PI-22

ASSESSMENT OF DOSE RESPONSE INFORMATION IN DRUG LABELING. D. A. Spyker, MD, P. Frohna, MD, P. Kuebler, PharmD, S. Kelsey, MD, A. Joshi, PhD, C. Ng, PhD, B. Lum, PhD, R. Bruno, PhD, J. Lu, PhD, R. Quesenberry, MA, S. Reoriguez, BA, D. Giltinan, PhD, L. R. Cantilena, MD, C. C. Peck, MD, Genentech, Inc, Uniform Services University of Health Sciences, Georgetown University, South San Francisco, CA.

Background: Dose guidance is an essential element of drug package inserts (PIs) and is a common change made in PIs post approval. **Methods**: We reviewed 229 PIs for products mentioning "dose response" (N=300) in the electronic *2003 Physicians Desk Reference* for date of last update (DU) and a dose response (DR) completeness score as a % of the maximum of 35 points (CS%). The CS comprised the scores (0-2 or 0-3) by each reviewer of the 15 data elements in 4 categories (see table). We performed duplicate reviews of 27 PIs to assess inter-rater correlation of the CS (Spearman rho). Variability was assessed via 95% confidence intervals (95% CI), [mean ± 1.96 std error of the mean] (SAS JMP ver 5.0.1a). **Results**: The DU, found in 224 (98%), ranged from 6/93 to 8/03. Inter-rater correlation (N=27) of the CS was rho = 0.53, p= 0.0045).

DR Information Category	Max	CS% Median (range)	CS% Mean [95% CI]
DR in Development	15	36% (0%, 100%)	35% [31%, 38%]
DR of Adverse Events	6	17% (0%, 100%)	31% [27%, 35%]
DR for Efficacy	6	33% (0%, 100%)	33% [29%, 37%]
Dose adjustment	12	42% (0%, 100%)	43% [39%, 46%]
Total (CS%)	35	24% (0%, 93%)	37% [34%, 39%]

Conclusions & Recommendations: By these measures, there is limited dose response described in these PIs, especially DR of Adverse Events. Aware that recent NDA's contain FDA-encouraged DR trials, we recommend FDA and manufacturers incorporate useful DR data in drug labels and provide web-based access to DR data not presented in their PI.

PI-23

PREVALENCE OF THE SLOW METABOLIZER (SM) PHENOTYPE AND SINGLE DOSE PHARMACOKINETICS (PK) OF DESLORATADINE (DCL) IN A POPULATION OF HEALTHY ADULTS. G. S. Frick, R. A. Blum, S. J. Kovacs, C. Vitow, J. A. Stewart, W. K. Kraft, Thomas Jefferson University, Buffalo Clinical Research Center, Aventis Pharmaceuticals, CliniQuill Associates, LLC, Philadelphia, PA.

Purpose: To characterize the PK of DCL and 3-OH-DCL in SMs compared with normal metabolizers (NMs). DCL is metabolized to 3-OH-DCL by an unidentified enzyme(s). The product insert for DCL states that ~7% of the general population are apparent SMs, with higher prevalence estimates in blacks (~20%).

Methods: Blood samples were collected pre-dose and at 1, 2, 3, 4, 6, 7, 8, 12, and 24 hrs following a single oral 5 mg dose of DCL. Plasma was assayed for DCL and 3-OH-DCL by LC/MS/MS and exposure measures computed by non-compartmental methods using WinNonlin; C_{max} and T_{max} were determined from observed data. SMs were identified by $AUC_{(3\text{-OH DCL})}$:$AUC_{(DCL)}$ ratios <0.1.

Results: 170 non-smoking, male and female subjects 18–55 yrs of age received DCL. 14 of 170 (8.2%) subjects were identified as SMs; 7 had no measurable 3-OH-DCL concentrations. In addition to decreased hydroxylation, absorption appears delayed (possibly impaired) in SMs. DCL exposures are tabulated below.

	NMs				SMs			
	$AUC_{(0\text{-}24)}$ pg•hr/mL	C_{max} pg/mL	T_{max} h	C_{24h} pg/mL	$AUC_{(0\text{-}24)}$ pg•hr/mL	C_{max} pg/mL	T_{max} h	C_{24h} pg/mL
Min	9995	969	1	113	26916	1450	6	1128
Max	55776	5730	7	1470	73118	3777	24	3080
Median	26242	2252	3	442	40168	2227	12	1582
Mean	27114	2425		507	41955	2263		1782
SD	9384	875		250	13066	663		623
CV%	34.6	36.1		49.3	31.1	29.3		35.0

Conclusions: Plasma concentrations of DCL rise and fall more slowly in SMs. Consequently, SMs will accumulate DCL with recommended dosing and will be more susceptible to concentration-related adverse effects. Clinical risks of prolonged increased DCL exposure in SMs require further study, as do the underlying genotypes conferring different phenotypes for DCL PK. A mechanistic basis for both impaired absorption and metabolism is not immediately apparent.

PI-24

PHARMACOKINETICS OF A HUMAN MONOCLONAL ANTIBODY TO IL-12 P40 FOLLOWING SINGLE INTRAVENOUS INFUSION IN PATIENTS WITH MODERATE TO SEVERE PLAQUE-TYPE PSORIASIS. Y. W. Zhu, PhD, J. Zhang, PhD, C. Pendley, PhD, B. Frederick, M. Mascelli, PhD, A. B. Gottleib, MD, PhD, C. L. Kauffman, MD, C. Guzzo, MD, H. M. Davis, PhD, D. E. Everitt, MD, M. A. Graham, PhD, Centocor, Inc., UMDNJ-Robert Wood Johnson Medical School, Georgetown University Medical Center, Malvern, PA.

Purpose. To assess the pharmacokinetics (PK) of a human monoclonal antibody to IL-12 p40 (anti-IL-12 p40 mAb) following single intravenous (IV) infusion in patients with moderate to severe plaque-type psoriasis as part of a Phase I study. **Methods**. Patients (n = 18) were randomly assigned to receive a single ascending IV dose of the mAb (n = 4-5 per group). Blood samples were collected and serum mAb levels were measured using an ELISA method. Non-compartmental analysis was employed to calculate the PK parameters of the mAb. The relationship between PK and the severity of psoriatic lesions (Psoriasis Area and Severity Index, PASI) was also investigated to explore the relationship between drug exposure and efficacy. **Results**. The mAb was slowly eliminated from the circulation after a single IV infusion. The C_{max} and AUC were linearly correlated with the dose. Dose-dependent sustained improvements in PASI were observed. **Conclusions**. PK of the mAb following a single IV infusion were linear and dose-independent, and the systemic exposure increased in a dose-proportional manner. IV administration to patients is feasible in terms of its favorable elimination half-life and sustained clinical response.