SUMMARY REVIEW MEMO TEMPLATE

DATE: JANUARY 27, 2010

FROM: (b)(6)

SUBJECT: **P040024/S039**
RESTYLANE L AND PERLANE L INJECTABLE GELS

CONTACT: (b)(6)

TO: THE RECORD

BACKGROUND/ REASON FOR SUPPLEMENT

P040024/S039 is a 180 Day Supplement for two wrinkle filler devices with lidocaine: Restylane L and Perlane L Injectable Gels. The 2 devices were studied in a clinical trial under G080151. The devices are identical to the approved Restylane and Perlane Injectable Gel devices (P040024 and P040024/S006) except for the addition of lidocaine. The purpose of adding lidocaine to the wrinkle fillers is to reduce pain upon injection.

REVIEW TEAM

Table 1 below lists the participants in this review team and the section of the PMA that was reviewed:

Reviewer	Role
(b)(6) CDRH/ODE/DGRND	Lead Reviewer
(b)(6) MD, MPH CDRH/ODE/DGRND	Clinical Reviewer
(b)(6) PhD and (b)(6) CDRH/OSB/DPS	Statistics Reviewer
(b)(6)	Patient labeling Reviewer
(b)(6) PhD CDER/OPS/ONDQZ/DPAI	Lidocaine Information Reviewer

Table 1: Review team for P040024/S039

INDICATIONS FOR USE

Restylane® L is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

Perlane® L is indicated for implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.

DEVICE DESCRIPTION

Restylane L is a gel of hyaluronic acid generated by *Streptococcus* species of bacteria, chemically crosslinked with BDDE and suspended in phosphate buffered saline at pH=7 and concentration of 20mg/mL with 0.3% lidocaine.

Perlane L is a sterile gel of hyaluronic acid generated by *Streptococcus* species of bacteria, chemically cross-linked with BDDE and suspended in phosphate buffered saline at pH=7 and concentration of 20 mg/mL with 0.3% lidocaine. The median particles size is between 750 and 1000 microns.

PRECLINICAL/BENCH

Biocompatibility

The sponsor conducted biocompatibility testing on the proposed devices, including cytotoxicity, maximization sensitization and intracutaneous reactivity. Based on the results of the testing, the products were found to be biocompatible.

Stability Data

For each product 9 months of data for the long term condition (25˚C/60%RH) and 6 months of data for the accelerated (40˚C/75%RH) condition were provided. Additional supportive data from several development and clinical batches of drug product were also provided, extending through 18 months for long term stability condition. Based on the data, which show no trend in lidocaine-related degradants, a shelf life of 18 months is recommended for each product.

CLINICAL DATA

There were 2 separate clinical trials conducted: (1) a randomized, double-blind study comparing safety and tolerance of Restylane with and without addition of 0.3% lidocaine HCl during correction of nasolabial folds; and (2) a randomized, double-blind study comparing safety and tolerance of Perlane with and without addition of 0.3% lidocaine HCl during correction of nasolabial folds. The intent of the studies was to demonstrate a pain relieving effect during treatment when lidocaine hydrochloride was added to Restylane and Perlane. Each study enrolled 60 patients at 3 U.S. centers. Subjects received a single treatment of the wrinkle filler with added lidocaine in one NLF and a single treatment of the wrinkle filler without the lidocaine in the other NLF. Assessment of pain was made at the time of injection, and 15, 30, 45 and 60 minutes post injection using the visual analog scale (VAS). The global aesthetic improvement scale (GAIS) was used to measure the subject's satisfaction with the wrinkle improvement at the follow-up visit at 14 days. A wrinkle severity rating scale (WSRS) rated by the

investigator was used to evaluate the visual appearance of the NLFs at screening. Safety evaluations included an interview of the subject to gather information about adverse events, and subjects filled out a diary for 14 days post treatment documenting any additional adverse events.

There were 60 subjects enrolled and randomized in the Restylane L study and 60 subjects enrolled and randomized in the Perlane L study. The mean age was 52.1 years for Restylane L and 53.4 years for Perlane L. There were 32 subjects in the Restylane L study with darker Fitzpatrick Skin Types (21/60 or 35% Type IV and 11/60 or 18.3% Type V and VI). There were 31 subjects in Perlane L with darker Fitzpatrick Skin Types (22/60 or 36.7% Type IV and 9/60 or 15.0% Types V and VI). A summary of the demographics is presented in table 2 below:

Parameter	Product	
	Restylane L N = 60 Subjects	**Perlane L N = 60 Subjects**
Age (years)		
Mean	52.1	53.4
SD	6.6	8.0
Median	52.7	54.0
Minimum, Maximum	37.6, 64.2	34.4, 65.8
Gender		
Female	58 (96.7%)	56 (93.3%)
Male	2 (3.3%)	4 (6.7%)
Race/Ethnicity		
White	34 (56.7%)	39 (65.0%)
Hispanic/Latino	21 (35.0%)	16 (26.7%)
Black or African American	3 (5.0%)	5 (8.3%)
Asian	1 (1.7%)	0 (0%)
Other	1 (1.7%)	0 (0%)
Fitzpatrick Skin Type		
I+II+III	28 (46.7%)	29 (48.3%)
IV	21 (35.0%)	22 (36.7%)
V+VI	11 (18.3%)	9 (15.0%)
Baseline WSRS		
Score 3	30 (50.0%)	34 (56.7%)
Score 4	30 (50.0%)	26 (43.3%)
Prior cosmetic or aesthetic procedures		
No	46 (76.7%)	44 (73.3%)
Yes	14 (23.3%)	16 (26.7%)

Table 2: Demographics of study subjects

At the time of treatment, the mean VAS score for Restylane L was 14.7mm compared to the mean VAS score for Restylane of 44.9mm. At the time of treatment, the mean score for Perlane L was 15.2 compared to the mean VAS score for Perlane of 49.6mm. All pain scores decreased over the course of the 60 minutes, with the mean pain scores higher for Restylane and Perlane compared to Restylane L and Perlane L respectively. Tables 3 and 4 show the VAS measurements for the timepoints in the study.

Timepoint	VAS pain by treatment (mm)		VAS difference (mm)*	P-value**
	Restylane L	*Restylane*		
Treatment	14.7	44.9	30.3	<0.001
15 Minutes	6.1	23.2	17.2	<0.001
30 Minutes	2.5	11.7	9.2	<0.001
45 Minutes	1.4	7.0	5.6	<0.001
60 Minutes	1.0	3.2	2.2	<0.001

Source: Statistical Report: Appendix 16.1.9, Tables 1.24 - 1.26, Appendix 16.2.6.1
*Within-subject difference (*Restylane* side - *Restylane L* side) **One-sample T-test

Table 3: Subject's mean VAS assessment of pain by timepoint for Restylane and Restylane L

Timepoint	VAS pain by treatment (mm)		VAS difference (mm)*	P-value**
	Perlane L	*Perlane*		
Treatment	15.2	49.6	34.4	<0.001
15 Minutes	4.7	21.3	16.5	<0.001
30 Minutes	3.2	12.8	9.6	<0.001
45 Minutes	2.4	7.4	5.0	<0.001
60 Minutes	2.3	5.7	3.4	0.002

Source: Statistical Report: Appendix 16.1.9, Tables 1.23 - 1.25, Appendix 16.2.6.1
*Within-subject difference (*Perlane* side - *Perlane L* side)
**One-sample T-test

Table 4: Subject's mean VAS assessment of pain by timepoint for Perlane and Perlane L

The GAIS was used to measure the subject's satisfaction with the wrinkle improvement. At day 14, all subjects on the Restylane L side of the face and 98.3% on the Restylane side of the face showed improvement from baseline. At day 14, 95% of subjects on the Perlane L side and 96.7% or subjects on the Perlane side showed improvement from baseline. Tables 5 and 6 show the GAIS evaluation at day 14 visit for the Restylane and Perlane studies.

Category	GAIS			
	Restylane L		*Restylane*	
	n	%	n	%
Very Much Improved (4)	17	28.3	18	30.0
Much Improved (3)	29	48.3	29	48.3
Improved (2)	14	23.3	12	20.0
No Change (1)	.	0.0	1	1.7
Worse (0)	.	0.0	.	0.0

Source: Statistical Report: Appendix 16.1.9, Table 1.27, Appendix 16.2.6.2

Table 5: GAIS evaluation at day 14 for Restylane and Restylane L

Category	GAIS			
	Perlane L		*Perlane*	
	n	%	n	%
Very Much Improved (4)	24	40.0	24	40.0
Much Improved (3)	18	30.0	19	31.7
Improved (2)	15	25.0	15	25.0
No Change (1)	3	5.0	2	3.3
Worse (0)	0	0.0	0	0.0

Source: Statistical Report: Appendix 16.1.9, Table 1.26, Appendix 16.2.6.2

Table 6: GAIS evaluation at day 14 for Perlane and Perlane L

For the Restylane arm, the most commonly reported AEs were injection site erythema, injection site pain and implant site swelling. For the Perlane arm, the most commonly reported AEs were injection site pain, injection site erythema and implant site swelling. The severity of the device related implants are presented in table 7 for the Restylane and table 8 for the Perlane arm.

System Organ Class *Preferred Term*	*Restylane L* Grade of Intensity			Total	*Restylane* Grade of Intensity			Total
	Mild	Mod.	Sev.		Mild	Mod.	Sev.	
General disorders and administration site conditions								
Implant site haematoma	18	5	.	23	15	4	.	19
Implant site mass	1	.	.	1	2	.	.	2
Implant site pain	12	5	.	17	15	3	.	18
Implant site swelling	14	10	.	24	16	6	.	22
Injection site erythema	24	4	.	28	24	3	.	27
Injection site pain	19	4	.	23	22	4	.	26
Injection site pruritus	6	.	.	6	4	.	.	4
Vascular disorders								
Vasospasm	.	1	.	1	.	.	.	.
ALL*	94	29	.	123	98	20	.	118

Source: Statistical Report: Appendix 16.1.9, Table 1.42, Appendices 16.2.7.1 – 16.2.7.4
*One event in Subject 1012 was classified as systemic and not related to a specific treatment site. The diagnosis of the event was 'Light headedness', and the maximum intensity was 'Mild'.

Table 7: Severity of device related AEs for Restylane arm

System Organ Class *Preferred Term*	*Perlane L* Grade of Intensity Mild	Mod.	Sev.	Total	*Perlane* Grade of Intensity Mild	Mod.	Sev.	Total
General disorders and administration site conditions								
Implant site haematoma	13	6	.	19	16	7	.	23
Implant site mass	1	.	.	1	1	.	.	1
Implant site pain	13	1	.	14	13	1	.	14
Implant site swelling	18	6	.	24	18	6	.	24
Injection site erythema	20	4	.	24	22	3	.	25
Injection site pain	28	2	.	30	28	2	.	30
Injection site pruritus	8	1	.	9	4	1	.	5
Skin and subcutaneous tissue disorders								
Skin discolouration	1	.	.	1	.	.	.	.
ALL	102	20	.	122	102	20	.	122

Source: Statistical Report: Appendix 16.1.9, Table 1.41, Appendices 16.2.7.1 – 16.2.7.8
Abbreviations: Mod. = Moderate; Sev. = Severe

Table 8: Severity of device related AEs for Perlane arm

The duration of device related AEs are presented in table 9 for the Restylane arm and table 10 for the Perlane arm.

Primary System Organ Class *Preferred Term*	*Restylane L* Duration (days) nmiss*	n	Mean	Std	Min	Median	Max	*Restylane* Duration (days) nmiss*	n	Mean	Std	Min	Median	Max
General disorders and administration site conditions														
Implant site haematoma	0	23	4.7	2.8	1	4.0	11	0	19	5.8	2.9	2	5.0	12
Implant site mass	1	0	.	.	.	.	.	2	0	.	.	.	.	.
Implant site pain	0	17	3.1	1.6	1	3.0	7	0	18	2.6	1.6	1	2.0	7
Implant site swelling	0	24	4.9	1.8	2	4.5	9	0	22	4.6	2.6	2	4.0	13
Injection site erythema	0	28	3.3	2.0	1	2.5	8	0	27	3.2	1.9	1	2.0	8
Injection site pain	0	23	4.3	2.3	2	4.0	12	0	26	4.8	3.9	1	4.0	20
Injection site pruritus	0	6	2.5	1.4	1	2.0	5	0	4	2.8	1.7	1	2.5	5
Vascular disorders														
Vasospasm	1	0	.	.	.	.	.	.	.	.	.	.	.	.
ALL	2	121	4.0	2.2	1	4.0	12	2	116	4.1	2.9	1	4.0	20

Source: Statistical Report: Appendix 16.1.9, Table 1.43, Appendices 16.2.7.1 – 16.2.7.4
* AE is still ongoing at study end.
Abbreviations: n = number of subjects; std = standard deviation; Min = minimum; Max = maximum

Table 9: Duration of device related AEs for Restylane arm

System Organ Class *Preferred Term*	*Perlane L* Duration (days)							*Perlane* Duration (days)						
	nmiss*	n	Mean	Std	Min	Median	Max	nmiss*	n	Mean	Std	Min	Median	Max
General disorders and administration site conditions														
Implant site haematoma	.	19	6.9	2.5	2	7.0	12	1	22	6.6	3.1	1	7.0	15
Implant site mass	.	1	5.0	.	5	5.0	5	.	1	5.0	.	5	5.0	5
Implant site pain	.	14	3.0	2.3	1	2.0	9	.	14	3.1	2.0	1	3.0	9
Implant site swelling	.	24	5.5	2.2	1	6.0	10	.	24	5.4	2.7	1	6.0	14
Injection site erythema	.	24	5.4	3.7	2	4.5	18	.	25	5.4	3.7	2	5.0	18
Injection site pain	.	30	4.8	2.4	1	4.5	13	.	30	4.9	2.8	2	4.0	14
Injection site pruritus	.	9	3.9	1.6	2	4.0	7	.	5	4.8	1.5	3	5.0	7
Skin and subcutaneous tissue disorders														
*Skin discolouration***	.	1	8.0	.	8	8.0	8	.	.	.	.	.	.	.
ALL	.	122	5.1	2.8	1	5.0	18	1	121	5.2	3.0	1	5.0	18

Source: Statistical Report: Appendix 16.1.9, Table 1.42, Appendices 16.2.7.1 – 16.2.7.8
Abbreviations: n = number of subjects; std = standard deviation; Min = minimum; Max = maximum
* AE ongoing at study end
**Discolouration was a red/purple mark on the site of the nose of Subject 33024 (a White female).

Table 10: Duration of device related AEs for Perlane arm

The duration of the symptoms reported in the diaries are presented in table 11 for the Restylane arm and table 12 for the Perlane arm.

	Restylane L	*Restylane*	*Restylane L*				*Restylane*			
	Total subjects reporting symptoms n (%)	**Total subjects reporting symptoms n (%)**	**Number of days[2]**				**Number of days[2]**			
			1 n (%)	**2-7 n (%)**	**8-13 n (%)**	**14 n (%)**	**1 n (%)**	**2-7 n (%)**	**8-13 n (%)**	**14 n (%)**
Bruising	35 (58.3)	31 (51.7)	3 (8.6)	28 (80.0)	4 (11.4)	0 (0.0)	0 (0.0)	25 (80.6)	6 (19.4)	0 (0.0)
Itching	8 (13.3)	7 (11.7)	7 (87.5)	1 (12.5)	0 (0.0)	0 (0.0)	6 (85.7)	1 (14.3)	0 (0.0)	0 (0.0)
Pain	27 (45.0)	27 (45.0)	13 (48.1)	11 (40.7)	1 (3.7)	2 (7.4)	15 (55.6)	11 (40.7)	0 (0.0)	1 (3.7)
Redness	30 (50.0)	28 (46.7)	10 (33.3)	17 (56.7)	2 (6.7)	1 (3.3)	9 (32.1)	18 (64.3)	1 (3.6)	0 (0.0)
Swelling	40 (66.7)	36 (60.0)	4 (10.0)	29 (72.5)	7 (17.5)	0 (0.0)	8 (22.2)	21 (58.3)	5 (13.9)	2 (5.6)
Tenderness	41 (68.3)	39 (65.0)	13 (31.7)	20 (48.8)	5 (12.2)	3 (7.3)	9 (23.1)	25 (64.1)	3 (7.7)	2 (5.1)
Other[3]	4 (6.7)	7 (11.7)	0 (0.0)	2 (50.0)	0 (0.0)	2 (50.0)	1 (14.3)	5 (71.4)	0 (0.0)	1 (14.3)

Source: Statistical Report: Appendix 16.1.9, Table 1.38, Appendices 16.2.7.7 – 16.2.7.8
% = n/number of subjects in safety population
[1]Missing values are not reported.
[2] Percentage calculated using number of subjects reporting symptoms.
[3] Other included symptoms of vasospasm, lump/bump, small blue mark, and sinus drip. Diary entries of throbbing/flushing, cold, chafing, dryness, shadow, headache, bad back, and neck pain could not be associated with a particular product.

Table 11: Duration of symptoms after treatment – subject diary for Restylane arm

	Perlane L	*Perlane*	*Perlane L*				*Perlane*			
	Total subjects reporting symptoms n (%)	Total subjects reporting symptoms n (%)	Number of days[2]				Number of days[2]			
			1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)
Bruising	36 (60.0)	33 (55.0)	6 (16.7)	27 (75.0)	3 (8.3)	0 (0.0)	5 (15.2)	23 (69.7)	4 (12.1)	1 (3.0)
Itching	16 (26.7)	12 (20.0)	5 (31.3)	10 (62.5)	1 (6.3)	0 (0.0)	5 (41.7)	7 (58.3)	0 (0.0)	0 (0.0)
Pain	28 (46.7)	26 (43.3)	17 (60.7)	11 (39.3)	0 (0.0)	0 (0.0)	15 (57.7)	11 (42.3)	0 (0.0)	0 (0.0)
Redness	34 (56.7)	31 (51.7)	9 (26.5)	24 (70.6)	0 (0.0)	1 (2.9)	9 (29.0)	18 (58.1)	3 (9.7)	1 (3.2)
Swelling	42 (70.0)	39 (65.0)	4 (9.5)	33 (78.6)	4 (9.5)	1 (2.4)	6 (15.4)	29 (74.4)	3 (7.7)	1 (2.6)
Tenderness	50 (83.3)	49 (81.7)	6 (12.0)	40 (80.0)	4 (8.0)	0 (0.0)	8 (16.3)	35 (71.4)	6 (12.2)	0 (0.0)
Other[3]	3 (5.0)	1 (1.7)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)

Source: Statistical Report: Appendix 16.1.9, Table 1.37, Appendices 16.2.7.7 – 16.2.7.8
% = n/number of subjects in safety population
[1]Missing values are not reported.
[2] Percentage calculated using number of subjects reporting symptoms.
[3] Other included symptoms of acne, lumpiness, and red/purple mark. Diary entries of hurts to swallow, lack of energy, feeling of sickness, achy, headache, and broken capillaries could not be associated with a particular product.

Table 12: Duration of symptoms after treatment – subject diary for Perlane arm

The clinician stated that generally the data provided indicate that Restylane and Perlane with Lidocaine offer less painful injections of the device without increase or change in adverse event profiles. She noted that there were 8 Restylane and 13 Perlane subjects who received prior injections with other dermal filler devices; and the data indicate that there are higher rates of adverse events in subjects who had prior injections with dermal fillers. She recommended that this information be included in the labeling so that practitioners who perform dermal filler injections may be better able to advise patients on what to anticipate when treated with multiple dermal fillers injections. The sponsor included a table with the number of subjects who had prior wrinkle treatments and who experienced adverse events, in the labeling.

The statistician stated that both of the Lidocaine-containing treatments were effective in reducing pain as defined in the primary endpoint. With respect to safety, he states that a question arises about the observed trend towards a slightly larger number of adverse symptoms with the Lidocaine-containing treatments. These can be noted in the patient diary data for the Restylane and Perlane studies. While the comparisons for each category of adverse event were not individually statistically significant, differences in the same direction were observed for 5 out of 6 categories in the Restylane study and 6 out of 6 categories in the Perlane study. In combination, this represents a statistically significant trend against the Lidocaine treatments. He notes that actual differences were slight and may not be judged to be clinically significant. The clinician recommended that the safety finding appear in the labeling. From the clinician's review, she states that there is similar information between the Restylane/Perlane and Restylane L/Perlane L and all the safety information was included in the labeling.

SUMMARY OF INTERACTIVE REVIEW/CORRESPONDENCE

There was one Major Deficiency letter issued under this supplement. The outstanding issues of letter included questions on the stability data, clinical data, preclinical testing and labeling. The sponsor sufficiently addressed the issues of the letter in the subsequent amendment.

CONCLUSION

Based on the clinical data presented in the supplement, Restylane L and Perlane L have similar safety profiles as the approved Restylane and Perlane. The clinical data also show that the effectiveness of the devices is maintained as evidenced by the GAIS results from the subjects. The preclinical testing and stability data support the safety and effectiveness of the device.

RECOMMENDATION - I recommend that the supplement be **Approved**.

Reviewer name Date

Name, Chief, Branch Date