Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

ANALYSIS OF THE SENSORY PROFILE OF TWO NEW TRANSDERMAL PATCHES (V0116TD07AF019 AND V0116TD07AF020) 21 MG/24 H VERSUS A REFERENCE TRANSDERMAL PATCH (NICOTINELL TTS®) 21 MG/24H

Investigational product: V0116 TD

Study Design: Comparative, randomized, cross-over, single-centre, open sensory analysis study.

Protocol number: V00116 TD 201

Phase of development: II

Date of first enrolment: 28/01/2008

Date of last completed: 07/02/2008

Co-ordinator(s): Dr Anne MOUILLARD – 17, rue du Rempart Saint Etienne - 31000 TOULOUSE (France)

Sponsor Representative(s) for study report: Clinical Coordinator: *Jean-Marc EDMOND* - Institut de Recherche Pierre Fabre - *IDPF - 3, rue Ariane - 31521 RAMONVILLE Cedex (France) - Phone: +33 (0)561.73.74.91*
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Date of report: 11/06/2009

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: **V0116 TD**	**Referring to Module 5 of the Dossier**	
Name of active substance: **NICOTINE**	**Vol.: .....Page: .....**	

Title of study:	Analysis of the sensory profile of two new transdermal patches (V0116TD07AF019 and V0116TD07AF020) 21 mg/24h versus a reference transdermal patch NICOTINELL TTS® 21 mg/24h.	
Investigators:	Dr Anne MOUILLARD – 17, rue du Rempart Saint Etienne – 31000 TOULOUSE (France)	
Study centre(s):	Centre de Recherches sur la Peau (CERP) – 2, rue Viguerie – BP 3071 - 31025 TOULOUSE Cedex 3 (France)	
Publication (reference):	Not applicable	
Studied period *(years, months …)*: **(date of first enrolment)** **(date of last completed)**	First enrolment: 28/01/2008 Last completed: 07/02/2008	**Phase of development:** II
Objectives: **Primary:** **Secondary:**	Primary objective: To establish a comparative sensory profile of two new transdermal systems (V0116TD07AF019 and V0116TD07AF020) 21 mg/24h to a reference transdermal formulation NICOTINELL TTS® 21 mg/24h, by describing the following characteristics: use, touch and visual texture of the patch, sensations during patch application and after patch removal. In order, to choose the most acceptable product among the two transdermal systems developed. Secondary objective: To document the clinical local tolerability.	
Methodology:	Comparative, randomized, cross-over, single-centre, open sensory analysis study.	
Number of patients (planned and analysed):	12 healthy volunteers were planned and analyzed	
Diagnosis and main criteria for inclusion:	Regular or occasional smokers	
Test product, Dose, Mode of administration, Batch number:	1) V0116TD07AF019: Nicotine transdermal patch, designed to deliver 21 mg/24h, 30 cm², batch Nr CTD070 2) V0116TD07AF020: Nicotine transdermal patch, designed to deliver 21 mg/24h, 30 cm², batch Nr CTD071	
Other product, Dose, Mode of administration, Batch number:	Not applicable	
Duration of treatment:	The products were to be applied by the volunteers themselves on the external face of the arm, according the product recommendations, and were removed 10 minutes later. The successive area of applications were: the upper half of the external face of the right arm, then the external face of the left arm, then the lower half of the external face of the right arm. The three patches were tested successively on the same day during the same session.	

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Reference therapy, **Dose,** **Mode of administration,** **Batch number:**	NICOTINELL TTS® 21 mg/24h (Novartis Pharma): Nicotine transdermal patch, 30 cm², delivering 21 mg/24h, batch Nr 381200JB
Criteria for evaluation:	**Assessment criteria:**
Efficacy:	- Rating of sensory characteristics: • Sensory touch and visual texture during patch application: easiness of use, easiness of application on the skin, visibility, surface appearance, softness, suppleness, sticky of the patch surface, thickness, adherence, • Sensations 10 minutes after patch application: • burning, tension, stinging, comfort, adherence, • Sensations during patch removal: • rooting up, pain, • Sensations 5 minutes after patch removal: sediment of adhesive, redness, mark of the patch, stinging, burning, sticky skin, softness,
Safety:	- Local tolerance assessment (erythema, oedema, ulceration).
Statistical methods:	- Description of the sample studied, - Sensory profile: radar graph (means representation for each product and each descriptor), analysis of variance for each descriptor (SAS V8 software), - Tolerance: descriptive analysis.

Summary - Conclusions:

Efficacy results

A total of 13 subjects were selected, and 12 subjects were included and randomized, and composed the PP population. All the 12 subjects included completed the study. Demographic and baseline characteristics and efficacy analyses were performed on the PP population.

Eight subjects had a medical or surgical history. The Validation Committee considered that none of these medical and surgical histories were expected to interfere with the investigational products and that none of the concomitant treatments were expected to interfere with the investigational products.

The mean (SD) age of the population was 49.06 (4.66) years, the mean (SD) height was 165.58 (2.97) cm, and the mean (SD) weight was 60.92 (7.87) kg. All subjects (100%) were females. Two subjects (16.7%) used oral contraception, and two others (16.7%) had an intrauterine contraception device. The remaining 8 subjects (66.7%) were post-menopausal. All (100%) were current smokers. The compliance was 100%.

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The results of the sensorial analysis are summarized in the two tables below.

Descriptive statistics for the assessments performed during patch application

Descriptor	V0116TD07AF019	V0116TD07AF020	NICOTINELL
	Mean (SD) (pixels)	Mean (SD) (pixels)	Mean (SD) (pixels)
Easiness of use	320 (136)	327 (145)	337 (137)
Easiness of application on the skin	421 (135)	430 (85)	437 (111)
Surface appearance	379 (164)	395 (137)	416 (194)
Softness	**397 (143)**	**392 (119)**	**252 (127)**
Suppleness	**329 (118)**	**295 (113)**	**147 (125)**
Adherence	**451 (93)**	**441 (121)**	**175 (106)**
Sticky of the patch surface	21 (50)	18 (31)	63 (119)
Thickness	**130 (118)**	**151 (108)**	**372 (177)**
Visibility	**126 (96)**	**178 (138)**	**556 (59)**
Burning	30 (72)	25 (48)	36 (88)
Tension	102 (48)	166 (121)	148 (110)
Stinging	**67 (102)**	**14 (35)**	**27 (71)**
Comfort	367 (174)	330 (176)	339 (140)
Adherence	**413 (152)**	**397 (147)**	**163 (71)**

Bold characters indicate a statistically significant difference (Analysis of variance)

Descriptive statistics for the assessments performed upon patch removal and 5 minutes later

Descriptor	V0116TD07AF019	V0116TD07AF020	NICOTINELL
	Mean (SD) (pixels)	Mean (SD) (pixels)	Mean (SD) (pixels)
Rooting up	**230 (171)**	**356 (155)**	**519 (69)**
Pain	**354 (164)**	**270 (153)**	**109 (104)**
Sediment of adhesive	144 (156)	80 (103)	71 (120)
Redness	**251 (143)**	**159 (130)**	**65 (65)**
Mark of the patch	262 (182)	214 (189)	239 (182)
Stinging	48 (90)	27 (52)	28 (49)
Burning	67 (84)	54 (110)	16 (31)
Sticky skin	124 (184)	39 (64)	28 (60)
Softness	318 (211)	398 (140)	409 (159)

Bold characters indicate a statistically significant difference (Analysis of variance)

In the conditions of the study and with the descriptors selected, compared to the reference NICOTINELL TTS®, the two patches V0116TD07AF019 and V0116TD07AF020:

- Were perceived as having a softer and suppler touch,
- Were more adherent upon application as well as 10 minutes later,
- Were less thick and less visible on the skin,
- Were more difficult to remove, and induced more pain and more redness.

Moreover, compared to the patch V0116TDAF020, the patch V0116TDAF019:

- Induced more stinging after a 10 minutes application,
- Was more difficult to remove after a 10 minutes application, and induced more redness.

Safety results

Two subjects experienced erythema before application of the third patch, one before NICOTINELL TTS®, and one before V0116TD07AF019. These erythema were rated “very slight” (Grade 1) by the investigator.

No adverse event or serious adverse event was recorded, and no subject discontinued the study.

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The analysis of erythema indicated that no severe erythema was seen with NICOTINELL TTS®, V0116TD07AF019 and V0116TD07AF020, and only one "moderate" erythema was reported after V0116TD07AF019. The frequency of erythema induced by V0116TD07AF020 was lower than that induced by V0116TD07AF019, as indicated by the lower number of erythema of Grade ≥2 seen with V0116TD07AF020compared to V0116TD07AF019. The reference product NICOTINELL TTS® induced slightly less erythema than both V0116TD07AF019 and V0116TD07AF020.

In 8 out of the 12 subjects, the three patches induced an aggravation of erythema by at least 1 grade. For V0116TD07AF019, erythema aggravated by 2 grades in 3 subjects (25.0%) and by 3 grades in 1 subject (8.3%). For V0116TD07AF020, erythema aggravated by 1 grade in 11 subjects (91.7%) and by 2 grades in 1 subject (8.3%). No oedema or ulceration was observed before or after application of each of the three patches.

From Visit 1 to Visit 2, vital signs showed a decrease of both mean SBP and DBP by approximately 6 mm Hg, and a slight increase of mean heart rate by approximately 2.5 bpm. Since the measurements at Visit 2 were performed after patch removal and therefore after the transdermal administration of a very low dose of nicotine that was estimated to be around 0.14 mg per volunteer, this reaction did not seem to result from the investigational products.

Conclusion

The primary objective of this study was to establish the sensory profile of the two new transdermal systems V0116TD07AF019 and V0116TD07AF020 21 mg/24h compared to a reference transdermal formulation NICOTINELL TTS® 21 mg/24h, by describing the following characteristics: use, touch and visual texture of the patch, sensations during patch application and after patch removal, in order to choose the most acceptable product among the two transdermal systems developed.

In the conditions of the study and with the descriptors chosen, compared to the reference NICOTINELL TTS®, the two patches V0116TD07AF019 and V0116TD07AF020 were described as having a softer and suppler touch, being more adherent upon application as well as 10 minutes later, and being more difficult to remove, and inducing more pain and more redness.

Moreover, compared to the patch V0116TDAF020, the patch V0116TDAF019 induced more stinging after a 10 minutes application, was more difficult to remove after a 10 minutes application, and induced more redness.

No adverse event or serious adverse event was observed, and no subject discontinued the study for a reason imputable to an adverse event or a local reaction.

The reference product NICOTINELL TTS® induced slightly less frequent erythema than both V0116TD07AF019 and V0116TD07AF020. The analysis of the presence of erythema showed that the local tolerance of V0116TD07AF020 was approximately equivalent to that of NICOTINELL TTS® and better than that of V0116TD07AF019, as indicated by the lower number of "well defined" and "moderate" (Grade 2 and over) erythema seen with V0116TD07AF020 (2 well defined erythema, 16.7%) compared to V0116TD07AF019 (3 well defined, 25.0% and 1 moderate, 8.3%, i.e. total of 4 grade 2 erythema). From before application of the patch to after patch removal, erythema aggravated for V0116TD07AF019 by 2 grades in 3 subjects (25.0%) and by 3 grades in 1 subject (8.3%). From before application of the patch to after patch removal, erythema aggravated for V0116TD07AF020 by 1 grade in 11 subjects (91.7%) and by 2 grades in 1 subject (8.3%). The evolution of erythema confirmed that V0116TD07AF020 was better tolerated than V0116TD07AF019. Neither oedema nor ulceration was observed before or after patch removal.

From Visit 1 to Visit 2, vital signs showed a decrease of both mean SBP and DBP by approximately 6 mm Hg and a slight increase of mean heart rate by approximately 2.5 bpm. Since the measurements at Visit 2 were performed after patch removal with delivery of a very low dose of nicotine estimated to be around 0.14 mg per volunteer, this reaction did not seem to result from the investigational products.

Overall, the product V0116TD07AF020 could be considered as preferred by the volunteers compared to the reference NICOTINELL TTS®. Moreover, the product V0116TD07AF020 could be considered as preferred to V0116TD07AF019. Both V0116TD07AF019 and V0116TD07AF020 were well tolerated, did not induce any systemic adverse event, and induced local erythema with a frequency similar to that of the reference product NICOTINELL TTS®. V0116TD07AF020 was better tolerated than V0116TD07AF019.

Date of report:

11/06/2009