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Comparison of the bioavailability and adhesiveness of different rotigotine transdermal patch formulations *Curr Med Res Opin* 2013; 1–2

Supplementary information

The reported studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines on Good Clinical Practice, and local regulations. Study protocols were reviewed by a national, regional, or investigational site ethics committee. All individuals provided written informed consent prior to participation.

Bioequivalence trials

Both bioequivalence studies (SP951 and SP0987) enrolled healthy Caucasian male volunteers, aged 18–55 years, with a BMI of 19–28 kg/m^2. Volunteers were excluded if they had previously participated in a clinical study of rotigotine, and/or had participated in another study of an investigational medical product within the previous 3 months. Further exclusion criteria included the following: history of chronic alcohol or drug abuse within the previous 2 years; positive alcohol or drug test; positive HIV, hepatitis B or C test; history of epilepsy or seizures; clinically relevant abnormality in physical examination, ECG, vital signs or safety laboratory examinations; relevant hepatic or renal dysfunction; known clinically relevant allergy or known/suspected clinically relevant drug hypersensitivity to any of the patch components; history of significant skin hypersensitivity to adhesives/transdermal products or recently unresolved contact dermatitis; intake of medication that may interfere with the test drug within 2 weeks prior to dosing; and/or a thickly hair-covered abdomen that may make it difficult to find a suitable patch application site.

In both studies, volunteers received each patch formulation for 24 hours in a cross-over design with a wash-out period of at least 5 days between applications. Patches were applied to the ventral abdomen, and pressed into place for 20–30 seconds to warm the adhesive. Cold chain patches were removed from the refrigerator at least 1 hour before application. A safety follow-up was performed 7–14 days after last patch removal. Participants remained in-house during each of the two treatment periods and were instructed to rest while wearing the patch and to abstain from taking any medications besides rotigotine. Patch adhesiveness was monitored throughout the application period and skin tolerability was assessed following patch removal. Blood samples for the determination of plasma concentrations of unconjugated rotigotine were collected and adverse events (AEs), safety laboratory examinations, vital signs measurements, 12-lead electrocardiograms, and physical examinations were monitored. Plasma concentrations of unconjugated rotigotine were determined by a validated liquid chromatography–tandem mass spectroscopy method with a lower limit of quantification of 0.01 ng/mL.

Sample sizes of 44 subjects for SP951 and 38 subjects for SP0987 were necessary to achieve 90% power for the assessment of bioequivalence. To allow for withdrawals and for exclusion of subjects from the pharmacokinetic set, 52 subjects were randomized in SP951 and 50 were randomized in SP0987. Pharmacokinetic analyses were performed using the pharmacokinetic set, which included all randomized individuals who: (1) had received at least one dose of study medication; (2) had a sufficient number of bioanalytical assessments to calculate reliable estimates for the primary pharmacokinetic parameters; and (3) had sufficient patch adhesiveness. Individuals who had <75% patch adherence at any time point or <90% patch adherence for >12 hours were excluded from the pharmacokinetic set. Primary pharmacokinetic parameters were analyzed using ANOVA for the log-transformed data. Patch formulations were considered to be bioequivalent if the 90% CIs for the treatment ratios of $AUC_{(0-tz)}$, $AUC_{(0-\infty)}$ (SP0987 only) and C_{max} were within the acceptance range for bioequivalence of 0.8–1.25. All individuals who received at least one dose of study medication were included in the safety analyses.

Patch adhesiveness trial

The SP1066 study enrolled men and women aged 18 years or older with a diagnosis of idiopathic PD. Patients were eligible for participation if they had received continuous treatment with commercially available rotigotine transdermal patches for at least 3 months, and had received treatment with a stable dose of rotigotine (including an 8 mg/24 h patch) for at least 2 weeks prior to enrollment. Patients were required to be reliable and capable of adhering to the study protocol. Patients were excluded for the following reasons: participation in another study of an

investigational medical product within the previous 30 days; history of chronic alcohol or drug abuse within the previous 6 months; any medical or psychiatric condition which, in the opinion of the investigator, could have compromised their wellbeing or ability to participate in the study; history or present condition of an atopic or eczematous dermatitis, psoriasis, or active skin disease; and/or any clinically relevant abnormality in the physical examination that, in the opinion of the investigator, could have jeopardized the safety of the patient or the validity of the results.

The total duration of the study was 4 weeks. This included an eligibility assessment (within 0–14 days prior to Day 1), a single application of the cold chain patch on each of two consecutive days, followed or preceded by a single application of the room temperature stable patch on each of two consecutive days, and a safety follow-up 7 days after final patch removal. In order to maintain the treatment blind, all study medication was stored under cold chain conditions. Patches were applied by the investigator to areas of intact, healthy, dry skin, on the abdomen, thigh, hip, flank, shoulder or upper arm and pressed into place with the palm of the hand for 20–30 seconds to warm the adhesive. Investigators were instructed to use the same body area for all four patch applications (e.g. Day 1: upper-right abdomen; Day 2: upper-left abdomen; Day 3: upper-right abdomen; Day 4: upper-left abdomen). Patch adhesiveness per day was rated by the investigator 24 hours after patch. Safety and tolerability was assessed throughout the study by monitoring AEs and evaluation of the skin at the application site. All statistical analyses were considered exploratory and no formal sample size calculation was performed. Primary analyses of the primary adhesiveness variables were carried out using the per-protocol set following a non-parametric statistical method. Sensitivity analyses of the primary adhesiveness variables were performed using a parametric statistical method.

