CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-934

PHARMACOLOGY REVIEW(S)

Evaluation of Pharmacology and Toxicology Data FEB 19 1999
Division of Dermatologic and Dental Drug Products, HFD-540
Draft Completed: February 11, 1999
Revised: February 12, 1999; February 19, 1999

NDA 20-934		
Submission number	**Submission Date**	**Center Receipt Date**
BZ	1/19/99	1/20/99

SPONSOR: Connetics Corporation

DRUG: Luxiq™, Betamethasone valerate foam 0.1%

INTRODUCTION:
Luxiq may contain the probable human carcinogen 1,3-butadiene since the specification for the hydrocarbon propellant used in Luxiq permits 0.5 mole % dienes. The sponsor has stated that the propellant actually contains less than 0.01 mole % dienes and that they would change the specification to 0.01 mole %. The sponsor has conducted a risk assessment for theoretical cancer risk from 1,3-butadiene exposure from the propellant with a specification for 1,3-butadiene of 0.01 mole %. In order to conduct this risk assessment a number of assumptions were made. This review will examine these assumptions to determine whether the risk assessment is reasonable.

RISK ASSESSMENT OF 1,3-BUTADIENE EXPOSURE:

Calculation of maximum possible exposure to 1,3-butadiene under conditions of use of Luxiq:
The sponsor has calculated several different exposure scenarios to the impurities present in the propellant of Luxiq. Listed below are the assumptions made by the sponsor and comments on the appropriateness of the assumptions.

1. The sponsor has assumed that the drug would be used twice per day.

   Comment: This is a reasonable assumption since it is the labeled use.

2. The sponsor has assumed that the foam would be applied to 5%, 20% or 50% of the body surface area.

   Comment: If the product was labeled for whole body use then, theoretically, the foam could be applied to greater than 50% body surface area. Therefore, using a calculation of 100% would be an even more exaggerated use scenario.

3. The sponsor has assumed application to a female of average weight (64.5 kg) with a 100% body surface area of 20,900 cm^2. This body surface area is the upper 95th percentile for females.

Comment: It would be more conservative to use a lower body weight such as 50 kg. However, since the body surface area of 20,900 cm^2 is the upper 95th percentile is seems unlikely that a female of 50 kg or 64.5 kg would have this large a body surface area. For example, by using the Dubois height-weight formula:
BSA (m^2) = weight(kg)$^{0.425}$ × height(cm)$^{0.725}$ × 0.007184
one can calculate that an individual of 64.5 kg and 163 cm would have a BSA of approximately 16,954 cm^2. Also according to this formula a 64.5 kg individual with BSA of 20,900 cm^2 would be 217.5 cm tall, which is not realistic. Consequently, using the 20,900 cm^2 BSA figure with the 64.5 or 50 kg weight should provide a conservative estimate of exposure.

4. The sponsor has assumed that the foam would be applied at approximately 3mg/cm^2. Therefore, 3.15 g would be used for 5% BSA (1,045 cm^2), 12.5 g for 20% BSA (4,180 cm^2) and 31.5 g for 50% BSA (10,450 cm^2).

   Comment: This seems reasonable since in the clinical trials approximately 3 g of foam was used for scalp application and 15 g was used for the HPA axis suppression study which specified application to ≥30% BSA. If 100% BSA was covered then for a BSA of 20,900 cm^2, 62.7 g would be required. This would be 125.4 g per day, which is more than one can per day.

5. The sponsor has assumed that the drug would be used for 365 days per year for 25 years.

   Comment: Dr. Huene agrees that this assumption would provide an estimate of exaggerated use.

6. The sponsor has assumed that the patient would apply the drug in a non-ventilated bathroom with a volume of 11 m^3 and remain in the room for 30 minutes following application.

   Comment: The sponsor has used 11 m^3 since this is the size of an average bathroom. The sponsor states that since the bathroom is usually the smallest room in the house that this would provide a conservative estimate. However using the lower range of bathroom volume of 8 m^3 would provide an even more conservative estimate.

7. The sponsor assumes an inhalation rate of 0.5 m^3/hr.

   Comment: This is a reasonable inhalation rate, which corresponds to a normal minute volume of 8.3 L/min.

8. In order to calculate the inhalation and dermal exposure to the 1,3-butadiene released to the air, the sponsor has assumed that 100% of the butadiene in the dispensed foam is released to the air.

Comment: This is an acceptable estimate since it maximizes the exposure through these two routes.

9. The sponsor has assumed that 0.1% of the dispensed butadiene would be found in the liquid phase of the foam in contact with the skin and that all of this would be absorbed.

   Comment: This assumption is supported by a series of theoretical calculations. The sponsor has shown by simple weighing experiments that approximately 50% of the propellant escapes to the air when the foam is dispensed. This differs from the sponsor's previous statement that "most of the propellant expelled from the can is trapped in the foam structure" until the foam collapses (volume 1.1 of original NDA submission, p. 48). The 50% figure is perhaps more reliable since it is based on actual data whereas the previous statement may have been conjecture. The remaining calculations are highly theoretical and make various assumptions about the behavior of butadiene in gas and liquid phases. The sponsor calculates that once dispensed, the butadiene would rapidly equilibrate between gas and liquid phases so that 4% of the butadiene would be in the liquid phase. Then after the foam is spread and collapses the butadiene level would drop to 0.1% of the original amount after about 2 seconds. Much of this would continue to be lost to the air; however, for exposure estimates, the sponsor assumes that it is all absorbed. Since the 0.1% value is determined largely by theoretical calculations it might be appropriate to use an assumption of 1% absorption to help account for uncertainty in the calculation.

10. The sponsor has calculated the absorption of butadiene through the skin from the air and determined that exposure through this route would be negligible.

    Comment: This is a reasonable assumption. The exact rate of penetration of butadiene through skin is not known. The sponsor has used 0.01 cm/hr as the vapor permeability coefficient of butadiene. This seems to be reasonable based on US EPA estimates of vapor permeability coefficients from fat/air partition coefficients (US EPA, Dermal Exposure Assessment: Principles and Applications, 1992). The EPA method predicts that compounds with fat/air partition coefficients <98 will have vapor permeability coefficients of <0.01 cm/hr. Butadiene has a fat/air partition coefficient of 22. Therefore, it is appropriate to use 0.01 cm/hr as an estimate of the vapor permeability coefficient since this should overestimate the absorption of butadiene through the skin. Using this estimate of the vapor permeability coefficient leads to calculated exposures from direct dermal absorption of butadiene from air which are several orders of magnitude lower than the exposures anticipated from inhalation.

Summary of exposure assumptions:

Some of the assumptions used by the sponsor are summarized in table 4.10 of the submission (p. 37). This table lists various parameter used for the determination of risk when the foam is applied to 5, 20 or 50% BSA. The table is reproduced below. The information in the table as presented by the sponsor is in regular type and additional values for some alternative assumptions that may be appropriate as discussed above are in italics.

Parameter	5% BSA	20% BSA	50% BSA	*100% BSA*	Basis
Surface area (cm^2)	1,045	4,180	10,450	*20,900*	95th percentile total body surface area for females
Dose of Luxiq	3.15 g/dose 6.3 g/day	12.5 g/dose 25 g/day	31.5 g/dose 63 g/day	*62.7 g/dose* *125.4 g/day*	Dose rate of 3 mg/cm^2; administered b.i.d.
Maximum quantity of butadiene released	0.0151 mg/dose 0.0302 mg/day	0.06 mg/dose 0.120 mg /day	0.151 mg/dose 0.302 mg/day	*0.30 mg/dose* *0.60 mg/day*	0.00479 mg butadiene per gram Luxiq *(Assuming 0.01 mole % specification)*
Bathroom air volume	11 m^3 *8 m^3*	11 m^3 *8 m^3*	11 m^3 *8 m^3*	11 m^3 *8 m^3*	Average reported by USEPA *Lower range of bathroom size*
Butadiene concentration in air	0.00137 mg/m^3 *0.00189 mg/m^3*	0.0055 mg/m^3 *0.0075 mg/m^3*	0.0137 mg/m^3 *0.0189 mg/m^3*	*0.0273 mg/m^3* *0.0375 mg/m^3*	Maximum quantity released divided by bathroom air volume
Exposure time	30 minutes/dose 60 minutes per day	30 minutes/dose 60 minutes per day	30 minutes/dose 60 minutes per day	30 minutes/dose 60 minutes per day	95th percentile of time spent in bathroom by females following a bath or shower (USEPA)
Exposure duration	25 years	25 years	25 years	25 years	
Inhalation rate	0.5 m^3/hr	0.5 m^3/hr	0.5 m^3/hr	0.5 m^3/hr	USEPA recommended short-term inhalation rate for sedentary activity
Body weight	64.5 kg *50 kg*	64.5 kg *50 kg*	64.5 kg *50 kg*	64.5 kg *50 kg*	National mean body weight for women 18-74 years of age all races *Smaller adult weight*

Calculation of chronic daily intake:

The total CDI was calculated by the sponsor by summing the chronic daily intake from the inhalation of butadiene in the air plus the absorption of butadiene through the skin from the liquid phase of the foam and from the air. Each of these routes is reviewed in more detail below.

Chronic daily intake via inhalation:

For the inhalation of butadiene from the air the sponsor used the following formula.

$$\text{CDI (mg / kg / day)} = \frac{\text{AC} \times \text{IR} \times \text{ET}}{\text{BW}} \times \frac{1\ \text{hr}}{60\ \text{min}} \times \frac{\text{ED}}{70\ \text{yrs}}$$

Where:

AC = butadiene air concentration (mg/m^3)

IR = inhalation rate (m^3/hr)

ET = exposure time (minutes/day) *Note: The sponsor listed the units of this parameter as minutes; however, the units should be listed as minutes/day so that the final units are mg/kg/day.*

ED = exposure duration (years)

BW = body weight (kg)

The following table presents the chronic daily intake from inhalation. The values derived from the sponsors calculations are presented in regular type while additional calculations using some of the alternative assumptions discussed above are in italics.

Exposure scenario	**CDI (mg/kg/day)**	***CDI (mg/kg/day) based on 50 kg body weight and 8 m^3 bathroom***
5% Body Surface Area	3.8×10^{-6}	*6.75×10^{-6}*
20% Body Surface Area	1.5×10^{-5}	*2.7×10^{-5}*
50% Body Surface Area	3.8×10^{-5}	*6.8×10^{-5}*
100% Body Surface Area	*7.6×10^{-5}*	*1.3×10^{-4}*

Chronic daily intake from the liquid phase via the dermal route:
The sponsor has calculated the chronic daily intake via the dermal route from butadiene in the liquid phase of the foam using the assumption that 0.1% of the butadiene will be present in the liquid phase 2 seconds after dispensing the foam. The chemistry reviewer, Dr. Ernie Pappas, and Chemistry Team Leader, Dr. Wilson Decamp, agree that this is a reasonable assumption. The sponsor has further assumed that all of this would be absorbed. The sponsor believes that this is actually an overestimate of absorption by this route although this conclusion is based on theoretical calculations not actual data. The chronic daily intake of butadiene from the dermal route was calculated according to the following formula.

$$\text{CDI (mg / kg / day)} = \frac{\text{ID} \times 0.001}{\text{BW}} \times \frac{\text{ED}}{70 \text{ yrs}}$$

where:

ID = initial butadiene dose (mg/day)

ED = exposure duration (years)

BW = body weight (kg)

The following table contains calculated chronic daily exposure via the dermal route from the liquid phase for the foam. The values derived from the sponsors calculations are presented in regular type while additional calculations using some of the alternative assumptions discussed above are in italics.

Exposure scenario	CDI (mg/kg/day)	*CDI (mg/kg/day) based on 50 kg body weight and 1% butadiene absorption*
5% Body Surface Area	1.7×10^{-7}	2.2×10^{-6}
20% Body Surface Area	6.6×10^{-7}	8.6×10^{-6}
50% Body Surface Area	1.7×10^{-6}	2.2×10^{-5}
100% Body Surface Area	3.3×10^{-6}	4.3×10^{-5}

Chronic daily intake from the air via the dermal route:
The sponsor has calculated the chronic daily intake via the dermal route from butadiene released to the air. These values were calculated according to the following formula.

$$\text{CDI (mg / kg / day)} = \frac{K_{p(est)}^{air} \times AC \times SA \times ET}{BW} \times \frac{1\ m^3}{1{,}000{,}000\ cm^3} \times \frac{1\ hr}{60\ min} \times \frac{ED}{70\ yrs}$$

Where:

$K_{p(est)}^{air}$ = estimated vapor permeability coefficient (K_p), (0.01 cm / hr)

AC = butadiene air concentration (mg/m^3)

SA = body surface area (cm^2)

ET = exposure time (minutes/day) *Note: The sponsor listed the units of this parameter as minutes; however, the units should be listed as minutes/day so that the final units are mg/kg/day.*

BW = body weight (kg)

ED = exposure duration (years)

The following table contains calculated chronic daily exposure via the dermal route from butadiene released to the air. The values derived from the sponsors calculations are presented in regular type while additional calculations using some of the alternative assumptions discussed above are in italics.

Exposure scenario	CDI (mg/kg/day)	*CDI (mg/kg/day) based on 50 kg body weight and 8 m^3 bathroom*
5% Body Surface Area	1.6×10^{-9}	2.8×10^{-9}
20% Body Surface Area	6.3×10^{-9}	1.1×10^{-8}
50% Body Surface Area	1.6×10^{-8}	2.8×10^{-8}
100% Body Surface Area	3.2×10^{-8}	5.6×10^{-8}

Total chronic daily intake:
The total chronic daily intake is a sum of the daily intakes from three different routes: inhalation from the air, dermal absorption from the liquid phase and dermal absorption from the air. The intake from the inhalation of butadiene in the air is the dominant source of exposure. The following table summarizes the total chronic daily intake of butadiene. The values derived from the sponsors calculations are presented in regular type while additional calculations using the alternative assumptions discussed above are in italics.

Exposure scenario	**Total CDI (mg/kg/day)**	***Total CDI (mg/kg/day) based on 50 kg body weight and 8 m^3 bathroom and 1% dermal absorption***
5% Body Surface Area	4.0×10^{-6}	*9.0×10^{-6}*
20% Body Surface Area	1.6×10^{-5}	*3.6×10^{-5}*
50% Body Surface Area	4.0×10^{-5}	*9.0×10^{-5}*
100% Body Surface Area	*7.9×10^{-5}*	*1.7×10^{-4}*

Calculation of theoretical cancer risk:
To calculate the risk of total excess cancer from exposure to butadiene the sponsor used the following formula.

Risk = CDI×SF

Where:

Risk = a unitless probability that one additional case of cancer will develop in an exposed population over a 70 year lifetime

CDI = chronic daily intake averaged over 70 years (mg/kg/day)

SF = inhalation slope factor, expressed in $(mg/kg/day)^{-1}$

The calculation of the chronic daily intake has been reviewed above.

The slope factor can be calculated from previous risk assessments of butadiene. A number of risk assessments of exposure to 1,3-butadiene have been conducted for occupational exposures. In a review of eight different risk assessments, Cagen et al. (*Toxicology* 113:215-220, 1996) found a wide range of risk estimates from less than 1 cancer death per 1000 exposed workers to over 200 deaths per 1000 workers exposed. These risk estimates are based on exposure to 1 ppm for 40 years, 50 weeks/year, 5 days/week, 8 hours/day. These risk estimates were derived from a variety of animal data. Some models used the mouse lung tumor data, which is the tissue that is the most sensitive while other models used pooled animal tumor data.

In another risk estimate, Dankovic et al. (*IARC Sci. Publ.* 127:335-44, 1993) estimated risk for workers exposed to 2 ppm for 8 h/day, 5 days/week, 50 weeks/year, for 45 years. The authors used data from B6C3F1 mice dosed with from 6.25 to 625 ppm in the NTP study. The excess risk ranged from 0.2 per 10,000 exposed individuals, based on female mouse heart haemangiosarcomas, to 600 per 10,000 exposed individuals, based on female mouse lung tumors. Varying model assumptions for the mouse lung tumor data provided risk estimates ranging from 60 per 10,000 to 1600 per 10,000.

In 1985 the US EPA calculated a unit risk for 1,3-butadiene exposure of 0.25 per ppm. This unit risk was based on animal data and assumed lifetime continuous exposure. In January of 1998 the USEPA published an external review draft entitled *Health risk assessment of 1,3-butadiene*. This document contained an updated estimate of the unit risk. The EPA determined that, *"The best estimate of human lifetime extra cancer risk from chronic exposure to 1,3-butadiene is 9 X 10^{-3} per ppm based on a linear extrapolation of the increased leukemia risks observed in occupationally exposed workers."* This risk estimate is lower than many of the previous risk estimates derived for 1,3-butadiene. This draft underwent review by an EPA scientific advisory board on 30 April to 1 May 1998. A final draft does not appear to have been released, yet.

The sponsor has used the EPA unit risk of 9×10^{-3} per ppm in their calculations. The 1998 EPA estimate may be more appropriate than earlier estimates since it is based on human epidemiologic data. Therefore, it seems reasonable to use this risk estimate for calculating the risk from butadiene in Luxiq.

The risk calculated by the EPA is expressed as risk per ppm. This can be converted to risk per $\mu g/m^3$ by the following calculations.

$mg/m^3 = ppm \times MW \div 24.45$

for butadiene

$$54.09 \div 24.45 = \frac{2.21\ mg/m^3}{ppm}$$

so

$$9 \times 10^{-3}\ \text{per ppm} = \frac{9 \times 10^{-3}}{ppm} = \frac{9 \times 10^{-3}}{2.21\ mg/m^3} = \frac{9 \times 10^{-3}}{2.21 \times 10^{3}\ \mu g/m^3} = 4.07 \times 10^{-6}\ \text{per}\ \mu g/m^3$$

The sponsor states that risk of 9×10^{-3} per ppm is equivalent to 4.09×10^{-6} $\mu g/m^3$. It is not clear why the sponsors calculations differ from mine although the small difference should not compromise the subsequent calculations.

The assumed exposure scenario for the EPA risk estimate is for exposure to butadiene for 70 years for a 70 kg individual breathing 20 m^3 air per day for 365 days per year. Therefore, if one factors out the weight of the individual and volume of air breathed, a slope factor with units of

$(mg/kg/day)^{-1}$ can be derived. This slope factor can provide risk estimates for the chronic daily intakes calculated above which are expressed as mg/kg/day averaged over 70 years.

The sponsor has provided the following equation relating air unit risk to slope factor based on average daily dose (p 46):

Risk per $\mu g/m^3$ = slope factor × 1/70 kg × 20 m^3/day × 10^{-3} µg/mg

However, this equation appears to be incorrect. Solving for the slope factor gives units of $(\mu g^2/kg/day/mg)^{-1}$ instead of the expected $(mg/kg/day)^{-1}$. In addition, one mg is equivalent to 10^3 µg not 10^{-3} µg.

In the next equation provided by the sponsor these errors appear to have been corrected. The inhalation slope factor (SF_i) is derived from the inhalation unit risk according to the following equation.

$$SF_i\ (mg/kg/day)^{-1} = \frac{\text{unit risk}\ (\mu g/m^3)^{-1} \times 70\ kg \times 10^3\ \mu g/mg}{20\ m^3/day}$$

The sponsor then applies this equation to the EPA unit risk for butadiene (4.09×10^{-6} per $\mu g/m^3$). In the equation as written in the report, the exponent was left off of the unit risk (i.e. 4.09 was used instead of 4.09×10^{-6}); however, the resulting value for the slope factor suggests that the correct value was actually used in the calculation. The slope factor was calculated as 0.014 $(mg/kg/day)^{-1}$. If a unit risk of 4.07×10^{-6} $\mu g/m^3$ is used, the slope factor is essentially the same.

Using a slope factor with the units $(mg/kg/day)^{-1}$ and total chronic daily intake with the units mg/kg/day, risk can be calculated as a simple product of these values:

Risk = $SF_i \times CDI$

The total carcinogenic risk from the total chronic daily intakes calculated above are listed in the following table. The values derived from the sponsors calculations are presented in regular type while additional calculations using the alternative assumptions discussed above are in italics.

Exposure scenario	**Total carcinogenic risk**	***Total carcinogenic risk based on 50 kg body weight and 8 m^3 bathroom and 1% dermal absorption***
5% Body Surface Area	6×10^{-8}	*1×10^{-7}*
20% Body Surface Area	2×10^{-7}	*5×10^{-7}*
50% Body Surface Area	6×10^{-7}	*1×10^{-6}*
100% Body Surface Area	*1×10^{-6}*	*2×10^{-6}*

The highest risk was calculated for a 50 kg female who applies Luxiq 365 days per year for 25 years, twice per day to 100 % body surface area in a small unventilated bathroom and remains in this bathroom for 30 minutes after each exposure. This risk estimate also assumes that 1% of the total butadiene in each dose would be absorbed directly from the foam. In this scenario the total carcinogenic risk is 2×10^{-6} which is equivalent to a risk of 1 cancer in 500,000 exposed individuals.

This exposure scenario seems greatly exaggerated and, therefore, risk from a more realistic use scenario is likely to be lower.

The risk assessment conducted by the sponsor uses the 1998 EPA unit risk of 9×10^{-3} per ppm. If the 1985 EPA unit risk or 0.25 per ppm had been used in the current calculations, the total carcinogenic risks would have been unacceptably high. For example, the slope factor for 0.25 per ppm would be 0.4 $(mg/kg/day)^{-1}$ Therefore, for 20% BSA application, the total carcinogenic risk using the sponsor's assumptions would have been 6×10^{-6} or 1 in 166,667. The 1998 value has not been published in a final report. If, in the future, this unit risk is found to be incorrect or if additional data becomes available which permits a more accurate risk estimate, then the cancer risk from 1,3-butadiene in Luxiq may need to be recalculated.

CONCLUSIONS: Based on current information about the cancer risk of butadiene and the sponsor's risk assessment, the specification of 0.01 mole % for dienes in the propellant appears to ensure a level of butadiene in Luxiq that does not exceed a cancer risk of 1×10^{-6} except in extreme exposure scenarios.

/S/ 2/19/99

Paul C. Brown, Ph.D.
Reviewing Pharmacologist

cc:
NDA 20-934
HFD-340
HFD-540
HFD-540/PHARM/BROWN
HFD-540/TL/AJACOBS
HFD-540/MO/HUENE
HFD-540/CHEM/PAPPAS
HFD-540/PM/CINTRON
HFD-105/DELAP

Concurrence Only:
HFD-540/DD/WILKIN 2/19/99
HFD-540/TL/AJACOBS 2/19/99

FEB 12 1999

Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products, HFD-540

Draft Completed: February 11, 1999
Revised:

NDA 20-934

Submission number	**Submission Date**	**Center Receipt Date**
BC	12/15/98	12/16/98

SPONSOR: Connetics Corporation

DRUG: Luxiq™, Betamethasone valerate foam 0.1%

SUMMARY: In this submission the sponsor has proposed lowering the specification for butadiene in the propellant to undetectable levels based on their current capillary gas chromatography method of detection. This would make the specification essentially equivalent to 0.01 mole %. This would mean that the product could still contain 4.8 ppm (4.8μg/g) 1,3-butadiene.

CONCLUSIONS: As stated in previous reviews, the presence of butadiene at any level probably presents a finite risk of carcinogenicity in humans. If patient exposure to butadiene is low enough then the risk of cancer may also be low enough to be considered acceptable for drug approval. The NDA might be approvable if the specification for 1,3-butadiene can be lowered to levels that the sponsor demonstrates does not present an unacceptable cancer risk.

Note: The sponsor was asked to conduct a risk assessment for 1,3-butadiene exposure from Luxiq foam. This risk assessment was submitted on 1/19/99 and is reviewed separately.

/S/ 2/11/99

Paul C. Brown, Ph.D.
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cc:
NDA 20-934
HFD-340
HFD-540
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HFD-540/TL/AJACOBS
HFD-540/MO/HUENE
HFD-540/CHEM/PAPPAS
HFD-540/PM/CINTRON

Concurrence Only:
HFD-540/DD/WILKIN 2/19/99
HFD-540/TL/AJACOBS 2/12/99

FEB 12 1999

Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products, HFD-540

Draft Completed: February 11, 1999
Revised:

NDA 20-934

Submission number	**Submission Date**	**Center Receipt Date**
AZ	11/23/98	11/24/98

SPONSOR: Connetics Corporation

DRUG: Luxiq™, Betamethasone valerate foam 0.1%

INTRODUCTION: This submission contains information about the toxicity of impurities found in the propellant. The propellant is obtained from a company in the U.K. and the specifications state that it may contain dienes at a total concentration of 0.5%. The propellant is therefore labeled as carcinogenic according to EEC guidelines since it may contain more than 0.1% 1,3-butadiene, which is a probable human carcinogen. The Division requested additional information on the long-term as well as short-term safety of the various impurities present in the propellant.

Genotoxicity and Carcinogenicity of 1,3-butadiene:
Preclinical studies show that 1,3-butadiene is mutagenic with metabolic activation. The mutagenic species appear to be epoxide metabolites. Studies *in vitro* suggest that metabolism of 1,3-butadiene is qualitatively similar in humans and experimental animals.

Preclinical studies have shown that 1,3-butadiene is a potent animal carcinogen. All doses tested have produced tumors in experimental animals (6.25 to 8000 ppm). These studies have not identified a no-effect level.

Epidemiologic studies of workers exposed occupationally to 1,3-butadiene have provided some evidence of carcinogenicity in humans. Gene mutations, chromosomal aberrations and sister chromatid exchanges have been detected in workers exposed to levels of 1,3-butadiene estimated at ≤1 ppm.

The International Agency for Research on Cancer has determined that 1,3-butadiene is *probably carcinogenic to humans* (Group 2A) (IARC Monograph 54:237-285, 1992). Similar conclusions have been reached by other agencies as well.

Calculation of maximum possible exposure to 1,3-butadiene under conditions of use of Luxiq:
The sponsor has calculated the exposure to the impurities present in the propellant of Luxiq assuming that the drug would be used twice per day at a dose of 5 g each time. The sponsor has also assumed that the impurities would be dispersed in a room with a volume of 10 m^3 (a 2×2×2.5 m room). The sponsor has taken 15 minutes (0.25 hr) as the exposure time at each use.

They have calculated daily exposure as an 8-hour time weighted average and acute exposure as a maximum concentration.

For 1,3-butadiene the sponsor has calculated the maximum exposure from a 5 g dose as 1.2 mg. This is equivalent to a daily TWA of 7.5×10^{-3} mg/m^3 or 3.394×10^{-3} ppm. The OSHA limit for 1,3-butadiene is a TWA of 1 ppm and the ACGIH limit is 2 ppm. The NIOSH limit is the least feasible dose since 1,3-butadiene is a suspected human carcinogen. The daily exposure to 1,3-butadiene permitted under OSHA or ACGIH guidelines is therefore approximately 295 to 590 fold higher than the exposure estimated by the sponsor.

The sponsor has also calculated that the 1.2 mg maximum dose of 1,3-butadiene from a 5 g dose of drug is equivalent to a single exposure maximum of 0.12 mg/m^3 or 0.0543 ppm. The OSHA short-term exposure limit is 5 ppm and the ACGIH limit is 2 ppm. The NIOSH short term exposure limit is the lowest feasible dose. The short-term exposure to 1,3-butadiene permitted under OSHA or ACGIH guidelines is therefore approximately 37 to 92 fold higher than the exposure estimated by the sponsor.

There are several aspects about the assumptions that the sponsor has made that might tend to underestimate the maximum exposure to 1,3-butadiene from the propellant. First the sponsor is using a 5 g dose to make the calculations. While 5 grams might be appropriate for a scalp application, the sponsor is also seeking approval for whole body use of Luxiq. In clinical trials a dose of 15 g was used for a body surface area of ≥30%. Therefore, if Luxiq was used on the whole body a dose of greater than 5 g would be likely. This would lead to a greater exposure to 1,3-butadiene. For example, a 50 g dose would increase the exposure over that calculated for 5g by a factor of 10. Therefore, the daily exposure to 1,3-butadiene permitted under OSHA or ACGIH guidelines would be approximately 30 to 59 fold higher than the exposure from a 50 g dose of the foam and the short term exposure to 1,3-butadiene permitted under OSHA or ACGIH guidelines would be approximately 4 to 9 fold higher.

Furthermore, the sponsor is assuming that all of the exposure would be through inhalation and that the impurities would be instantaneously distributed through a 10 m^3 volume. In fact, the sponsor has previously pointed out that "*most of the propellant expelled from the can is trapped in the foam structure*" until the foam collapses (volume 1.1 of original NDA submission, p. 48). Therefore, it appears that the propellant will be in contact with the skin and released in close proximity to the patient. It is not clear if any of the propellant or impurities can be directly absorbed through the skin.

CONCLUSIONS: The presence of butadiene at any level probably presents a finite risk of carcinogenicity in humans. If patient exposure to butadiene is low enough then the risk of cancer may also be low enough to be considered acceptable for drug approval. The NDA might be approvable if the specification for 1,3-butadiene can be lowered to levels that the sponsor demonstrates does not present an unacceptable cancer risk.

Note: The sponsor was asked to conduct a risk assessment for 1,3-butadiene exposure from Luxiq foam. This risk assessment was submitted on 1/19/99 and is reviewed separately.

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HFD-540/TL/AJACOBS
HFD-540/MO/HUENE
HFD-540/CHEM/PAPPAS
HFD-540/PM/CINTRON

Concurrence Only:
HFD-540/DD/WILKIN 2/19/99

HFD-540/TL/AJACOBS 2/12/99