **	7	4	5
- Painful:	11 **	3	1	-

* Immediately after the session and up to the following 5 days.

** The high incidence of "*moderate and painful*" symptoms in reference to the product during the first session, were attributed to fading anesthesia effects and to the novelty in visual and tactile perception by the patient.

3. POST MARKETING USE REPORTS:

The following adverse events were reported by commercial users of Glicolact (former brand name 2003-05) and *Derma Veil* (Brand name since 2005) in Mexico, most of which had been observed during the clinical studies:

- a. Bleeding has been occasionally reported as a non-serious event, typically referred to in association with the puncture of the needle during application of anesthesia and/or *Derma Veil*, with the reaction immediately evident as the needle is pulled out from the injection point. The event being resolved after pressing the site with gauze for a few seconds to a minute or two. As a consequence the area would develop an ecchymosis and/or erythema reaction.
- b. Ecchymosis (bruising) and/or erythema (redness) have been reported as the most common and frequent non-serious adverse reactions immediately evident within a few minutes after the injection procedure with the event being resolved after 15 to 20 minutes of application of ice compresses, and in some cases 12 to 48 hours after continuing with ice compress applications at home with some doctors also prescribing topical cream (corticosteroids) application until the event is resolved.

- c.** Edema and hematoma has been reported as a non-serious adverse reaction, typically referred to in association with trauma to the tissues by the puncture of the needle during application of anesthesia and/or *Derma Veil*. Time to onset ranged from half hour to 24 hours. Events resolved within 5-6 days without sequel. Relief prescriptions included anti-inflammatory, corticosteroids, and/or analgesics.
- d.** Acute pain, significant bruising and itching have been reported 8 to 24 hours after treatment session. Relief prescriptions included anti-inflammatory, corticosteroids, and/or analgesics. Events resolved within 5-7 days after treatment session without sequel.
- e.** Significant edema has been reported associated with pain. The events were mostly transitory. Relief prescriptions included anti-inflammatory, corticosteroids, and/or analgesics. Events resolved within 8-10 days without sequel.