Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

Urodynamic effect of one single vaginal application of 2 mL of V0162 gel (0.8%) in post-menopausal women with overactive bladder.

Investigational product:	V0162 (d-mequitazine – 0.8%) gel for vaginal use
Study Design:	Multicentre, double-blind, placebo-controlled, two parallel group study
EudraCT number:	2010-024271-10
Protocol number:	V00162 GL 2 03
Phase of development:	IIa
Date of first enrolment:	11 July, 2011
Date of last completed:	13 October 2011
Coordinating investigator:	Professor Piotr RADZISZEWSKI, Niepubliczny Zaklad Opieki Zdrowotnej Centrum, Medyczne Wola, PW Jumo Sp. Z.o.o., ul. Ciolka 30, 01-432 Warsaw, Poland (Tel.: +48228771609)
Sponsor Representative for study report:	Head of Therapeutic Area: Athmane BOUROUBI Centre de Recherche et Développement Pierre Fabre, BP 13562, 3 avenue Hubert Curien, 31035 Toulouse, France (Tel.: +33534506345)

Date of report: 11 June, 2012

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:	**Referring to Module 5 of the Dossier**	
Name of active substance: **d-mequitazine 0.8%**	**Vol.: .....Page: .....**	

Title of study:	Urodynamic effect of one single vaginal application of 2 mL of V0162 gel (0.8%) in post-menopausal women with overactive bladder.	
Coordinating Investigator:	Professor Piotr RADZISZEWSKI, Niepubliczny Zaklad Opieki Zdrowotnej Centrum, Medyczne Wola, PW Jumo Sp. Z.o.o., ul. Ciolka 30, 01-432 Warsaw, Poland	
Principal Investigators	* Pr Piotr RADZISZEWSKI (centre n°5201 in Warsaw) * Pr Andrzej BORKOWSKI (centre n° 5202 in Warsaw) * Dr Krzysztof PLISZEK (centre n°5204 in Bielsko-Biala) * Dr Piotr FRACKIEWICZ (centre n°5205 in Torun)	
Study centres:	3 recruiting urology centres in Poland (n°5201, 5202 and 5204)	
Publication (reference):	No publications based on this study have been written to date	
Studied period: **(date of first enrolment)** **(date of last completed)**	3 months 11 July 2011 13 October 2011	**Phase of development: IIa**
Objectives:		
Primary:	To determine the urodynamic effects of one single vaginal application of 2 mL of 0.8% V0162 gel (V0162GL) over 24 hours in post-menopausal female patients with overactive bladder (OAB).	
Secondary:	* To evaluate the Lower Urinary Tract Symptoms (LUTS) of one single vaginal application of 2mL of 0.8% V0162 gel in post-menopausal female patients with OAB, * To evaluate clinical and biological tolerability of 2mL of 0.8% V0162 gel in post-menopausal female patients with overactive bladder (OAB)	
Methodology:	Multicentre, randomised (2:1 ratio), double-blind, placebo controlled, two parallel group study. All patients were to attend 3 study visits: selection visit (V1, Day -7 to Day -4), inclusion visit (randomisation, V2, Day 1) and end of study visit (V3, Day 2).	
Number of patients (planned and analysed):	Thirty-six (36) patients were planned, divided into 24 patients in the V0162GL treatment group and 12 patients in the placebo group. Seventy eight (78) patients were screened, 32 patients were randomised and completed the study (21 patients in the V0162GL treatment group and 11 patients in the placebo group).	

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Diagnosis and main criteria for inclusion:	Eligible patients met all the following criteria: • Female aged 18 years and above, • Post-menopausal female: the post-menopause was defined as the time after which a woman has experienced 12 consecutive months of amenorrhea (lack of menstruation), • Non-neurogenic overactive bladder (OAB) symptoms defined by urinary frequency (≥8 micturitions per 24 hours), urgency (at least one episode per 24 hours), urgency incontinence (at least one episode of incontinence per 24 hours) and nocturia (at least one episode per 24 hours), • Symptoms of OAB for 6 months or more, • Urodynamically-confirmed detrusor overactivity: defined as a phasic increase in detrusor pressure of at least 5cm of water in the presence of typical symptoms, • Maximum urinary flow rate (Q max) ≥15 mL/s at randomisation visit (V2, Day 1), • Responders to prior antimuscarinic therapy within one year, • Negative urine culture, • Patient accepted to participate to the study and able to understand and sign an approved Informed Consent Form, • Patient able to understand the protocol and to come to the control visits, • Patient who, in the judgement of the investigator was likely to be compliant during the study, • Patient registered with a social security or health insurance system.
Test product, **Dose,** **Mode of administration,** **Batch number:**	V0162 gel (V162GL) for vaginal use (d-mequitazine 0.8%) One single application of 2 mL of 0.8% V0162GL corresponding to 16 mg of d-mequitazine. The gel was applied into the vagina (with a 5 mL syringe). CLP 089 (expiry date: 02/2012).
Duration of treatment:	One day (single dose).
Reference therapy, **Dose,** **Mode of administration,** **Batch number:**	Placebo gel One single application of 2 mL of placebo gel. The gel was applied into the vagina (with a 5 mL syringe). CLP 088 (expiry date: 02/2012).
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Criteria for evaluation:

Efficacy:

Primary criterion

The number of detrusor contractions before application and at T2 hours (V2/Day 1) and T24 hours (V3/Day 2) after one single vaginal application of study treatment.

Secondary criteria

The other urodynamic parameters measured at 2 hours (V2/Day 1) and 24 hours (V3/Day2) post-application:

- Filling phase:
  - The amplitude of first phasic contraction (cmH_2O),
  - The baseline detrusor pressure (cmH_2O),
  - The volume (mL) corresponding to first sensation of bladder filling,
  - The volume at first phasic contraction (mL),
  - The volume (mL) at which contraction occurred,
  - The pressure of the detrusor at which contraction occurred (P_{det}),
  - The cystometric bladder capacity (mL),
  - The detrusor pressure at the end of filling phase (cmH_2O).
  - The calculated bladder compliance (mL/cmH_2O),
  - The volume (mL) at which incontinence occurred and the corresponding pressure of the detrusor (P_{det}),
- Voiding phase:
  - The volume (mL) voided per micturition,
  - The maximum detrusor pressure (cmH_2O) ($P_{det, max}$).
  - The maximum flow rate (Q_{max}),
  - The volume (mL) of residual urine (V_{res}) (measured prior to urodynamic investigations and during cystometry after micturition with the catheter present).

Lower urinary tract symptoms (LUTS) evaluation:

- Urinary symptoms: recorded by the patient on a diary during the run-in period (Day -3, Day -2, Day -1) and between Day 1 and Day 2, allowed to calculate:
  - The number of micturitions per 24 hours,
  - The number of nocturia episodes per 24 hours,
  - The number of urgencies per 24 hours,
  - The number of episodes of incontinence per 24 hours.

Safety:

- Adverse events (AE) were recorded at each visit,
- Laboratory investigations (haematology, biochemistry and urinalysis) were performed at Visits 1 and 3 ,
- Vital signs (systolic and diastolic blood pressure and heart rate) were assessed in supine and standing position, at each visit,
- A 12-lead Electrocardiogram (ECG) was recorded at each visit.

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Statistical methods:

Efficacy:

Primary criterion

Primary analysis: the changes from baseline (before application) at T2 hours and T24 hours (after application) were compared between the two treatment groups (V0162GL and placebo) by a non-parametric analysis of the covariance (based on ranks) with treatment group as fixed effect and the baseline as covariate.

Secondary criteria

For each urodynamic parameter, the changes from baseline (before application) at T2 and T24 hours after application were analysed in the same way as the primary criterion.

Safety:

Descriptive statistics for all safety variables.

All results (even those not analysed) were displayed in individual data listings.

Data sets:

Two (2) data sets were defined: Full Analysis Set (FAS) used to perform the analysis of safety, and Per Protocol (PP) set used to perform the analysis of efficacy.

Summary - Conclusions:

All the 32 randomised patients were post menopausal women with overactive bladder and without stress urinary incontinence. The median age (min; max) was 68.88 years (47.4; 83.1) and the median body mass index (min; max) was 28.44 kg/m^2 (21.8; 45.8).

24/32 patients presented at least one medical history, in all cases this was a surgical and medical procedure. 27/32 patients suffered from at least one concomitant disease, which was most commonly a vascular disorder (20/32) or a metabolism and nutrition disorder (11/32). Patient demography was similar for both groups.

All randomised patients were included in the FAS: 11 in the placebo group and 21 in the V0162GL group. As there were no major deviations, the PP data set was identical to the FAS.

Efficacy results

On the main criterion (number of detrusor contractions) 2 mL of 0.8 % of V0162GL did not show any effect versus placebo at T2 hours and T24 hours after a single vaginal application in post-menopausal patients suffering of overactive bladder. At both time points, the mean change observed in the placebo group was quantitatively greater [-0.9 (± 2.5) at T2 hours and -0.8 (± 2.3) at T24 hours] than in the V0162GL group [-0.4 (± 2.3) and -0.3 (± 2.3) respectively]; no statistical difference was observed between the two groups.

On the other urodynamic parameters (secondary criteria, including the amplitude of the first phasic contraction) 2 mL of V0162GL (at a concentration of 0.8%, 16 mg) did not show any effect versus placebo at T2 hours and T24 hours after a single vaginal application.

Over the 24 hours following study treatment application, no differences between the two treatment groups were observed on the lower urinary tract symptoms (LUTS).

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Safety results

No SAE occurred and no AE led to definitive withdrawal.

Overall, 7/32 patients reported 8 AE; among them 6/32 patients reported 6 TEAE: 2/11 patients in the placebo group (with 2 TEAE) and 4/21 patients in the V0162GL group (with 4 TEAE). The most common TEAE was urinary tract infection (with Escherichia Coli > 10^6/mL): 4/6 TEAE reported by 4/6 patients with TEAE, 2 patients in each treatment group. Moreover, in the V0162GL group, another patient reported a positive urine culture (Enterococcus, 10^4/mL), and the other patient experienced hyperkalaemia.

All the TEAE were considered as "not suspected" in their relationship to study drug according to the investigators and were of mild or moderate intensity. They were mainly not resolved at the end of evaluation (study end visit performed at Day 2, 24 hours after study drug application).

Neither TEAE at the application site (local TEAE), nor anticholinergic side effects known with anti-muscarinic drugs were reported in this study.

In the V0162GL group, abnormal laboratory results were reported for some patients and none were considered clinically significant by the investigator, except in 2 patients for potassium and cholesterol (reported as adverse event). Only one Clinically Noteworthy Abnormal Laboratory Values (CNALV) of low neutrophils was reported (patient n°5201008) in the V0162GL group.

With respect to vital signs (blood pressure and heart rate), no general trends were observed, and although changes that exceeded predefined limits were observed, they were not clinically significant.

There were a few abnormal ECG, but none of these abnormalities were considered clinically significant by the investigator. In both groups, no increase of more than 60 ms were observed for QTcB and QTcF values from baseline to end of evaluation. In the V0162GL group all QTcF values were ≤ 450 ms and only 1 patient had a QTcB value in the]450, 480] interval.

A single application of 2 mL of 0.8% V0162GL by intravaginal route was found to be safe and well tolerated.

Conclusion

Under study conditions, the V0162 gel at the dose of 2 mL of 0.8% (i-e a dose of 16 mg of d-mequitazine), did not show any effect on the urodynamic parameters versus placebo at T2 hours and T24 hours on the target population (post menopausal women with overactive bladder), its tolerance was satisfactory.

Date of report: 11 June 2012

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