EMA/588790/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Doxorubicin SUN

International non proprietary name: Doxorubicin

Procedure No. EMEA/H/C/002049

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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I. Recommendation

Based on the CHMP review of the data and the Applicant's response to the questions raised by CHMP at Day 180 on quality, safety and efficacy, the CHMP considers that the application for Doxorubicin 2mg/ml Concentrate for Solution for Infusion in the treatment of:

- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.
- For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.
- In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.

is not approvable since there are outstanding major non-clinical and clinical objections which preclude a recommendation for marketing authorisation at the present time.

II. Executive Summary

This centralised abridged application, under Article 10(3) concerns a generic liposomal formulation of doxorubicin, under the trade name Doxorubicin 2mg/ml concentrate for solution for infusion. The reference product is Caelyx® 2mg/ml concentrate for solution for infusion, a centrally authorised product since 1996.

Doxorubicin HCl for injection, an anthracycline chemotherapeutic agent, has been approved as a cytotoxic cancer therapy in Europe since the 1970s. In addition to adverse events typical of a chemotherapeutic agent, doxorubicin HCl for injection has an increased risk of cardiac adverse effects. To reduce the toxicity profile, especially doxorubicin-induced cumulative cardiotoxicity, encapsulated doxorubicin in methoxypolyethylene glycol (MPEG)-coated liposomes was developed, reducing uptake by reticulo-endothelial system of the liver, spleen and bone marrow, resulting in increased circulation time. The pegylated liposome formulation of doxorubicin was first approved in the US in 1995 as Doxil, followed by marketing authorization in Europe in 1996 under the Caelyx brand name.

II.1 Quality aspects

Drug Substance

The chemical-pharmaceutical documentation and Quality overall Summary in relation to Doxorubicin 2mg/ml Concentrate for Solution for Infusion are of sufficient quality in view of the present European regulatory requirements. The active substance doxorubicin HCl is subject of a monograph in the European Pharmacopoeia and a current certificate of suitability. The drug substance specification is generally acceptable. The current CEP stated a re-test period of 24 months.

Drug Product

The proposed product, a liposome formulation, is doxorubicin hydrochloride encapsulated in liposomes with surface-bound methoxypolyethylene glycol (MPEG). This process is known as pegylation and protects liposomes from detection by the mononuclear phagocyte system (MPS), which increases blood circulation time. The development of both dosage forms has been described, the choice of excipients justified and their functions explained. The product specifications cover appropriate parameters for both dosage forms. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches of each presentation. Batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Based on the stability data a proposed shelf-life of 20 months is considered acceptable.

II.2 Non clinical aspects

Introduction

The qualitative and quantitative composition and physicochemical properties of SPARC's proposed Doxorubicin HCl Liposome Injection and Caelyx are similar. The comparative analysis of lipid content between SPARC's product and Caelyx indicated similar content and physico-chemical characteristics of lipid component. Based on the similarity of composition and physico-chemical properties, SPARC considered the proposed product as essentially similar to Caelyx.

SPARC originally completed seven nonclinical studies to support the comparability of Doxorubicin HCl Liposome Injection and Caelyx. These studies compared the pharmacology (2 studies), safety pharmacology (1 study), pharmacokinetic/distribution (3 studies) and toxicity (1 study) of SPARC's product versus the innovator product.

In response to queries raised by the Rapporteur, the Applicant acknowledged the deficiencies in the design, conduct and analysis of the originally submitted studies (summarised below). The Applicant has now initiated four new tissue distribution studies, two in the rat and two in the mouse, one study at a low and the other study at a high dose level in each species. In addition an additional pharmacodynamic study has been conducted. These studies will be briefly considered below. It should be noted that two of the four tissue distribution studies (the low dose studies) are currently ongoing and the final study reports are not available, consequently it is not currently possible to complete an assessment of the new non-clinical data. In addition, there is the outstanding the issue of the forthcoming GLP inspection of the applicant's test facilities, hence a final assessment of the non-clinical data cannot currently be finalised.

Assessor's comment:

The final study reports have been submitted. The pivotal studies are the pharmacokinetic studies.

The GLP inspection has now been conducted. The new studies were conducted in compliance with GLP.

Pharmacology

To compare the antitumour efficacy between Doxorubicin HCl Liposome Injection and Caelyx, SPARC conducted two pharmacodynamic studies. The studies were performed in syngeneic fibrosarcoma (WEHI164)-bearing BALB/c mice and human mammary carcinoma (MX-1)-bearing athymic nude BALB/c mice. In both studies, the antitumour efficacy was assessed by considering 3 measures of tumour burden (percentage T/C, tumour regression and specific tumour growth delay).

Tests of statistical significance were derived from ANOVA using a Bonferroni adjustment, presumably to account for the multiple (2) comparisons to placebo control.

In the syngeneic fibrosarcoma bearing mice, both Doxorubicin HCl Liposome Injection and Caelyx showed significant anti-tumour activity.

For study BRP-08-247 (human mammary carcinoma bearing mice) data for each PD measure are considered potentially unreliable given the changes in number of animals per group over the course of follow-up. With reference to the relevant table, it is clear that data are missing earlier and more frequently on the active treatment arms than on placebo. The exclusions from the active formulations are primarily due to observed toxicity, but the 'observed cases' type analysis presented has the potential to be biased unless exclusion is independent of tumour volume. If exclusion is not independent, in particular if animals with high tumour volume have been excluded from the active treatment arms and not from placebo, then the groups will not be comparable at any given timepoint and the estimated effects will be biased. Further discussion of these exclusions and the reliability of the PD data presented is required to support reliable inference from this study. In summary, there are concerns regarding the granting of a marketing authorisation. These are concerns over the design, conduct and reporting of the pharmacodynamic study (study BRP-08-247).

SPARC conducted an *in vitro* haemolytic potential test of SPARC's Doxorubicin HCl Liposome Injection in human blood. Average haemoglobin concentrations were comparable between SPARC's product and Doxil and no haemolysis was observed in either product.

The Applicant has conducted a further study in which the efficacy of doxorubicin HCl liposome injection was compared to that of Caelyx following dosing in human mammary carcinoma bearing athymic nude

mice at 3 dose levels. The antitumour activity was comparable between the SPARC Ltd product and Caelyx. Also, at all 3 dose levels, the mortality and body weight changes of the two products were comparable.

Pharmacokinetics

The Applicant conducted three studies. One study was designed to support claims of bioequivalence of SPARC's Doxorubicin HCl Liposome Injection to Caelyx, and two studies to compare tissue distribution between the two products.

Bioequivalence study

In the bioequivalence study, the Cmax, AUC0-t, and AUC0-∞ values were comparable between Doxorubicin HCl Liposome Injection and Caelyx. The 90% confidence intervals for Cmax and AUC ratios (test to reference) fell within 80 to 125% supporting the claim that Doxorubicin HCl Liposome Injection is bioequivalent to Caelyx. In addition, there were no significant differences between the products with respect to Tmax, T1/2, Kel, Cl, and MRT. The data are considered to support the claim of bioequivalence of the test product to the reference product in fibrosarcoma-bearing mice.

Tissue distribution studies

The innovator liposomal formulation of doxorubicin, Caelyx, has been shown to alter the tissue distribution of the drug, giving a more favourable benefit risk balance for the liposomal formulation over administration of free doxorubicin. To assure the same efficacy and safety as Caelyx, therefore, any generic product must achieve the same tissue distribution as the innovator product. This is especially important as formulation factors are known to influence this distribution. As it is not possible to study this distribution in man, the data generated in these two mammalian models are pivotal to the regulatory decision regarding the approvability of a generic doxorubicin liposomal product. The underlying premise is that if Doxorubicin SUN is truly comparable to Caelyx, that its tissue distribution will also be comparable in these two mammalian models.

SPARC performed two tissue distribution studies, one in fibrosarcoma-bearing BALB/c mice and the other in non-tumour bearing Sprague-Dawley rats. In the case of both studies the study design followed one of the studies submitted for approval of the innovator product, using the same dose, number of animals and time points for analysis.

In the case of the study in fibrosarcoma-bearing mice (Study BRP-08-244) the batch of test product used was the same as that for the bioequivalence study in mice (Study LD-007), but different from that used for the human bioequivalence study. The method of analysis used by the applicant (checking for significant differences at individual time points) is not suitable for assessing the comparability of the time course of drug exposure in various tissues, as evidenced by a number of misleading statements in the Pharmacokinetics written summary:
(1) While the Applicant claims that for both SPARC's Doxorubicin HCl Liposome Injection and Caelyx the mean peak concentrations in tumour, heart, spleen, and liver tissues were reached in 4 hours, this is not the case for tumour (reference), spleen (test and reference), liver (test).
(2)The applicant states that in the kidneys, levels of doxorubicin were consistently high during the study period, indicating its major role in excretion of doxorubicin. The Applicant further states that tumour and heart tissues displayed the next highest levels of doxorubicin, followed by spleen and liver tissues which had the lowest levels. However, in the graph compiled by the assessor, the persistence of drug in the kidneys does not appear any more remarkable than any other tissue, the spleen has comparable (test) or the highest drug levels (reference) of any tissue (not among the lowest).

There appears to be persistence of drug in a number of tissues, which raises the question as to whether the sampling duration was sufficient to give a reliable estimate of the relative extent of exposure of individual tissues to doxorubicin from the two products. The Applicant should justify the duration of sampling.

The comments regarding the method of data analysis are the same as above for Study BP-08-244. In both studies, the applicant should use a more appropriate analysis method for key data, quantifying peak (C_{max}) and total exposure (AUC) and confidence intervals around these (e.g., Bailer's method for analysis of data from serial sacrifice designs). The Applicant should comment on the implications of any differences in doxorubicin distribution between the two products.

The apparent persistence of drug in some tissues is even more apparent in the data from the rat study, perhaps due to the shorter duration of sampling (72 h as opposed to 96 h in the mouse study). As mentioned for BP-08-244, this raises the question as to whether the sampling duration was sufficient to give a reliable estimate of the relative extent of exposure of individual tissues to doxorubicin from the two products. The Applicant should justify the duration of sampling.

The Applicant has initiated 4 new tissue distribution studies as a means of answering the queries raised by the Rapporteur. The results of two of these studies have now been submitted. The design, conduct and reporting of these studies is to an acceptable standard. Since two of the studies are ongoing, it is not possible to currently complete a final assessment of the pharmacokinetics of the SPARC product. This major objection cannot currently be resolved.

Assessor's comment:

The two original tissue distribution studies submitted with this application were deficient in terms of the doses utilised, study duration, choice of analyte, data analysis methods and interpretation of results. The Applicant conducted an additional four studies of tissue distribution, two of which were submitted with the Day 120 response and two with the Day 180 response. Upon review, it was found that there were errors in the method of calculation of plasma and tissue AUC utilised in all four studies. The Applicant identified the source of the error and submitted revised reports on the 6th June 2011 and additional documentation around software utilised in data analysis on the 7th June 2011. These late revised reports were assessed to support a regulatory decision regarding the equivalence of tissue distribution of Doxorubicin SUN to Caelyx.

While the Applicant concluded comparability of tissue distribution of the two products, there were major concerns regarding the reliability of the data and signals of a lack of equivalence between the two products.

Toxicology

The active ingredient, doxorubicin HCl, is an established drug substance for which there are extensive safety studies in animals and clinical experience. Similarly, extensive safety characterization on liposomal doxorubicin, Caelyx, has been obtained through nonclinical toxicity studies and clinical experience.

To compare the toxicity of SPARC's Doxorubicin HCl Liposome Injection and Caelyx, SPARC performed a non-GLP single-dose toxicity study in CD-1 mice in comparison to Caelyx. This study was conducted in SPARC's own test facility. Each product was administered as a single intravenous dose at 10, 20, or 40 mg/kg. One group of animals was sacrificed on Day 8 and one group on Day 97. A total of 15 animals/sex/dose were used in the study, of which 5/sex/dose were sacrificed for haematology analyses on Day 8, another 5/sex/dose sacrificed for biochemistry analyses and histopathology on Day 8, and the remaining 5/sex/dose were employed for observations up to Day 97 and histopathology.

The parameters evaluated included mortality, food consumption and body weights, clinical chemistry, haematology, gross and histopathology. For both products the anticipated findings were noted. There appeared to be no toxicologically significant differences between the two products.

No new toxicity studies were requested and none have been conducted.

Non-clinical conclusions

There are two major objections and one other concern.

The first major objection is that the results of the low dose studies in mouse and rat are required. Additional graphs to allow interpretation of the confidence intervals calculated by the Applicant are needed to support the claim of equivalent tissue distribution between the test and reference products. These should be presented for the four individual studies (low and high dose in the mouse and rat) and compared across dose levels for each species.

The second major objection concerns GLP inspection issues. The non-clinical studies should have been conducted in accordance with GLP. Since the data submitted by the applicant was generated in test facilities in a country which is not part of the GLP-monitoring programme a GLP inspection is required of representative samples of the previously submitted studies and also of the recently completed and

ongoing studies. A GLP report concluding that the sites and studies inspected were in compliance with the principles of GLP is necessary for the MAA to be considered approvable.

The other concern is that an explanation is required regarding (1) the handling of missing values in calculation of summary statistics and pharmacokinetic parameter values, (2) why some concentrations are reported as 0.00 and others as BLQ and (3) how a value is determined to be NC. The potential impact on the calculations presented by the Applicant should be evaluated and discussed.

Assessor's comment:

Concerning the first major objection, the results of tissue distribution studies have been submitted. However, there remains an outstanding major objection regarding the reliability of the data and signals of a lack of equivalence between the two products.

The second major objection concerns the GLP inspection issue. The GLP inspection requested by the CHMP on 18 November 2010 in order to establish the GLP status of pivotal non-clinical studies has been conducted. On the basis of this inspection it can be confirmed that the new studies have been conducted in compliance with GLP. This issue is resolved.

The other concern has not been resolved.

II.3 Clinical aspects:

The Applicant has submitted data from three bioequivalence studies in support of this application as follows:

Study ID	**Dose/patient population**	**Reference product**	**Number analysed (n)**
PKD/08/038	50mg/m^2 ovarian cancer	Caelyx (Europe)	23
PKD/09/031	30mg/m^2 multiple myeloma	Caelyx (Europe)	26
PKD/09/030	50mg/m^2 ovarian cancer	Doxil (US)	41

Biowaiver

Liposomes are complex formulations. It is not known what causes non-linear pharmacokinetics of liposomal doxorubicin at doses higher than 10-20mg/m^2. Hence, it is not known what dose would be the most sensitive to establish bioequivalence. At Day 120, CHMP considered that the request for a biowaiver for the 20mg/m^2 and 30mg/m^2 doses was not justified, and requested an additional study at the 20mg/m^2 dose.
The Applicant was not able to recruit sufficient patients with Kaposi's Sarcoma for a 20mg/m^2 study. Instead, an additional bioequivalence study (PKD/09/031) was conducted at the 30mg/m^2 dose, in patients with multiple myeloma. The Applicant has elected to delete the Kaposi's sarcoma indication from the SPC.
In the responses to the D180 CHMP LoQ, the Applicant concluded dose proportionality in the range 30mg/m^2 to 50mg/m^2, with reference to the literature. However, the justification is considered inadequate. The Applicant should provide a robust justification for the extrapolation of data from the 50mg/m^2 dose to lower doses (20mg/m^2 and 30mg/m^2). In order to assess linearity, the Applicant should consider all data available in the public domain with regard to dose proportionality and review the data critically. Assessment of linearity should consider whether differences in dose-adjusted AUC meet a criterion of ±25%. The process for the literature search should be described. Some studies referenced by the Applicant appear to show dose proportionality but the Caelyx SPC concludes non-proportionality. This discrepancy should be explained.

Bioequivalence Study PKD/08/038 (50mg/m^2 dose: advanced ovarian cancer, against Caelyx)

Doxorubicin 2mg/ml concentrate for solution for infusion (test product) and Caelyx 2mg/ml concentrate for solution for infusion (reference product) were compared at the 50mg/m^2 dose during a randomized, multi centre, open label, two treatment, two period, two sequence, single dose, crossover study, conducted under fed (normal low fat breakfast) conditions in patients with ovarian cancer.

An intravenous infusion of test or reference product was administered 30 minutes after a normal low fat breakfast, according to the randomisation schedule. Sampling was carried out pre-dose, and at 0.25, 0.5, 0.75, 1.0, 1.083, 1.25, 1.5, 2, 4, 6, 9, 25, 49, 97, 169, 241 and 337 hours post-dose. The washout period was 28 days. Total, encapsulated and free (un-encapsulated) doxorubicin, and doxorubicinol (main metabolite) were measured in plasma using validated LC/MS/MS methods. 29 patients were randomised, of which 23 completed the study and were analysed.

Results

Total doxorubicin

The concentration-time curve is adequately characterised. Bioequivalence is established for total doxorubicin, within 80.00-125.00% criteria. The Applicant has also provided 90% CIs for log-transformed data of V_d and clearance, which are also within 80.00-125.00%.

Table 1: Summary of results for total doxorubicin (PKD/08/038)

TABLE- 14.2 – 1A								
SUMMARY OF RESULTS								
TOTAL DOXORUBICIN (N = 24)								
Pharmacokinetic Parameters								
Parameters	Doxorubicin Hydrochloride 2 mg/ ml (50 mg/m^2 Dose) Liposome Injection Test (A)				Caelyx (Doxorubicin Hydrochloride) 2 mg/ ml (50 mg/m^2 Dose) Liposome Injection Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-t} (µg.h/mL)	3695.1939	±	992.02642	26.8	3860.6204	±	1257.40164	32.6
AUC_{0-inf} (µg.h/mL)	3935.0503	±	1153.06713	29.3	4190.1313	±	1424.41610	34.0
AUC_{0-t}/ AUC_{0-inf} (%)	94.537	±	3.3186	3.5	92.450	±	10.3898	11.2
C_{max} (µg/mL)	34.9661	±	5.09528	14.6	36.0450	±	6.06056	16.8
T_{max} (h)	2.4861	±	1.36948	55.1	2.3368	±	2.19677	94.0
*T_{max} (h)	2.000 (1.000 -6.000)	±	-	-	1.500 (1.000 -9.000)	±	-	-
K_{el} (h^{-1})	0.00980	±	0.002920	29.8	0.00971	±	0.002617	26.9
$T_{1/2}$ (h)	76.4234	±	20.84232	27.3	76.1372	±	19.35725	25.4

*Median values (range) are presented. Source: Appendix 16.2.6.1

Table 2: Summary of statistical analysis for total doxorubicin (PKD/08/038)

TABLE-14.2 -1B SUMMARY OF STATISTICAL ANALYSIS TOTAL DOXORUBICIN (N = 23) Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
AUC_{0-t}	8.16	8.20	3513.33	3652.32	96.19	89.83 to 103.01	13.39	0.3396
AUC_{0-inf}	8.22	8.26	3730.07	3870.70	96.37	89.69 to 103.54	14.05	0.3839
C_{max}	3.49	3.51	32.68	33.32	98.08	93.42 to 102.97	9.50	0.4991

Source: Appendix 16.1.9.2

[1] Calculated using least square means according to the formula: $e^{LSM\,(Doxorubicin\ HCl^{(A)} - Caelyx^{(B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data;
[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(least\text{-}square\ mean)}$
[4] P-value is for product effect

Encapsulated doxorubicin
The concentration-time curve is adequately characterised. Bioequivalence is established for encapsulated doxorubicin, within 80.00-125.00% criteria. The Applicant has also provided 90% CIs for log-transformed data of V_d and clearance, which are also within 80.00-125.00%.

Table 3: Summary of results and statistical analysis for encapsulated doxorubicin (PKD/08/038)

Doxorubicin HCl Liposome Injection, 2 mg/ml (50 mg/m^2 dose) Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals Study No. PKD/08/038 (Fed Bioequivalence data of Entrapped Doxorubicin from Doxorubicin HCl Liposome Injection, 2 mg/ml (50 mg/m^2 dose) (N=23)#						
Parameter	Test	Reference	Ratio %	90% C.I	Intra Subject CV%	P –value[1]
AUC_{0-t} (ng*hr/mL)	3487169.00	3631747.00	96.02	89.45 to 103.07	13.86	0.3339
AUC_{0-inf} (ng*hr/mL)	3701410.00	3847706.00	96.20	89.30 to 103.63	14.56	0.3789
C_{max} (ng/mL)	32440.07	33167.33	97.81	93.02 to 102.84	9.80	0.4544
Vd (ml)	2250.84	2126.74	105.83	98.42 to 113.80	14.21	0.1927
Cl (ml/hr)	20.43	19.65	103.96	96.51 to 111.99	14.56	0.3779

[1]P-value is for product effect

The Applicant has also provided an analysis of partial AUCs as requested by CHMP at Day 120:

Table 4: Summary of statistical analysis of partial AUCs for encapsulated doxorubicin (PKD/08/038)

Ln- Transformed Data (n=23)								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				

AUC_{0-48}	14.02	14.03	1228769.41	1244562.45	98.73	94.1 to 103.59	9.37	0.6509
AUC_{49-337}	14.61	14.66	2213784.41	2329992.26	95.01	86.42 to 104.46	18.61	0.3622

[1] Calculated using least square means according to the formula: $e^{LSM\ Doxorubicin\ HCl(A) - LSM\ Caelyx\ (B)}$ X 100
[2] 90% Geometric Confidence Interval using In-transformed data;
[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(least\text{-}square\ mean)}$

[4] P-value is for product effect

Free Doxorubicin

The following tables summarise the submitted PK and statistical analyses of free doxorubicin:

Table 5: Summary of results for free (un-encapsulated) doxorubicin (PKD/08/038)

Parameter	Test		Reference	
	Mean	**SD**	**Mean**	**SD**
C_{max} (ng/ml)	372.66	278.30	323.43	164.53
T_{max} (hr) *	1.5	(0.75-97)	4.0	(0.75-49)
AUC_{0-t} (ng*hr/ml)	31652.21	13328.66	32728.28	19119.15
AUC_{0-inf} (ng*hr/ml)	35679.68	16659.33	35896.73	21722.73
$T_{1/2}$ (hr)	105.49	53.88	83.78	25.69
Vd (ml)	363136.82	199834.09	331387.10	194443.69
Cl (ml/hour)	2485.19	905.51	2819.86	1364.97

Table 6: Summary of statistical analysis for free (un-encapsulated) doxorubicin (PKD/08/038)

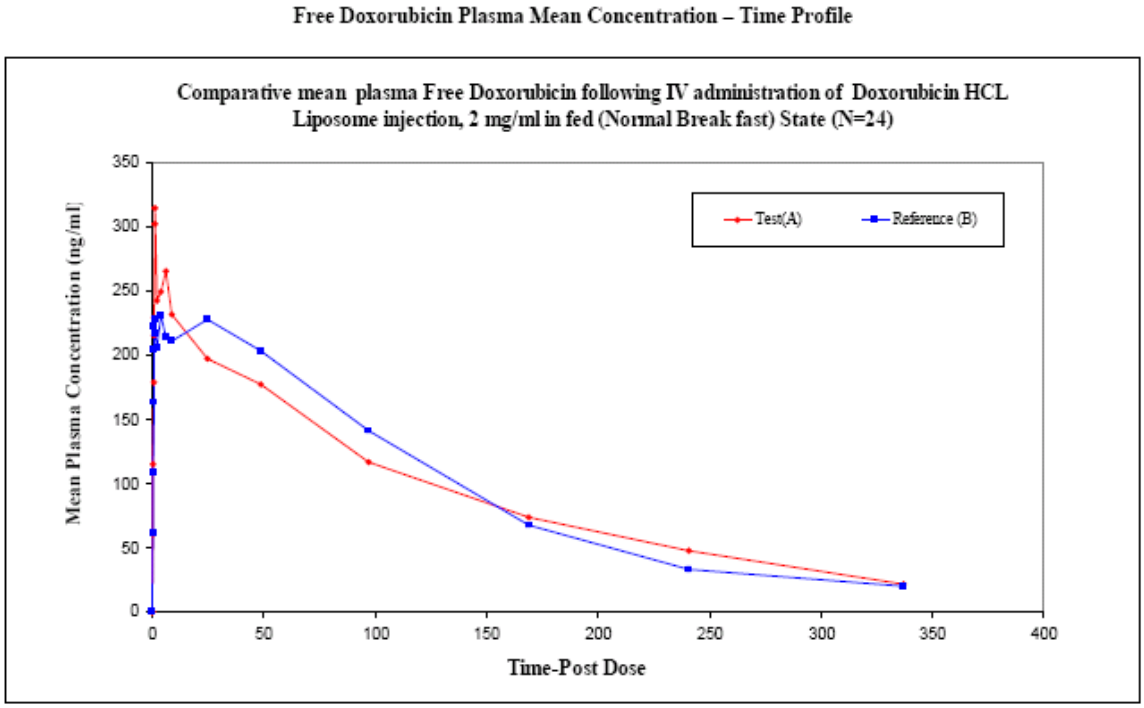
Doxorubicin HCl Liposome Injection, 2 mg/ml (50 mg/m^2 dose)
Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals

Study No. PKD/08/038
(Fed Bioequivalence data of Free Doxorubicin from Doxorubicin HCl Liposome Injection, 2 mg/ml (50 mg/m^2 dose) (N=23)*)

Parameter	Test	Reference	Ratio %	90% C.I	Intra Subject CV%	P –value[1]
AUC_{0-t} (ng*hr/mL)	25137.13	23336.66	107.72	92.51 to 125.42	30.30	0.4090
AUC_{0-inf} (ng*hr/mL)	28812.39	25815.19	111.61	95.07 to 131.02	32.00	0.2508
C_{max} (ng/mL)	244.89	207.96	117.76	91.78 to 151.08	51.52	0.2708
Vd (ml)	385716.8	372461.6	103.56	84.71 to 126.61	40.67	0.7667
Cl (ml/hr)	2624.08	2928.75	89.60	76.32 to 105.18	32.00	0.2508

[1]P-value is for product effect

Figure 1: Linear plot of mean plasma concentration time profile of free (un-encapsulated) doxorubicin (PKD/08/038)



Test (A): Doxorubicin Hydrochloride Liposome Injection, 2 mg/ml (50 mg/m^2 dose)

Reference (B): Caelyx Liposome Injection, 2 mg/ml (50 mg/m^2 dose)

The Applicant has also provided an analysis of partial AUCs as requested by CHMP at Day 120:

Table 7: Summary of statistical analysis of partial AUCs for free (un-encapsulated) doxorubicin (PKD/08/038)

Ln- Transformed Data (n=23)								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means [1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value [4]
	Test	Reference	Test	Reference				
AUC_{0-48}	8.89	8.85	7246.31	6983.76	103.76	85.76 to 125.53	38.40	0.7413
AUC_{49-337}	9.77	9.68	17424.83	15957.42	109.20	93.21 to 127.93	31.57	0.3488

[1] Calculated using least square means according to the formula: $e^{LSM\ Doxorubicin\ HCl(A) - LSM\ Caelyx\ (B)}$ X 100

[2] 90% Geometric Confidence Interval using ln-transformed data;

[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(least\text{-}square\ mean)}$

[4] P-value is for product effect.

The 90% confidence intervals for AUC0-t and Cmax are not within 80.00-125.00% standard bioequivalence criteria. Therefore bioequivalence of free (un-encapsulated) doxorubicin between the test and reference product has not been established.

Doxorubicinol

Doxorubicinol is the main metabolite of doxorubicin and is therefore could be considered a surrogate for free doxorubicin. This analyte was measured as a post-study protocol amendment. 90% CIs for AUC_{0-t} and C_{max} are provided, and are within 80.00-125.00% criteria. However, the sampling period was insufficient to adequately characterise the concentration-time curve. There was carry-over into Period II of the order of 5-10% of C_{max} for over 60% of subjects, indicating an insufficient wash-out period. Removal of these subjects leaves inadequate data to establish bioequivalence.

The Applicant has provided a statistical comparison of carryover: there appears to be a slightly greater carryover following test product, compared to reference product. Evidence for bioequivalence of doxorubicinol from Study PKD/08/038 is considered inadequate.

Bioequivalence Study PKD/09/031 (30mg/m^2 dose: multiple myeloma, against Caelyx)

In response to the Day 180 LoOI, the Applicant has submitted new data from a bioequivalence study in patients with multiple myeloma at the 30mg/m^2 dose. Doxorubicin 2mg/ml concentrate for solution for infusion (test product) and Caelyx 2mg/ml concentrate for solution for infusion (reference product) were compared during a randomized, multi-centre, open label, two treatment, two period, two sequence, single dose, crossover study, conducted under fed (normal low fat breakfast) conditions.

An intravenous infusion of test or reference product was administered 30 minutes after normal low fat breakfast, according to the randomisation schedule. Sampling was carried out pre-dose, and at 0.25, 0.5, 0.75, 1.0, 1.083, 1.25, 1.5, 2, 4, 6, 9, 25, 49, 97, 169, 241 and 337 hours post-dose. The washout period was 20 days. Total, encapsulated and free (un-encapsulated) doxorubicin was measured in plasma using validated LC/MS/MS methods. 34 patients were randomised, of which 26 completed the study and were analysed.

Results

Total doxorubicin

The concentration-time curve is adequately characterised. Bioequivalence is established for total doxorubicin, within 80.00-125.00% criteria. Volume of distribution and clearance are also comparable.

Table 8: Summary of results and statistical analysis for total doxorubicin (PKD/09/031)

TABLE- 14.2 – 1A SUMMARY OF RESULTS TOTAL DOXORUBICIN (N = 26) Pharmacokinetic Parameters								
Parameters	Doxorubicin Hydrochloride 2 mg/ ml (30 mg/m^2 Dose) Liposome Injection Test (A)				Caelyx (Doxorubicin Hydrochloride) 2 mg/ ml (30 mg/m^2 Dose) Liposome Injection Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-t} (µg.h/mL)	2088.4647	±	656.85501	31.5	2224.2048	±	777.74626	35.0
AUC_{0-inf} (µg.h/mL)	2278.8086	±	755.96277	33.2	2534.4800	±	882.70261	34.8
AUC_{0-t}/ AUC_{0-inf} (%)	92.178	±	3.6721	4.0	88.268	±	10.4295	11.8
C_{max} (µg/mL)	18.8008	±	4.19488	22.3	20.3349	±	4.55155	22.4
T_{max} (h)	3.8301	±	4.91161	128.2	2.5865	±	1.60411	62.0
*T_{max} (h)	1.750 (1.083 – 25.000)	±	-	-	2.000 (1.083 – 6.000)	±	-	-
K_{el} (h^{-1})	0.00835	±	0.002002	24.0	0.00851	±	0.003367	39.6
$T_{1/2}$ (h)	87.0568	±	18.48509	21.2	91.1359	±	30.64700	33.6
AUC Extrapolation (%)	7.822	±	3.6721	46.9	11.732	±	10.4295	88.9
V_d (mL)	2822.560	±	694.9198	24.6	2657.877	±	886.8946	33.4
Cl (mL/hr)	23.644	±	8.2687	35.0	21.816	±	8.8697	40.7

***Median values (range) are presented.** **Source: Appendix 16.2.6.1**

TABLE-14.2 -1B SUMMARY OF STATISTICAL ANALYSIS TOTAL DOXORUBICIN (N = 26) Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
AUC_{0-t}	7.58	7.63	1967.89	2060.44	95.51	83.74 to 108.93	26.31	0.5539
AUC_{0-inf}	7.66	7.75	2117.37	2321.97	91.19	79.65 to 104.40	27.11	0.2540
C_{max}	2.89	2.95	17.95	19.09	94.04	85.61 to 103.31	18.65	0.2736
V_d	7.91	7.87	2730.06	2628.84	103.85	95.31 to 113.16	17.01	0.4571
Cl	3.13	3.04	22.86	20.85	109.67	95.78 to 125.56	27.12	0.2540

Source: Appendix 16.1.9.2

[1] Calculated using least square means according to the formula: $e^{(LSM\ Doxorubicin\ HCl\ (A) - LSM\ Caelyx\ (B))} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data;
[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(least\text{-}square\ mean)}$
[4] P-value is for product effect

Encapsulated doxorubicin

The concentration-time curve is adequately characterised. Bioequivalence is established for encapsulated doxorubicin, within 80.00-125.00% criteria. Volume of distribution and clearance are also comparable.

Table 9: Summary of results and statistical analysis for encapsulated doxorubicin (PKD/09/031)

TABLE- 14.2 – 2A								
SUMMARY OF RESULTS								
ENCAPSULATED DOXORUBICIN (N = 26)								
Pharmacokinetic Parameters								
Parameters	Doxorubicin Hydrochloride 2 mg/ ml (30 mg/m^2 Dose) Liposome Injection Test (A)				Caelyx (Doxorubicin Hydrochloride) 2 mg/ ml (30 mg/m^2 Dose) Liposome Injection Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-t} (µg.h/mL)	1930.9051	±	574.69933	29.8	2027.6580	±	603.30140	29.8
AUC_{0-inf} (µg.h/mL)	2075.9988	±	627.35175	30.2	2331.0442	±	634.76921	27.2
AUC_{0-t}/ AUC_{0-inf} (%)	93.296	±	2.8180	3.0	87.274	±	10.7513	12.3
C_{max} (µg/mL)	19.0365	±	4.99128	26.2	19.2202	±	4.24916	22.1
T_{max} (h)	2.9230	±	2.09221	71.6	2.5641	±	1.86450	72.7
*T_{max} (h)	1.750 (1.083 – 9.000)	±	-	-	2.000 (1.000 – 9.000)	±	-	-
K_{el} (h^{-1})	0.00855	±	0.001336	15.6	0.00819	±	0.002870	35.0
$T_{1/2}$ (h)	83.0207	±	13.24874	16.0	90.8775	±	20.61615	22.7
AUC Extrapolation (%)	6.704	±	2.8180	42.0	12.726	±	10.7513	84.5
V_d (mL)	3004.155	±	875.5600	29.1	2906.682	±	1076.5821	37.0
Cl (mL/hr)	25.579	±	8.5336	33.4	22.945	±	8.8407	38.5

*Median values (range) are presented. Source: Appendix 16.2.6.6

TABLE-14.2 -2B								
SUMMARY OF STATISTICAL ANALYSIS ENCAPSULATED DOXORUBICIN (N = 26)								
Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
#AUC_{0-t}	7.58	7.63	1952.68	2055.03	95.02	84.16 to 107.29	23.83	0.4765
#AUC_{0-inf}	7.64	7.75	2074.27	2317.68	89.50	78.58 to 101.93	25.58	0.1568
C_{max}	2.93	2.95	18.79	19.07	98.52	89.08 to 108.97	20.02	0.8017
#V_d	7.87	7.86	2627.93	2586.92	101.59	89.71 to 115.04	24.42	0.8295
#Cl	3.14	3.03	23.18	20.75	111.73	98.10 to 127.26	25.58	0.1569

#N=25 Source: Appendix 16.1.9.4

[1] Calculated using least square means according to the formula: $e^{(\text{LSM Doxorubicin HCl (A)} - \text{LSM Caelyx (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data;
[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(\text{least-square mean})}$
[4] P-value is for product effect

The Applicant has provided a statistical analysis of partial AUCs (AUC_{0-48}, AUC_{49-337}) at the request of CHMP. The partial AUCs of the test and reference products are not comparable for 0-48 hours.

Table 10: Summary of statistical analysis of partial AUCs for encapsulated doxorubicin (PKD/09/031)

TABLE-3								
SUMMARY OF STATISTICAL ANALYSIS ENCAPSULATED DOXORUBICIN (N = 18)								
Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
AUC_{0-48}	8.27	8.48	3892.55	4821.37	80.74	69.00 to 94.47	21.89	0.0325
AUC_{49-337}	9.23	9.26	10206.40	10488.63	97.31	82.08 to 115.37	23.43	0.7774

Source: Appendix 16.1.9.7

[1] Calculated using least square means according to the formula: e (^{LSM}Doxorubicin HCl$^{(A)}$ – ^{LSM} Caelyx $^{(B)}$) X 100
[2] 90% Geometric Confidence Interval using ln-transformed data;
[3] Least-square geometric means calculated from the analysis of the ln-transformed data as e $^{(least\text{-}square\ mean)}$
[4] P-value is for product effect

The Applicant has clarified that Table 10 contains a typographical error: the sample size was n=26 for AUC0-48, and n=25 for AUC 49-337, not n=18.

Free doxorubicin

The following tables summarise the submitted PK and statistical analyses of free doxorubicin.

Table 11: Summary of results and statistical analysis for free (un-encapsulated) doxorubicin (PKD/09/031)

TABLE- 14.2 – 3A								
SUMMARY OF RESULTS								
FREE DOXORUBICIN (N = 26)								
Pharmacokinetic Parameters								
Parameters	Doxorubicin Hydrochloride 2 mg/ ml (30 mg/m^2 Dose) Liposome Injection Test (A)				Caelyx (Doxorubicin Hydrochloride) 2 mg/ ml (30 mg/m^2 Dose) Liposome Injection Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-t} (ng.h/mL)	14892.6669	±	6711.35408	45.1	15736.6395	±	8452.89619	53.7
AUC_{0-inf} (ng.h/mL)	17200.5105	±	7171.95627	41.7	21311.8835	±	15801.00354	74.1
AUC_{0-t}/ AUC_{0-inf} (%)	85.516	±	8.7192	10.2	80.835	±	17.9125	22.2
C_{max} (ng/mL)	120.477	±	61.4113	51.0	153.728	±	101.4359	66.0
T_{max} (h)	23.6423	±	30.73352	130.0	16.6666	±	17.43203	104.6
*T_{max} (h)	17.000 (1.000 – 97.000)	±	-	-	9.000 (1.000 – 49.000)	±	-	-
K_{el} (h^{-1})	0.00704	±	0.002443	34.7	0.00724	±	0.004231	58.4
$T_{1/2}$ (h)	108.6294	±	32.96806	30.3	124.0119	±	82.11684	66.2
AUC Extrapolation (%)	14.484	±	8.7192	60.2	19.165	±	17.9125	93.5
V_d (mL)	506604.597	±	229964.7733	45.4	477140.415	±	226828.3683	47.5
Cl (mL/hr)	3240.220	±	1170.2315	36.1	3037.145	±	1414.8750	46.6

*Median values (range) are presented. Source: Appendix 16.2.6.11

TABLE-14.2 -3B								
SUMMARY OF STATISTICAL ANALYSIS FREE DOXORUBICIN (N = 19)								
Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
#AUC_{0-t}	9.55	9.64	14039.09	15330.86	91.57	79.43 to 105.57	19.50	0.2883
#AUC_{0-inf}	9.70	9.78	16267.19	17619.69	92.32	79.45 to 107.29	20.61	0.3579
C_{max}	4.81	5.10	122.80	164.75	74.54	61.79 to 89.92	26.26	0.0169
#V_d	12.94	12.87	417543.60	387519.00	107.75	81.73 to 142.05	38.88	0.6351
#Cl	7.99	7.91	2953.82	2727.09	108.31	93.21 to 125.87	20.61	0.3579

#N=18 Source: Appendix 16.1.9.8

[1] Calculated using least square means according to the formula: $e^{(LSM\ Doxorubicin\ HCl\ (A) - LSM\ Caelyx\ (B))} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data;
[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(least\text{-}square\ mean)}$
[4] P-value is for product effect

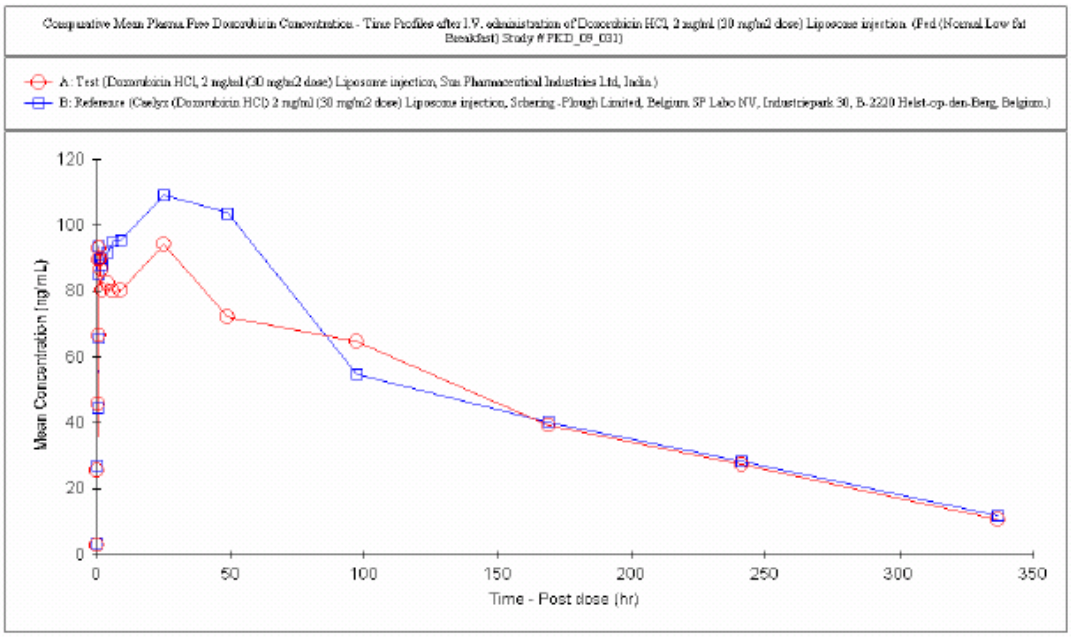
Table 12: Summary of statistical analysis of partial AUCs for free (un-encapsulated) doxorubicin (PKD/09/031)

TABLE-4								
SUMMARY OF STATISTICAL ANALYSIS FREE DOXORUBICIN (N = 18)								
Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
AUC_{0-48}	6.47	6.53	642.69	686.06	93.68	84.92 to 103.34	19.50	0.2653
AUC_{49-337}	7.16	7.23	1282.27	1375.28	93.24	78.88 to 110.21	33.24	0.4786

Source: Appendix 16.1.9.11

[1] Calculated using least square means according to the formula: $e^{(LSM\text{Doxorubicin HCl}(A) - LSM\text{Caelyx}(B))} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data;
[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(\text{least-square mean})}$
[4] P-value is for product effect

Fig 2: Linear plot of mean plasma concentration time profile of free doxorubicin (n=26)



The observation of significant pre-dose levels of free doxorubicin (up to 38.4% of C_{max}) for 3 subjects, in Period 1, has been discussed by the Applicant (see Section VII). It is assumed that these subjects received doxorubicin prior to the study. All 3 were excluded from the analysis.

The 90% confidence intervals for AUC_{0-t} and C_{max} are not within 80.00-125.00% standard bioequivalence criteria. Therefore bioequivalence of free (un-encapsulated) doxorubicin between the test and reference product has not been established.

Doxorubicinol

The Applicant has not provided a pharmacokinetic analysis of doxorubicinol for study PKD/09/031 on the basis that there would be significant carryover, due to the shorter washout period of 20 days. Given that significant carryover was observed in the 50mg/m2 study (washout period 28 days), this justification is accepted.

Bioequivalence Study PKD/09/030 (50mg/m2 dose: ovarian cancer, against Doxil)

This study was designed to assess the bioequivalence of Doxorubicin Hydrochloride Liposome injection, 2 mg/ml (50 mg/m2 dose) of Sun Pharma Advanced Research Company Limited, India and Doxil® (Doxorubicin Hydrochloride Liposome injection), 2 mg/ml (50 mg/m2 dose) of Ben Venue Laboratories, Inc., Bedford, OH 44146., USA, in patients with ovarian cancer, under fed (normal low fat breakfast) conditions.

This was a randomized, multi centre, open label, two treatment, two period, two sequence, single dose, crossover study. A statement of GCP was provided. Ethical approval was obtained for each centre. An intravenous infusion of test of reference product was administered 30 minutes after normal low fat breakfast, according to the randomisation schedule. Sampling was carried out pre-dose, and at 0.25, 0.5, 0.75, 1.0, 1.083, 1.25, 1.5, 2,4,6,9,25,49,97,169,241 and 337 hours post-dose. The washout period was 28 days. Free and encapsulated doxorubicin was measured in plasma using validated LC/MS/MS methods. The analytical method is satisfactory.

60 subjects with ovarian cancer were enrolled and randomised at 5 centres in India, of which 41 completed the study and were analysed. All drop-outs were accounted for.

Assessor's comment:

It is stated in the study report: 'Expecting +/- 5 % variation in T/R Ratio with expected intra subject CV of around 22.5 %, 24 subjects were required to prove bioequivalence. However based on the variability of free doxorubicin sample size was increased from 24 to 36 evaluable subjects in order to improve the result and meet the BE criteria for free doxorubicin and a post study amendment was done for the same.'

The Applicant should clarify whether an interim analysis of the first 24 evaluable subjects was carried out, and present the results. If an interim analysis was carried out, the final analysis should be re-done using 95% confidence intervals.

Results

Encapsulated doxorubicin

Table 13: Summary of results for encapsulated doxorubicin (PKD/09/030)

TABLE 1A
SUMMARY OF RESULTS
LIPOSOME ENCAPSULATED DOXORUBICIN (N = 41)
Pharmacokinetic Parameters

Parameters	Doxorubicin Hydrochloride 2 mg/ ml (50 mg/m^2 Dose) Liposome Injection Test (A)				Doxil® (Doxorubicin Hydrochloride) 2 mg/ ml (50 mg/m^2 Dose) Liposome Injection Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-t} (µg.h/mL)	3145.4467	±	1127.35895	35.8	3056.5224	±	1236.68355	40.5
AUC_{0-inf} (µg.h/mL)	3474.7355	±	1383.88411	39.8	3370.2604	±	1270.95200	37.7
AUC_{0-t}/ AUC_{0-inf} (%)	91.902	±	8.3434	9.1	90.354	±	11.4959	12.7
C_{max} (µg/mL)	34.179	±	8.2229	24.1	33.592	±	8.1891	24.4
T_{max} (h)	2.9264	±	2.38462	81.5	3.2988	±	2.40567	72.9
*T_{max} (h)	2.000 (1.000 – 9.000)	±	-	-	2.000 (1.000 – 9.000)	±	-	-
K_{el} (h^{-1})	0.00958	±	0.002285	23.9	0.00976	±	0.002673	27.4
$T_{1/2}$ (h)	80.8774	±	47.37563	58.6	75.5453	±	18.61186	24.6
AUC Extrapolation (%)	8.098	±	8.3434	103.0	9.646	±	11.4959	119.2
V_d (mL)	2685.584	±	962.9801	35.9	2750.552	±	1235.5182	44.9
Cl (mL/hr)	25.194	±	10.0436	39.9	26.851	±	13.8206	51.5

*Median values (range) are presented.

Table 14: Summary of statistical analysis for encapsulated doxorubicin (PKD/09/030)

TABLE 1B SUMMARY OF STATISTICAL ANALYSIS LIPOSOME ENCAPSULATED DOXORUBICIN (N = 41) Ln- Transformed Data								
PK Variables	Least Square Means		Geometric		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value [4]
	Test	Reference	Test	Reference				
#AUC_{0-t}	8.01	7.98	3011.97	2911.71	103.44	95.49 to 112.06	20.96	0.4792
#AUC_{0-inf}	8.10	8.06	3298.46	3168.67	104.10	96.06 to 112.81	21.07	0.4045
C_{max}	3.50	3.48	33.27	32.37	102.78	97.80 to 108.01	13.16	0.3575
#Vd	7.81	7.82	2470.42	2481.90	99.54	90.99 to 108.89	23.60	0.9310
#Cl	3.11	3.15	22.48	23.40	96.07	88.65 to 104.11	21.07	0.4048

#N=40

[1] Calculated using least square means according to the formula: $e^{(\text{LSM Doxorubicin HCl (A)} - \text{LSM Doxil® (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data;

[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(\text{least-square mean})}$

[4] P-value is for product effect

Table 15: Summary of statistical analysis of partial AUCs for encapsulated doxorubicin (PKD/09/030)

TABLE-2 SUMMARY OF STATISTICAL ANALYSIS LIPOSOME ENCAPSULATED DOXORUBICIN (N = 41) Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
AUC_{0-48}	7.03	7.01	1129.85	1109.60	101.83	94.86 to 109.30	18.86	0.6692
#AUC_{49-337}	7.56	7.50	1917.27	1811.69	105.83	95.88 to 116.81	25.74	0.3388

#N=40 **Source: Appendix 16.1.9.5**

[1] Calculated using least square means according to the formula: $e^{(\text{LSM Doxorubicin HCl (A)} - \text{LSM Doxil® (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data;

[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(\text{least-square mean})}$

[4] P-value is for product effect

Free (un-encapsulated) doxorubicin

Table 16: Summary of results for free (un-encapsulated) doxorubicin (PKD/09/030)

TABLE- 14.2 – 2A								
SUMMARY OF RESULTS								
FREE DOXORUBICIN (N = 41)								
Pharmacokinetic Parameters								
Parameters	Doxorubicin Hydrochloride 2 mg/ ml (50 mg/m^2 Dose) Liposome Injection Test (A)				Doxil® (Doxorubicin Hydrochloride) 2 mg/ ml (50 mg/m^2 Dose) Liposome Injection Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-t} (ng.h/mL)	25735.5298	±	14554.09686	56.6	24549.3522	±	12977.08388	52.9
AUC_{0-inf} (ng.h/mL)	28047.6784	±	15139.08303	54.0	52297.0763	±	156414.37089	299.1
AUC_{0-t}/ AUC_{0-inf} (%)	91.197	±	6.6438	7.3	88.250	±	17.2971	19.6
C_{max} (ng/mL)	283.101	±	205.9202	72.7	261.423	±	121.4049	46.4
T_{max} (h)	20.4024	±	34.48903	169.0	21.7670	±	34.27512	157.5
*T_{max} (h)	4.000 (1.000 – 169.000)	±	-	-	4.000 (0.250 – 169.000)	±	-	-
K_{el} (h^{-1})	0.00858	±	0.002734	31.9	0.00918	±	0.003630	39.6
$T_{1/2}$ (h)	91.0730	±	36.11544	39.7	127.6092	±	256.06243	200.7
AUC Extrapolation (%)	8.803	±	6.6438	75.5	11.750	±	17.2971	147.2
V_d (mL)	444632.000	±	235836.7224	53.0	431542.363	±	281089.2811	65.1
Cl (mL/hr)	3496.688	±	1729.1513	49.5	3690.513	±	2730.6161	74.0

*Median values (range) are presented.

Table 17: Summary of statistical analysis for free (un-encapsulated) doxorubicin (PKD/09/030)

TABLE-14.2 -2B								
SUMMARY OF STATISTICAL ANALYSIS FREE DOXORUBICIN (N = 41)								
Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
#AUC_{0-t}	9.92	9.88	20430.59	19612.10	104.17	90.15 to 120.38	38.84	0.6357
#AUC_{0-inf}	10.01	9.98	22331.79	21672.15	103.04	89.59 to 118.52	37.51	0.7195
C_{max}	5.35	5.36	209.66	212.91	98.47	84.11 to 115.28	43.44	0.8698
#V_d	12.90	12.84	400816.00	375360.50	106.78	87.82 to 129.84	54.14	0.5744
#Cl	8.11	8.14	3319.98	3421.03	97.05	84.37 to 111.62	37.51	0.7195

#N=40

[1] Calculated using least square means according to the formula: $e^{(\text{LSM Doxorubicin HCl (A)} - \text{LSM Doxil® (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data;
[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(\text{least-square mean})}$
[4] P-value is for product effect

Table 18: Summary of statistical analysis of partial AUCs for free (un-encapsulated) doxorubicin (PKD/09/030)

TABLE-4								
SUMMARY OF STATISTICAL ANALYSIS FREE DOXORUBICIN (N = 41)								
Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
AUC_{0-48}	8.74	8.71	6228.67	6082.65	102.40	89.59 to 117.04	36.38	0.7662
#AUC_{49-337}	9.56	9.49	14166.33	13222.21	107.14	90.89 to 126.30	44.15	0.4832

#N=40 Source: Appendix 16.1.9.10

[1] Calculated using least square means according to the formula: $e^{(LSM\text{Doxorubicin HCl}^{(A)} - LSM\text{Doxil}^{®\,(B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data;
[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(\text{least-square mean})}$
[4] P-value is for product effect

Assessor's comment:

Subject #10 was excluded from the analysis, after missing the last 4 timepoints of Period 2 (reference). According to the protocol, subjects were to be excluded from the analysis if ambulatory samples were missed and extrapolated AUC was found to be greater than 20%. An additional analysis including subject #10 has been provided:

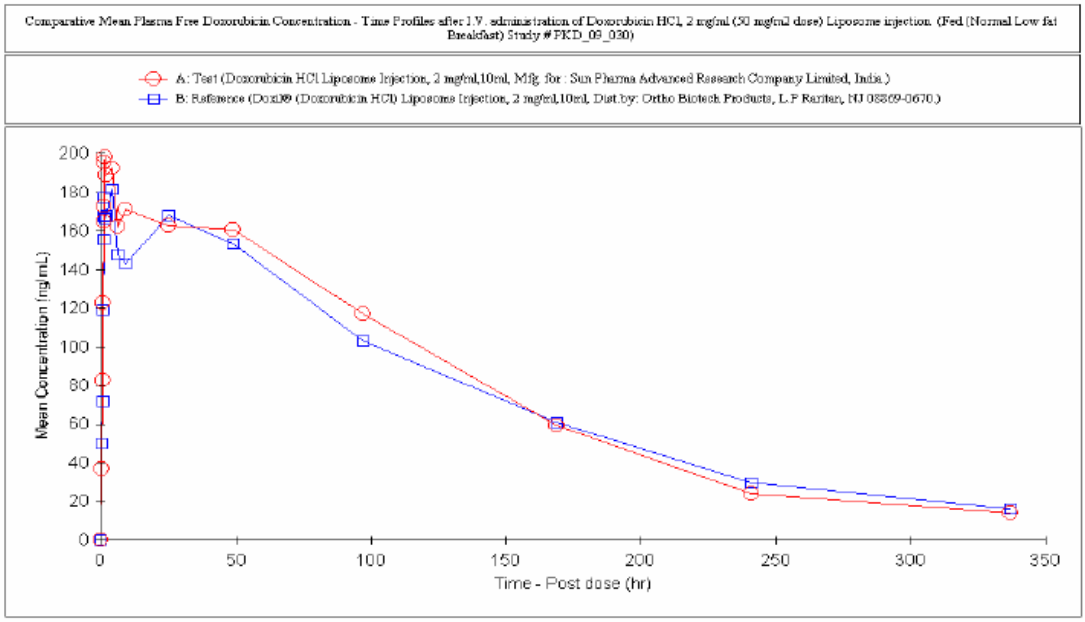
TABLE-3								
SUMMARY OF STATISTICAL ANALYSIS FREE DOXORUBICIN (N = 41)								
Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
AUC_{0-t}	9.93	9.88	20477.91	19545.33	104.77	91.05 to 120.57	38.34	0.5787
AUC_{0-inf}	9.99	10.06	21762.84	23435.76	92.86	75.25 to 114.60	60.02	0.5559
C_{max}	5.35	5.36	209.66	212.91	98.47	84.11 to 115.28	43.44	0.8698
V_d	12.90	12.82	399835.4	371134.2	107.73	89.09 to 130.28	53.44	0.5123
Cl	8.13	8.06	3403.44	3160.49	107.69	87.26 to 132.89	60.02	0.5559

Source: Appendix 16.1.9.9

[1] Calculated using least square means according to the formula: $e^{(LSM\text{Doxorubicin HCl}^{(A)} - LSM\text{Doxil}^{®\,(B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data;
[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(\text{least-square mean})}$
[4] P-value is for product effect

Decisions to exclude patients from the analysis should not be made on the basis of PK parameters, even if pre-specified in the protocol. The 90%CIs for AUC_{0-inf} fall outside the 80.00-125.00% crtiteria when this subject is included. However, the exclusion of subject #10 is not unreasonable, as the absence of values beyond 48 hours would make an AUC_{0-inf} very unreliable.

Figure 3: Linear plot of mean plasma concentration profile of free (un-encapsulated) doxorubicin (PKD/09/030)



Doxorubicinol

The measurement and analysis of doxorubicinol, the main metabolite, was specified in the protocol. However no data are submitted. The results of the pharmacokinetic and statistical analyses should be presented.

Assessor's comment:

Bioequivalence of encapsulated and free doxorubicin has been shown, within 90%CIs of 80.00-125.00% for AUC_{0-t} and C_{max}, between the test product and the US reference product Doxil, subject to satisfactory responses to the LoOI regarding interim analysis and doxorubicinol data. T_{max}, volume of distribution, clearance and partial AUCs are also comparable between test and reference.

Clinical discussion

The measurement of free (un-encapsulated) doxorubicin is a reflection of the rate and extent of tissue release from liposomes. Therefore the clinical pharmacokinetic profiles of free (un-encapsulated) doxorubicin, as well as encapsulated doxorubicin, should be sufficiently similar to the reference product. Doxorubicinol data may also reflect rate and extent of liposomal release, but so far there is insufficient evidence of comparability. To ensure acceptable efficacy and safety, liposome release should occur in comparable tissues. Therefore evidence of comparable non-clinical tissue distribution is required, in addition to evidence of comparable rate and extent of release in humans.

Comparable clinical pharmacokinetics has only been demonstrated so far for encapsulated doxorubicin, including 80.00-125.00% confidence intervals for C_{max} and AUC. The results for free doxorubicin are shown below in Table 19:

Table 19: Summary of ratios of geometric means and 90% CIs for AUC and C_{max} of free (un-encapsulated) doxorubicin

Study ID	Dose/patient population	Reference product	Number analysed	Ratio (90% CIs) AUC_{0-t}	Ratio (90% CIs) AUC_{0-inf}	Ratio (90%CIs) C_{max}
PKD/08/038	50mg/m^2 ovarian cancer	Caelyx	23	107.72 **(92.51-125.42)**	111.61 **(95.07-131.02)**	117.76 **(91.78-151.08)**
PKD/09/031	30mg/m^2 multiple myeloma	Caelyx	26	91.57 **(79.43-105.57)**	92.32 **(79.45-107.29)**	74.54 **(61.79-89.92)**
PKD/09/030	50mg/m^2 ovarian cancer	Doxil	41	104.17 **(90.15-120.38)**	103.04 **(89.59-118.52)**	98.47 **(84.11-115.28)**

Free (un-encapsulated) doxorubicin is comparable, within 80.00-125.00% to Doxil (US reference product), but not Caelyx. This may be due to insufficient power of the Caelyx studies. The Applicant has provided a pooled analysis of data from the 50mg/m^2 and 30mg/m^2 studies against Caelyx. However it is judged unacceptable in principle to pool together studies which fail to demonstrate bioequivalence, particularly when carried out using different doses in different patient populations.

The Applicant has presented evidence to demonstrate that Caelyx and Doxil are pharmaceutically equivalent The Applicant is requested to provide a combined analysis of pharmacokinetic data of encapsulated and free (un-encapsulated) doxorubicin from studies PKD/08/038 (Caelyx) and PKD/09/030 (Doxil) at the 50mg/m^2 dose.

A robust justification for a biowaiver is required in order to extrapolate data at the 50mg/m^2 dose to lower doses. The Applicant has deleted the indication in Kaposi's Sarcoma. However, an indication in multiple myeloma at the 30mg/m^2 level remains. Even if the multiple myeloma indication were deleted, lower doses may be used in breast and ovarian cancer, as recommended in the SPC for patients with hepatic impairment, or in the management of toxicity.

Clinical conclusion

There are outstanding clinical major objections at Day 195. From the bioequivalence data submitted, it cannot be concluded that the test formulation of liposomal doxorubicin is essentially similar to the reference product.

II.4 Pharmacovigilance system

The Applicant has provided satisfactory responses to the pharmacovigilance concerns. However, a revised DDPS incorporating all the responses should be provided, specifically:

- The activities performed in conjunction with other departments
- A paragraph on signal detection and any label changes

Provided that the responses are incorporated into the DDPS then the CHMP may consider that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management plan

The applicant has provided a justification for the absence of a risk management plan. The application concerns a generic of a reference medicinal product for which no safety concern requiring additional risk minimization activities has been identified. The active ingredient has been in use for many years. Subject to satisfactory demonstration of comparable efficacy and safety with the reference product, a

risk management plan is not considered necessary. If additional safety concerns are identified as the procedure progresses, a risk management plan may be required.