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Pharmacokinetic, Adhesion and Safety Evaluation of a Transdermal Patch in Healthy Volunteers following Single and Multiple Application

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ABSTRACT

PURPOSE
Transdermal delivery offers a number of advantages over conventional routes of administration including providing a controlled release over an extended period. Pharmacokinetic studies comprise generally single-dose and multiple-dose investigations considering particular aspects like fluctuation and concentration time profile after patch removal. In this presentation, the pharmacokinetic, adhesion and safety profiles of a transdermal patch were compared under normal activities following single and multiple transdermal applications.

METHODS
In each of these trials, 36 healthy volunteers were enrolled. Subjects received a single dose or a 3-patch application treatment, and each patch was worn for 24 hours. The application site was standardized. Blood samples were collected over at least a 24-hour period, and plasma concentrations of the parent drug were assayed using a validated HPLC method using MS/MS detection. Main PK parameters were calculated using a non-compartmental approach. Skin adhesiveness and irritation were evaluated at different timepoints using recognized scoring systems.

RESULTS
Following single/multiple transdermal administration, a Cmax of 2295/2824 pg/ml was observed 16 hours after application. Repeated application of the transdermal formulation resulted in a 1.5-fold increase of the systemic exposure (AUC) (33453 pg*h/mL vs 49580 pg*h/mL). More than 90% of the patches had essentially no lift off the skin 24 hours after application, and none of them completely detached. Following multiple administrations, one subject had an adhesion score 3 (< 50% adhered but not detached), which required reattachment. Minimal erythema was reported in most of the subjects following removal of the patch formulations, and none of them demonstrated evidence of irritation (score≥3) 12 hours post-removal. The transdermal drug product was well tolerated, following single and multiple transdermal administration; no serious adverse events were observed.

CONCLUSION
Results from this study demonstrate a case where the observed change in drug absorption was not associated with increased local irritation.

PURPOSE

Transdermal systems are a desirable form of drug delivery because of the obvious advantages over other routes of delivery. The general acceptability of transdermal products by patients is very high, which is also evident from the increasing market for transdermal products. The transdermal drug delivery market, worth $12.7 billion dollars in 2005, is expected to reach $32 billion in 2015[1]. For the review and approval of a generic transdermal drug product, a PK endpoint study is required by the regulatory agency. Adhesion performance must also be evaluated and compared in either the PK bioequivalence study or in a separate parallel or crossover adhesion study.
In this presentation, the PK, adhesion and safety profiles of a transdermal patch were compared under normal activities following single and multiple transdermal applications.

METHODS

CLINICAL CONDUCT
Endpoints were evaluated in single center, randomized, laboratory-blinded, trials. Subjects were screened within 28 days prior to study start. Healthy adult volunteers (male and non-pregnant female subjects between 18-55 years, within acceptable body weight and height ranges, not using tobacco products in the last 12 months, with a negative urine drug/alcohol screen) were selected. Each subject was submitted to vital signs measurement, a 12-lead ECG and laboratory evaluations (including serum chemistry, hematology, and urinalysis).

The transdermal patch was applied to 36 subjects as a single dose as well as multiple dose applications. The transdermal patch was applied to clean, dry, hairless, intact healthy skin on the upper arm, and worn for 24 hours. Subjects did not apply topical products to the skin area where the patch was placed, as this could have impaired the adhesive performance or irritation potential. The transdermal patch was pressed firmly in place, making sure contact was complete.

PK ENDPOINTS
Blood samples for pharmacokinetic measurements were collected prior to and up to 36 hours (serial sampling) after the single patch application. They were also collected over a 72-hour period after a 3-patch application treatment. Plasma concentrations of the moiety were assayed using a validated HPLC method using MS/MS detection. Main PK parameters were calculated with a validated PK software using a non-compartmental approach.

ADHESION AND IRRITAITON
Patch adhesiveness was assessed 0.08, 6, 12 and 18 hours after application and immediately before patch removal at the end of the 24-hour application. Patch reinforcement was allowed. A five-level scoring system was used:

0 = ≥90% adhered (essentially no lift off the skin)

1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)

2 = ≥ 50% to < 75% adhered (less than half of the system lifting off)

3 = < 50% adhered but not detached (more than half the system lifting off the skin without falling off)

4 = patch detached (patch completely off the skin)

Skin irritation was assessed approximately 0.08, 1 and 12 hours after patch removal. The FDA-recommended scales were used to evaluate and score the dermal responses (1-7) and other effects (A-G).

RESULTS

SAFETY RESULTS
All subjects completed the study following single dosing, while one subject withdrew consent during the multiple application. About 28% and 36% of the subjects reported AEs related to the drug product following single dosing and multiple applications. Overall, the applications were generally safe and well tolerated by the subjects included in the studies.

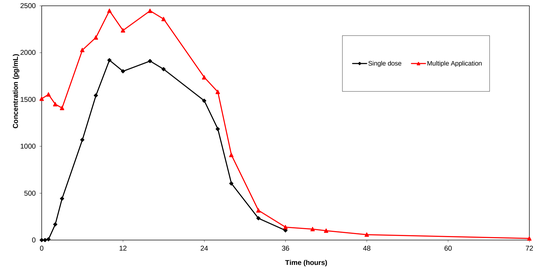
PHARMACOKINETIC RESULTS
Repeated application of the transdermal formulation resulted in a 1.5-fold increase of the systemic exposure (AUC). The mean terminal half-life value was 12 hours following multiple applications.

TABLE 01: PHARMACOKINETIC PARAMETERS

Parameter	Single Dose		Multiple Application	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	2295	55	2824	40
C_{24} (pg/mL)	1487	34	1737	34
T_{max} (hours) *	16.00	6.00-26.00	16.00	10.00-26.00
AUC_{24} (pg·h/mL)	33453	56	49580	40
AUC_{36} (pg·h/mL)	40260	50	58730	38

* Median, Min-Max

FIGURE 01: LINEAR PROFILE OF THE MEAN



ADHESION AND IRRITATION RESULTS
More than 90% of the patches had essentially no lift off the skin 24 hours after application, and none of them completely detached. Minimal erythema was reported in most of the subjects following removal of the patch formulations, and were resolved within 24 hours.

TABLE 02: ADHESION SCORES

Time After System Application (hours)	Single Dose		Multiple Application	
	MEAN	MIN-MAX	MEAN	MIN-MAX
0.08	0.00	0 - 0	0.00	0-0
6	0.00	0 - 0	0.00	0-0
12	0.00	0 - 0	0.00	0-0
18	0.00	0 - 0	0.00	0-0
24	0.03	0 - 1	0.03	0-1

TABLE 03: IRRITATION SCORES

Time After System Removal (hours)	Single Dose		Multiple Application	
	MEAN	MIN-MAX	MEAN	MIN-MAX
0.08	0.56	0-2	0.97	0-2
1	0.89	0-2	0.91	0-2
12	0.69	0-2	0.46	0-1

CONCLUSION

The methodology of this study is particularly important to assess accurately the PK, safety and tolerability of investigated drugs. This can be applied for the development of a new drug product or for the determination of bioequivalence between two formulations.

[1] Ther Deliv. 2010 July ; 1(1): 109–131.