CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20738

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Teveten™

(eprosartan mesylate)

Tablets

NDA 20-738

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-738

Teveten (eprosartan mesylate) Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Teveten Tablets**, **SmithKline Beecham Pharmaceuticals** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Eprosartan mesylate is a synthetic drug which is administered orally in the treatment of mild to moderate hypertension. The drug substance and drug product will be manufactured by the applicant in Ireland and the United Kingdom, respectively. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Eprosartan may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Chemical and physical test results indicate that the drug entering the environment will exist predominantly in the aquatic environment. Eprosartan is degraded to the Z-isomer of eprosartan upon exposure to light. Because eprosartan may persist in the environment for some time, the toxicity of the substance to organisms was characterized. Based on these studies, there are no adverse environmental effects anticipated at the expected environmental concentrations.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. In the United States returned, expired or rejected goods will be disposed of by the manufacturer at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

3/26/97
DATE

PREPARED BY
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Environmental Assessment Team
Center for Drug Evaluation and Research

3/13/97
DATE

CONCURRED
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Center for Drug Evaluation and Research

Attachment: Environmental Assessment

1 DATE

21 August 1996

2 NAME OF APPLICANT

SmithKline Beecham Pharmaceuticals

3 ADDRESS

SmithKline Beecham Pharmaceuticals
P.O. Box 7929
One Franklin Plaza
Philadelphia, PA 19102

4 DESCRIPTION OF THE PROPOSED ACTION

4.1 Description of the Requested Approval

SmithKline Beecham Pharmaceuticals is requesting approval to manufacture, package and market Teveten™ (eprosartan mesylate) Tablets (NDA # 20-738). The drug product will be prepared as oral capsules (50, 100, 200, 300 & 400 mg), packaged in clear PVC/PVdC blisters. An Environmental Assessment has been submitted pursuant to 21 CFR § 25.31a(a).

4.2 Need for the Proposed Action

The therapeutic indication for eprosartan (SK&F 108566) is for the treatment by oral route of first line mono-therapy in mild-to moderate hypertension. SK&F 108566 will be administered at an initial starting dose of 400 mg, u.i.d.; maintenance dose 400-800 mg uid or in two divided doses.

4.3 Locations where Proprietary Drug Intermediates, Drug Substance and Drug Product will be Produced

Eprosartan mesylate, the drug substance in the product which is the subject of the proposed action, is manufactured at the following facility:

SmithKline Beecham (Cork) Limited
Currabinny
Carrigaline
County Cork
Ireland

SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) is located approximately twelve miles south of Cork City on the southern shores of Cork Harbor. There is a total landbank of 130 acres, but the facility occupies only 28 acres. The immediate area is rural, with some farms and dwellings within a half mile radius of the boundary fence. The site discharges an aqueous waste into Cork Harbor after on-site biological treatment.

Key starting materials are manufactured at an overseas Contract Manufacturer. The name and address of this Contract Manufacturer is provided in Confidential Appendix 3. A description of the location and surroundings of the plant is also included in this Appendix.

Eprosartan (SK&F 108566) drug product (50, 100, 200, 300 and 400 mg tablets) will be manufactured and packaged at the following facility:

SmithKline Beecham Pharmaceuticals Co.
Magpie Wood
Manor Royal
Crawley
West Sussex RH10 2QJ
U.K.

The Crawley facility for drug product manufacture is located in a light industrial area near the city of Crawley, England (U.K.).

4.4 Locations where Product will be Used

The subject of this Environmental Assessment is the use of eprosartan in hospitals, clinics, and/or patient's homes within the United States. Predominant use is expected to coincide with areas of greatest population density, beyond that use is not expected to be concentrated in any particular geographic region.

4.5 Locations where Product will be Disposed of

Disposal of returned, expired and rejected drug substance and/or proprietary drug substance intermediate will be done in accordance with the environmental certification obtained from each site. See Non-Confidential Appendix 1 for a copy of each certification.

All eprosartan drug product returned, expired and rejected goods will be collected at Division KENCO Group Inc., 1704 Mid Park Drive, Knoxville, Tennessee 37291, and shipped to one of the facilities listed below for disposal by high temperature incineration.

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

Ogden Martin Systems of Lake, Inc.
3830 Rogers Industrial Park Road
Okahumpka, Florida 34762

SmithKline Beecham Pharmaceuticals in Bristol, Tennessee is permitted by the Tennessee Air Pollution Control Board to operate an infectious waste incinerator under Permit No. 443118. The Air Pollution Control Board regulates air emissions in the state of Tennessee and is part of the Department of Environment and Conservation. The Bristol site was issued a "Conditional Major Source" Operating Permit on June 14, 1996. This permit allows the facility to incinerate returned goods and in-house manufacturing waste. It expires on November 1, 2005.

Ogden Martin Systems of Lake, Inc. in Okahumpka, Florida is licensed by the Florida Department of Environmental Regulation (Orlando, Florida) to destroy hazardous material under permit number A035-193877 (expiration date - October 25, 1996), and under solid permit number S035-279397 (expiration date - December 18, 2000).

At US hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures and /or that in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills,

incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

5 DESCRIPTION OF THE CHEMICAL SUBSTANCE THAT IS THE SUBJECT OF THE PROPOSED ACTION

5.1 Nomenclature

BAN, USAN, INN:	Eprosartan, Eprosartan mesylate
Brand/Proprietary Name:	Teveten™ Tablets
Chemical Name:	(E)-alpha-[[2-butyl-1-[4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene]-2-thiophenepropanoic acid, monomethanesulfonate

5.2 Chemical Abstract Service (CAS) Registration Number

0144143-96-4

5.3 Molecular Formula

Salt: $C_{23}H_{24}N_2O_4S \bullet CH_4O_3S$

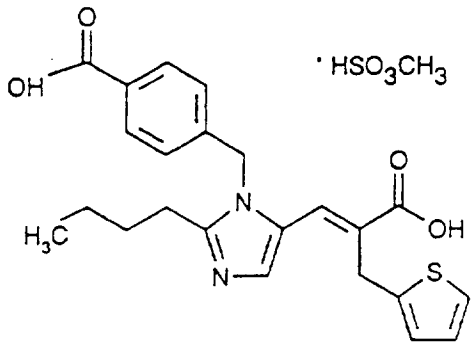
Zwitterion: $C_{23}H_{24}N_2O_4S$

5.4 Molecular Weight

520.625 methanesulfonate salt
424.519 free zwitterion

5.5 Structural Formula

Eprosartan mesylate



5.6 Physical Description

White to off-white powder

5.7 Additives

Not applicable

5.8 Impurities

No impurities are likely to be present at levels > 1% in eprosartan drug substance.

6 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Introduction from Production of Substances

6.1.1 Drug Substance Production at Cork

The Cork, Ireland manufacturing facility claims and certifies (see Non-Confidential Appendix 1 for the signed certification) that it is 1) in compliance with all local and national environmental laws; 2) in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and 3) that approval of this application (NDA # 20-738) and the subsequent increase in production at the facility is not expected to affect

compliance with current emission requirements or compliance with environmental laws.

6.1.2 Drug Substance Intermediate Production at Contract Manufacturing Facility

The proprietary drug product intermediate (Contract Manufacturer) manufacturing facility claims and certifies (see Confidential Appendix 3 for the signed certification) that it is 1) in compliance with all local and national environmental laws; 2) in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and 3) that approval of this application (NDA # 20-738) and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

6.1.3 Drug Product Production at Crawley

The drug product manufacturing facility claims and certifies (see Non-Confidential Appendix 1 for the signed certification) that it is 1) in compliance with all local and national environmental laws; 2) in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and 3) that approval of this application (NDA # 20-738) and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

6.2 Expected Introduction Concentration from Use of Drug Product

The 5th year production estimate, the expected introduction concentration (EIC) and the expected environmental concentration (EEC) calculations for eprosartan are included in Confidential Appendix 4. All concentrations are reported as the concentration of the active moiety.

The EIC for eprosartan in the aquatic environment, assuming all drug substance produced is used, even distribution throughout the U.S. per day, and no metabolism or depletion mechanisms, is calculated in Confidential Appendix 4 using the following equation [1]:

EIC-Aquatic (ppm) = A x B x C x D

where A = kg/year production
B = 1/liters per day entering POTW's*
C = year/365 days
D = 106 mg/kg (conversion factor)

* 1.115×10^{11} liters per day entering publicly owned treatment works (POTW's). Source: 1992 Needs Survey, Report to Congress, September 1993, EPA-832-R-93-002

The EIC-Aquatic for SK&F 108566 was determined to be greater than 1 part per billion. As a result, detailed information for EA format items 7, 8, 9, 10, 11 and 15 follows.

6.3 Introduction from Disposal of Drug Product

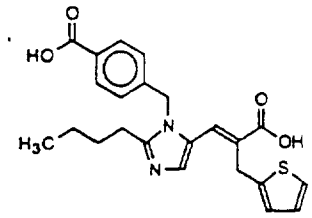
The returned goods of eprosartan oral capsules will be collected and disposed of as described in Item 4.5 of this assessment. Based on the controlled and highly efficient thermal destruction of unused eprosartan oral tablets, no significant amount of material should be introduced into the environment from disposal.

7 FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1 Metabolism

The metabolism and pharmacokinetics of ^{14}C-eprosartan were investigated in four male human subjects [2]. The primary route of excretion was feces, accounting for 90 and 61% of oral and intravenous doses, respectively. The only drug-related component identified in plasma or feces was eprosartan. In urine, approximately 20% of the radioactivity excreted was an acyl glucuronide of eprosartan, with the remaining 80% being unchanged eprosartan. These data indicate that the large majority of eprosartan administered to humans is excreted unchanged. In addition, the glucuronide urinary metabolite is expected to rapidly hydrolyze back to the parent after excretion. Therefore, the environmental fate and effects of the parent compound only are considered in this document (Figure 1).

Figure 1. Structure of SK&F 108566.



7.2 Physical Properties

The following physical properties were determined for eprosartan. Details are provided in the following sections.

Property	Value	Comment
Dissociation Constants	pK_1 4.11	see 7.2.1
	pK_2 5.68	
	pK_3 6.89	
Aqueous Solubility	910 mg/L @ pH 7	see 7.2.2
Octanol/water Distribution Coefficient	0.243 @ pH 6.83	see 7.2.3
QSAR Henry's Law Constant	3.4×10^{-12} m^3•atm/mol	see 7.2.4
Sludge Adsorption	K_p = 24.3 mL/g	see 7.2.5
UV/vis Spectrum (pH 7.64)	λ_{max} at 232 and 294 nm	see 7.3.2
	ε_λ = 25700 and 13700 $m^{-1} \cdot cm^{-1}$	
	cutoff at ~340 nm	

7.2.1 Dissociation Constants

Eprosartan was determined to have three pK_a values [3]. The group assignments shown below were predicted based on known pK_a values of substituent groups [4].

pK_a	group	type	value
pK_1	ring COOH	acidic	4.11
pK_2	ring N	basic	5.68
pK_3	COOH	acidic	6.89

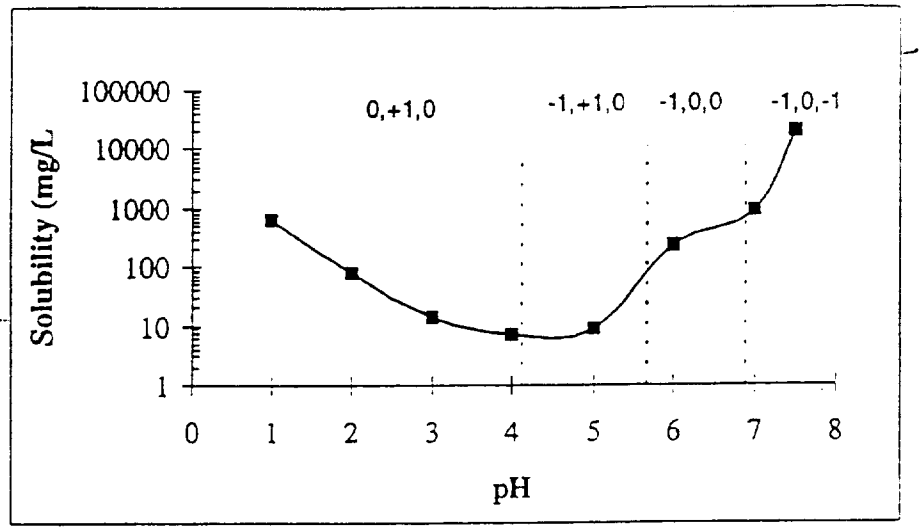
The ionization of eprosartan affects the behavior of the molecule over the environmental pH range of 5 to 9, as discussed in the following sections.

7.2.2 Aqueous Solubility

Solubility data for eprosartan are summarized below [3].

Solvent		Solubility (mg/L)
EtOH		> 100000
aqueous:	pH 1	610
	pH 2	84
	pH 3	14
	pH 4	7
	pH 5	9
	pH 6	240
	pH 7	910
	pH 7.5	> 20000

The solubility data reflect the ionization of the molecule as a function of pH as shown in the following figure. The vertical dashed lines indicate the pK_a values. The groups of three numbers across the top of the plot indicate the charge on the functional groups corresponding to pK_{a1}, pK_{a2}, and pK_{a3}, respectively.



7.2.3 Octanol/Water Distribution and Partition Coefficients

The octanol/water partition coefficient (K_{ow}) of eprosartan was determined to be 0.047 (log K_{ow} = -1.43) at pH 7.4 [3]. K_{ow} expresses the concentration ratio of eprosartan free base (only) in the organic and aqueous phases; ionic species are neglected. Theoretically, K_{ow} is independent of solution pH. However, ionization of the functional groups affects the lipophilicity of the molecule at environmental pH levels. The octanol/water distribution coefficient (D_{ow}) expresses the concentration ratio of all species and may vary as a function of pH.

Therefore, D_{ow} was determined at three pH values and in unbuffered water using the shake flask method [5]; results are summarized below.

Aqueous Phase	Mean D_{ow}	Log Mean D_{ow}
pH 4.84 buffer	33.3	1.52
pH 6.83 buffer	0.243	-0.614
pH 9.03 buffer	0.00284	-2.55
water (pH 6.65)	0.696	-0.157

These data are in reasonable agreement with the pH 7.4 K_{ow} value reported above. Comparison of the D_{ow} values obtained for pH 6.83 buffer and water indicate that the ionic strength of the aqueous phase had little effect on the distribution of eprosartan. The data indicate that eprosartan is highly hydrophilic and that the bioconcentration potential is extremely low.

7.2.4 Henry's Law Constant

The potential volatility of a chemical in the environment may be quantified by the Henry's law constant; the distribution ratio of a chemical in air and water in a closed system. A Henry's law constant of 3.4×10^{-12} atm•m^3/mol was calculated [6] for eprosartan using quantitative structure activity relationships (QSAR). Chemicals with Henry's law constants less than ~10^{-7} atm•m^3/mol are less volatile than water [7]. Eprosartan is predicted to be essentially non-volatile in the environment.

7.2.5 Activated Sludge Adsorption

An experiment was conducted to determine the extent of adsorption of eprosartan to freshly-collected activated sludge solids [8]. ^{14}C-eprosartan was equilibrated in sludge/wastewater test systems at five initial concentrations ranging from 126 to 1270 ug/L. Three vessels were sampled after 1.4 and 2.3 hours of contact time to determine the rate of adsorption. After equilibrium was established, all vessels were sampled at 4.3 hours.

At the 4.3 hour sampling point, the mean extent of adsorption was 6.0 ± 3.0 percent (SD, N=18). At the sludge total suspended solids concentration used (2670 mg/L), the corresponding mean sludge/water distribution ratio (K_d) was 24.3 ± 9.7 mL/g (log mean K_d 1.39). The extent of adsorption in a WWTP can be predicted using equation 1.

$$\text{Fraction Adsorbed} = K_{d\text{-sludge}} \cdot S / (1 + (K_{d\text{-sludge}} \cdot S)) \qquad \text{equation 1}$$

where:
S = solids to water ratio (g/mL)

Assuming that $K_{d\text{-sludge}}$ = 24.3 mL/g and S = 0.0025 g/mL, the extent of eprosartan adsorption in a wastewater treatment plant is ~6 percent. Therefore, the majority of eprosartan which enters wastewater treatment plants is expected to

remain in the aqueous phase and enter the aquatic environmental compartment via effluent.

7.3 Transformation and Depletion Mechanisms

7.3.1 Aerobic Biodegradation

The mineralization of eprosartan was investigated using a Columbus respirometry system [9]. Eprosartan was added to a dilute microbial inoculum at 27.6 mg/L (15 mg C/L) and oxygen utilization and CO_2 evolution were monitored over time. No evidence of eprosartan mineralization was obtained.

The biotransformation of eprosartan was investigated using batch activated sludge methodology at a starting concentration of 10 mg/L. During a 45-day test period, no biodegradation was observed based on quantification of parent compound in the test matrix by HPLC [9].

Based on these findings, biodegradation will not be a likely depletion mechanism for eprosartan in the environment.

7.3.2 UV/vis Spectrum and Photolysis

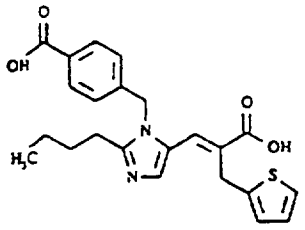
The direct aquatic photolysis kinetics of eprosartan were estimated from the UV/vis spectrum assuming a conservative quantum yield of 0.001 [10, 11]. At pH 7.64 and 9.22, the UV absorbance cutoff is ~340 nm. The estimated photolysis half-lives were on the order of 14 to 17 days in summer and 61 to 80 days in winter. The UV absorbance spectrum shifted to lower wavelengths at pH 4.93; the cutoff was ~320 nm. At pH 4.93, the estimated photodegradation half-lives were 109 days in summer and 391 days in winter. These estimates assume ideal irradiance conditions and the actual quantum yield may be different than 0.001 [11].

Given significant UV absorbance above 300 nm, direct aquatic photolysis kinetics of eprosartan were experimentally determined [10]. Solutions of eprosartan were exposed to ambient sunlight in quartz vessels in Swedeland, Pennsylvania (~40 °N latitude) during May 1996. Two types of vessels were photo-exposed to ambient sunlight: dark controls were quartz tubes wrapped with foil to exclude light, test vessels were quartz tubes that were not foil-wrapped. The initial

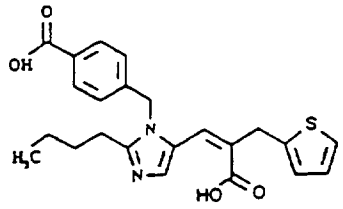
nominal eprosartan concentration was 2 mg/L. Preliminary experiments indicated that eprosartan was unstable in pH 4.5 acetate buffer at room temperature. Reverse-phase HPLC analysis revealed three overlapping peaks that eluted ~1 minute after the eprosartan retention time. The degradation reaction occurred without photo-exposure within ~20 minutes of adding eprosartan to the acetate buffer at room temperature. Comparable experiments at the same pH using HCL indicated no degradation. This indicated that acetate buffer catalyzed eprosartan degradation. In order to pursue photolysis studies all subsequent experiments utilized only pH 7 phosphate buffer.

In phosphate buffer, a 2 mg/L solution of eprosartan proved to be stable for at least six days when stored in the dark at ~4 °C. In photo-exposed test vessels, eprosartan reacted almost completely within 20 minutes of exposure , ($t_{1/2}$ < 10 minutes), yielding a degradant HPLC peak with a relative retention time of 1.14 (versus eprosartan). In dark controls, the same reaction appeared to occur but at a much slower rate. The first-order dark controls' reaction rate constant was 0.110 hr^{-1} ($t_{1/2}$ = 6.3 hours). A thermal hydrolysis experiment confirmed that the degradation was not thermally promoted as results indicated no eprosartan degradation when heated to50°C in dark for 42 hours [13]. This indicated that the degradation mechanism was primarily photolytically promoted. The degradation in the dark controls was most likely due to light leakage.

For the phosphate buffered solutions, diode array spectra of eprosartan and the degradant peaks indicated that the degradant had decreased absorbance in the range of >280 nm compared to eprosartan. Based on the relative retention times, diode array spectra, and mass spectrometry [12], the degradant has been identified as SB 206328, the Z isomer of eprosartan.

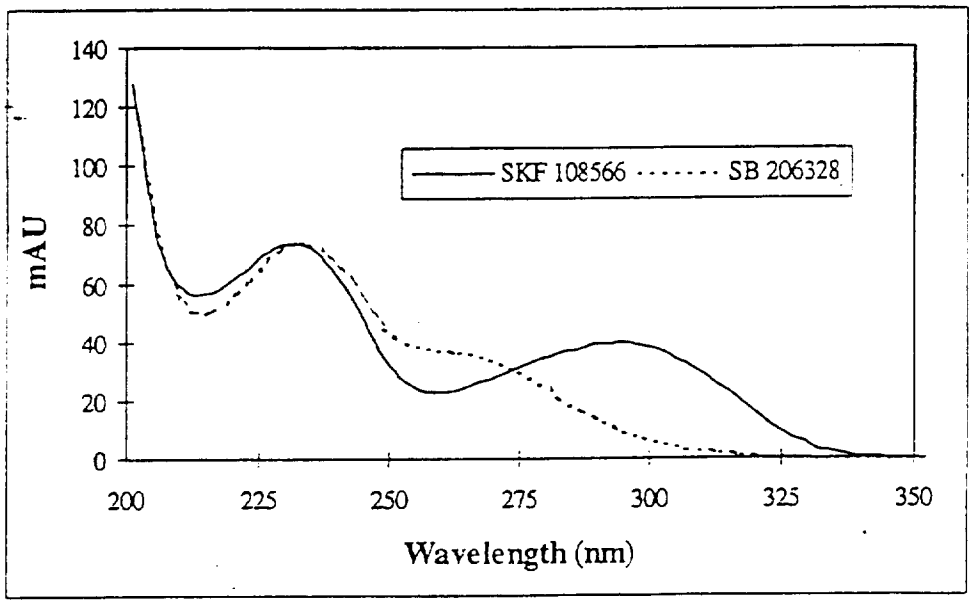


SK&F 108566
eprosartan



SB 206328
Z-isomer of eprosartan

No additional photodegradation of SB 206328 was observed when exposed to sunlight for up to 142 hours (~6 days). The diode array spectrum SB 206328 showed little absorbance at wavelengths >300 nm, strongly suggesting that the compound is not susceptible to further degradation by photolysis.



7.4 Expected Environmental Concentrations (EEC)

The EEC value and accompanying calculations are provided in Confidential Appendix 4. Accounting for adsortive losses to WWTP biomass and assuming a conservative dilution factor of three for surface receiving waters, the EEC is expected to be 3.2 times lower than the EIC.

7.5 Summary - Predicted Environmental Fate of Eprosartan in the Environment

Eprosartan which enters wastewater treatment plants (WWTPs) is not expected to be significantly biodegraded. Sludge/water distribution data suggest that the mass partitioning of eprosartan between WWTP effluent and sludge solids will be on the order of 94% to effluent and 6% to sludge. Therefore, almost all of the

eprosartan which enters a WWTP is predicted to be emitted to the aquatic environment in effluent. Eprosartan is expected to be relatively mobile in the aquatic environment and has little or no tendency to bioconcentrate in biota.

Photolytic stability data (see section 7.3.2) suggest that eprosartan will be rapidly transformed to SB 206328 on exposure to sunlight in the surface water zone of the aquatic environment.

8 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Human and Mammalian Health Effects Summary

8.1.1 Acute Oral Toxicity Studies [14]

Eprosartan is an angiotensin II antagonist and is being investigated for treatment of hypertension. The primary human excretion product in urine and feces is the parent compound.

Single oral doses up to 1000 mg/kg caused no drug-related effects in rats or dogs in toxicity studies, and no functional effects on cardiovascular, respiratory or renal systems in the safety pharmacology studies. Single intravenous doses up to 300 mg/kg produced no target organ toxicity in male or female rats, though females receiving ≥ 10 mg/kg showed reduced weight gain.

8.1.2 Chronic Oral Toxicity Studies [14]

In 30-day oral and 14-day intravenous toxicity studies in rats and dogs, no significant drug-induced toxicity was observed at dosages up to 1000 mg/kg per day orally or 30 mg/kg per day intravenously. No significant drug-induced target organ toxicity was detected in chronic oral studies, including six-month studies in rats and dogs at dosages up to 1000 mg/kg per day and a three-month mouse study at doses up to 2000 mg/kg per day.

8.1.2.1 Carcinogenicity

According to the MSDS, studies have not been conducted with this material and it is not listed as a carcinogen by SB, IARC, NTP or US OSHA.

8.1.2.2 Mutagenicity [14]

SK&F 108566-J was not mutagenic in bacteria or mammalian cells *in vitro* (Ames & mouse lymphoma tests) or *in vivo* (mouse micronucleus test) and did not cause chromosomal aberration in human lymphocytes in an *in vitro* assay.

8.1.2.3 Reproductive Toxicity [14]

In oral reproductive performance studies, there were no effects on mating, fertility or gonadal function in male or female rats given eprosartan oral dosages up to 1000 mg/kg per day. In an oral developmental toxicity study in pregnant rats treated on days 6-17 of gestation, SK&F 108566-J produced no maternal toxicity and no fetal mortality or developmental toxicity at dosages up to 1000 mg/kg per day.

In oral developmental toxicity studies in pregnant rabbits treated on days 6-28 of gestation (organogenesis and late pregnancy), SK&F 108566-J produced maternal toxicity at dosages ≥ 3 mg/kg per day and fetal mortality at dosages of ≥10 mg/kg per day. No maternal toxicity was evident at a dosage of 1 mg/kg per day, and no fetal mortality or developmental toxicity was evident at a dosage of 3 mg/kg per day.

8.2 Aquatic Toxicity Studies

8.2.1 Acute Aquatic Toxicity of Eprosartan (SK&F 108566)

For evaluation of potential aquatic toxicity, the parent compound itself (SK&F 108566) was studied since it is the primary excretion product. Thus, any adverse environmental effects observed during testing with eprosartan are expected to represent a 'worst-case' scenario. All eprosartan concentrations are reported as the free zwitterion.

Since the calculated maximum expected environmental concentration (MEEC) of eprosartan exceeded 1 ppb using the Tier 0 calculation, aquatic toxicity testing was initiated using an extended Tier 1 approach [1]. Acute aquatic toxicity studies were conducted with eprosartan (SK&F 108566) using *Daphnia magna* [15, 21], *Lepomis macrochirus* (bluegill sunfish) [16], *Vibrio fischeri* (Microbics Microtox®) [17], and activated sludge microorganisms (OECD 209) [18].

The acute toxicity of eprosartan solutions to these organisms is summarized below:

Toxicity Test	Toxicity Endpoint and SK&F 108566 concentration*
Daphnia magna 48-hr acute	EC50 > 120 mg/L NOEC ≥ 120 mg/L
Lepomis macrochirus, 96-hr acute	LOEC = 32 mg/L NOEC = 16 mg/L EC50 > 88 mg/L
Vibrio fischeri, 15 minute (Microtox®)	EC50 > 36 mg/L
Activated sludge respiration (OECD 209)	EC50 > 140 mg/L NOEC > 140 mg/L

* due to reduced solubility limitations in test waters, toxicity endpoints are reported as greater than values.

The two acute single species toxicity tests were conducted up to the water solubility limit of eprosartan in EPA-reconstituted hard water for the *Lepomis macrochirus* and *D. magna* assays. Apparently, eprosartan solubility was greatly reduced in the hard dilution water as compared to deionized water at pH 7 [see Section 7.2.2]. Neither of the species used experienced any increased mortality at the eprosartan concentrations tested as compared to the controls. In addition, *D. magna* exhibited no adverse behavioral effects at 120 mg/L eprosartan.

The toxicity of various eprosartan (SK&F 108566) concentrations to bluegill sunfish (*Lepomis macrochirus)* is summarized below [16]:

Nominal eprosartan concentration (mg/L)	Measured eprosartan concentration at T_0 (mg/L)	Lepomis macrochirus mortality (%)
Control	n/a	10
16	15	15
32	30	20
64	53	10
80	69	5
88	75	5

* All concentrations expressed as free zwitterion.

It is evident from these data that eprosartan exhibited no dose response fish mortality during this study, relative to the controls. The minor increase in mortality at 32 mg/L can be attributed to an unusual event that occurred involving two test vessels (32 and 64 mg/L) as well as the control vessel on day 3 of the study. During this event, solution volume was lost from three vessels due to accidental shaking. However, the two highest test concentrations and the 16 mg/L vessel were not affected by this unusual event and, as control survival was still acceptable as prescribed by regulatory guidelines (OECD 203), the event was deemed not to have a negative effect upon the study.

Fish exposed to eprosartan at measured solution concentrations of 32, 64, 80, and 88 mg/L exhibited erythema with no active hemorrhaging although gentle prodding of the gill resulted in bleeding from the lamellae. Similar findings were apparently not noted in mammalian studies. It is plausible that the eprosartan, through its antagonist effect on angiotensin, caused vasodilatation and possible increased cell permeability which was most pronounced in the gill lamellae. This observation of erythema was not obvious in fish exposed to 16 mg/L eprosartan and should not therefore be an expected effect at environmental concentrations. Based upon the observations of erythema, the no-observable-effects-concentration (NOEC) was determined to be 16 mg/L.

Eprosartan was not inhibitory to *Vibrio fischeri* (Microbics Microtox® assay) at concentrations of 36 mg/L. Microbial inhibition testing using activated sludge microorganisms indicated that eprosartan was not inhibitory at solution concentrations up to and including 140 mg/L.

8.2.2 Acute Toxicity of Photolytically-Degraded Eprosartan

As discussed in Section 7.3.2, sunlight exposure of aqueous eprosartan test solution produced a rapid transformation of eprosartan (SK&F 108566) into its Z-isomer (SB 206328). As this photoisomerization may be likely in surface waters a comparative toxicity assessment of SB 206328 was conducted. Although a relative increase in toxicity would be unlikely in the Z-isomer given the relatively low observable toxicity in SK&F 108566 and the relatively facile isomerization, an acute toxicity assay was conducted with *Daphnia magna*. This toxicity test utilized photolytically-degraded eprosartan solution that was demonstrated via HPLC to consist primarily of SB 206328 with an approximate 7% SK&F 108566 residual. The concentration of SB 206328 in the test solution was determined to be 78.7 mg/L and 81.1 mg/L at test initiation and termination,respectively.

No mortality or behavioral effects, as compared to controls, were observed in the *D. magna* exposed to this photolytically-degraded eprosartan solution that consisted predominantly of eprosartan Z-isomer (SB 206328) [22].

8.3 Aquatic Compartment Assessment Factor Calculation

Using the ratio of a single species toxicity value divided by the maximum expected introduction concentration (EIC_{aq}) or the expected environmental concentration-aquatic (EEC_{aq}), one can calculate assessment (safety) factors that compare predicted environmental concentrations with known toxicity data. The calculations conducted using the EIC assume no depletion mechanisms whereas the calculations using the EEC consider the small eprosartan loss attributed to sludge sorption and water dilution at the WWTP outfall. The WWTP outfall dilution factor was conservatively assumed to be 3 so as to provide protection during low water flow periods [19]. The equation used for these calculations, a modification of the quotient method [20], is as follows:

$$\text{Assessment Factor} = \frac{\text{Appropriate Toxicity Test Endpoint}}{\text{Environmental Concentration}} \qquad \text{(Equation 8-1)}$$

An assessment (safety) factor less than or equal to 1 indicates an increased probability of unacceptable ecological risk while a higher safety factor is indicative of acceptable risk, since the anticipated environmental concentration is less than the toxicity value. The FDA guidance dated November, 1995, lists three action levels dependent upon the assessment factor obtained at various tiered levels of testing [1]. These are described below:

TEST TIER AND DESCRIPTION	ASSESSMENT FACTOR
1 - One Suitable Test Organism	1000
2 - Aquatic Organism Base Set Testing	100
3 - Chronic Toxicity Testing	10

Eprosartan assessment (safety) factors were calculated using the NOEC values since E(L)C_{50} values could not be calculated from the data because no toxicity was observed at the hard water saturated solution concentrations of eprosartan.. Therefore, it should be noted that these calculated assessment factors are conservative in nature.

A summary of the calculated assessment factors, using the expected environmental concentrations described in Confidential Appendix 4 and the toxicity values previously described, follows:

Concentration Value Used	Toxicity Test	Toxicity Value Endpoint	Calculated Risk Assessment Factor
EIC-aquatic	*D. magna* 48-hr acute	NOEC	>30,000
EEC-aquatic	*D. magna* 48-hr acute	NOEC	>90,000
EIC-aquatic	*Lepomis macrochirus* 96-hr acute	NOEC	>4,200
EEC-aquatic	*Lepomis macrochirus* 96-hr acute	NOEC	>13,300

It can be concluded from these toxicity data and assessment factor calculations that (1) eprosartan exhibited no significant effect, as compared to controls, to either *L. macrochirus* or *D. magna* at solution concentrations less than or equal to 16 mg/L, (2) eprosartan exhibited no toxicity to activated sludge microorganisms or the bacterium *Vibrio fischeri* at the concentrations tested, and (3) assessment factors calculated before consideration of sludge sorption and receiving water dilution and using the conservative NOEC toxicity values were in excess of 4,000 for *L. macrochirus* and 30,000 for *D. magna*. All of these calculated assessment values greatly exceed the FDA EA Tier 1 criteria of 1000. It should be noted that if an E(L)C_{50} value could be predicted, the assessment factors would even be greater.

Therefore, it can be concluded, that at concentrations expected to be emitted into and exist in the environment, eprosartan should exhibit no acute toxicity to aquatic organisms.

9 USE OF RESOURCES AND ENERGY

9.1 Use of Resources and Energy at Cork, Ireland

The percent of total site energy resources expected to be utilized at the Cork facility to produce SK&F 108566 drug substance is estimated to be 11.7% of the site's total electricity consumption and 7.4% of the natural gas usage. The effects on the use of resources for the production of SK&F 108566 drug substance are expected to be minimal because of the existing controls and treatment units that will be used.

9.1.1 Effect Upon Endangered Species and Historic Places

The production of SK&F 108566 substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by SK&F 108566 substance production or waste disposal activities since the production will take place outside of the United States.

9.2 Use of Resources and Energy at the Drug Substance Intermediate Contract Manufacturing Facility

The percent of total site energy resources expected to be utilized at the contract manufacturing facility to produce SK&F 108566 drug substance is estimated to be less than 1% of the site's total consumption. The effects on the use of resources for the production of the drug starting material/intermediate are expected to be minimal because of the existing controls and treatment units that will be used.

9.2.1 Effects Upon Endangered Species and Historic Places

The production of the drug starting materials/intermediates and the disposal of associated wastes should have no effect on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by Eprosartan production or waste disposal activities since the production will take place outside of the United States.

9.3 Use of Resources and Energy at the Crawley, U.K. Manufacturing Facility

The percent of total site energy resources expected to be utilized at the Crawley facility to produce eprosartan drug product is estimated to be 1% of the site's total electricity consumption and 0.5% of the total steam usage. The effects on the use of resources for the production of eprosartan drug product are expected to be minimal because of the existing controls and treatment units that will be used.

9.3.1 Effect Upon Endangered Species and Historic Places

The production of eprosartan drug product and the disposal of associated wastes should have no effect on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by eprosartan drug product production or waste disposal activities since the production will take place outside of the United States.

10 MITIGATION MEASURES

10.1 Production Mitigation at Cork, Ireland

Plans to minimize waste output have been considered and implemented at the outset of eprosartan development and production. The Integrated Pollution Control (IPC) license contains guidelines for the establishment of an Environment Management Programme to assess all operations for the use of cleaner technology and the minimization of waste. Potential environmental impacts associated with production at Cork are also minimized by the following:

Most waste streams are incinerated, and the gases scrubbed before being discharged. Scrubber liquors are biotreated in the on-site wastewater treatment facility before being discharged;

Several waste streams from eprosartan production will be sent off-site for recovery of solvents; and one waste stream will be sent off-site for recovery of a catalyst; and

Airstreams from the process buildings are scrubbed prior to venting to the atmosphere.

10.2 Mitigation at the Drug Substance Intermediate Contract Manufacturing Facility

The company initiated its integrated total waste management programme at a very early stage. As a consequence, in developing processes, a lot of engineering goes into waste avoidance and waste minimization. If recycling of used-up products is no longer possible, hazardous waste is incinerated in the facility's own high temperature rotary kiln with off-gas scrubbing. A company-owned, state-of-the-art landfill completes the waste mangement system.

10.3 Mitigation at Crawley

Potential adverse environmental impacts associated with the proposed action are minimized at the Crawley facility by the following:

Dilute aqueous waste disposed of through the site aqueous effluent goes to a publicly owned treatment works; the effluent discharge has to meet certain waste treatment parameter criteria.

The Crawley facility operates to site and departmental emergency procedures. Plant operators are trained under an established training plan, and a personal training record is maintained for each operator.

Disposal protective overalls, overshoes, hats and gloves together with appropriate dust respirators are worn by plant personnel when handling individual batch materials, intermediates and finished products. All reactions are carried out under closed systems whenever possible to avoid creating excessive dust, and local exhaust ventilation is used at points of activity, such as loading, unloading and transferring materials. Appropriate Standard Operating Procedures are followed for the use and cleaning of equipment and manufacturing areas.

A procedure for cleaning spills is included in the operating instructions. Due to the relatively small quantities of materials involved, there are no containment dikes or other spill control devices to contain potential spills. In the event of a spill, as much of the spilled material is collected as practicable and weighed for reconciliation purposes. The material is then disposed of using methods described in its Material Hazard sheet. Powder spills are cleaned using a Type H dedicated vacuum cleaner, and the collected material is disposed of by the same route as other solid waste materials.

11 ALTERNATIVE TO THE PROPROSED ACTION

From production of SK&F 108566, no potential adverse environmental impacts have been identified for the proposed action. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy. The approval of eprosartan (SK&F 108566) oral tablets for the treatment of hypertension will provide an important benefit to patients requiring its administration, with no known adverse environmental risk.

12 LIST OF PREPARERS

12.1 List of Contributors

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For a list of contributors for the Contract Manufacturer, see Confidential Appendix 3 .

12.2 List of Preparers

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13 CERTIFICATION

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the SmithKline Beecham Environmental Research Laboratory.

The undersigned official certifies that the EA summary document (pages 4 - 32) and Appendices 1 - 2 (pages 36 - 47) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6.

Date: August 23rd 1996

Signature: R. Lee Webb.

R. Lee Webb, Ph.D.
Director
Analytical Sciences
SmithKline Beecham

14 REFERENCES

[1] Food and Drug Administration, November 1995, *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements,* Center for Drug Evaluation and Research (CDER), Washington, D.C.

[2] A Study to Determine the Balance/Excretion, Pharmacokinetics, and Biotransformation of Eprosartan (SK&F 108566) Given as Single Oral (100 mg) and Single Intravenous (20 mg) Doses on Separate Occasions to Healthy Adult Male Subjects, SmithKline Beecham Pharmaceuticals Report 108566/020 (HH-1001/SKF-108566/1), 10 May 1995

[3] Eprosartan (SK&F 108566) IND 39,721, SmithKline Beecham Pharmaceuticals, 1 June 1993

[4] Albert, A. and E.P. Serjeant, 1984, *The Determination of Ionization Constants, Chapman and Hall,* NY, 217 pps.

[5] SmithKline Beecham Environmental Research Laboratory, P.S. Ziegenfuss study# 95-021, Report No. ERL 9613, "Eprosartan (SK&F 108566): Octanol/Water Distribution Coefficient", 17 July 1996

[6] MicroQSAR Chemical Modeling and Information System, 1987, Technical Database Services, Inc., NY.

[7] Lyman, W.J., W.F. Rheel, and D.H. Rosenblatt, 1990, Handbook of Chemical Property Estimation Methods, American Chemical Society, Washington, D.C.

[8] SmithKline Beecham Environmental Research Laboratory, P.S. Ziegenfuss study# 95-022, Report No. ERL 9614, "Eprosartan (SK&F 108566): Adsorption to Activated Sludge", 18 July 1996

[9] SmithKline Beecham Environmental Research Laboratory, D.R. Orvos, L.C. Hsu/R.E. Hannah, study #95-014, ERL Memorandum, "SK&F 108566: Assessment of Activated Sludge Biodegradation", 3 June 1996

[10] SmithKline Beecham Environmental Research Laboratory, P.S. Ziegenfuss study# 95-023, Report No. ERL 9615, "Eprosartan (SK&F 108566): UV/vis Spectra and Estimated Direct Aquatic Photolysis Kinetics," 18 July 1996

[11] Leifer, A., 1988, *The Kinetics of Environmental Aquatic Photochemistry: Theory and Practice*, American Chemical Society, Washington, D.C., 304 pps.

[12] SmithKline Beecham Environmental Research Laboratory Memorandum, J.L. Brum/R.E. Hannah, Study #95-023, "SK&F 108566: Aqueous Photolysis Structural Analysis by LC/ESI/MS", 21 June 1996

[13] SmithKline Beecham Environmental Research Laboratory Memorandum, P. Vaughan/R.E. Hannah/P.S. Ziegenfuss, Study #95-023, "Summary of Thermal/Hydrolytic Stability Experiment of SK&F 108566, (Eprosartan)", 6 June 1996

[14] SmithKline Beecham, March, 1995, SB 108566J:Toxicology Overview.

[15] SmithKline Beecham Environmental Research Laboratory, D.R. Orvos, J.L. Brum, study #96-007, ERL Report No. 9618: "Eprosartan (SK&F 108566): Acute *Daphnia magna* Toxicity", 19 July 1996

[16] SmithKline Beecham Environmental Research Laboratory, D.R. Orvos, J.L. Brum, A.L. Worthey, study #96-012, Report No. ERL 9621, "Eprosartan (SK&F 108566): Acute Fish Toxicity", 19 July 1996

[17] SmithKline Beecham Environmental Research Laboratory, D.R. Orvos, A.L. Worthey, Report No. ERL 9623, "Eprosartan (SK&F 108566): Acute Microtox Toxicity," 22 July 1996

[18] SmithKline Beecham Environmental Research Laboratory, P.S. Ziegenfuss study# 95-029, Report No. ERL 9616, "Eprosartan (SK&F 108566): Respiration Inhibition to Activated Sludge Microflora", 18 July 1996

[19] Rapaport, R.A. 1988. Prediction of consumer product chemical concentrations as a function of publicly owned treatment works treatment type and riverine dilution. Environ. Chem. Toxicol. 7:107-115.

[20] Oak Ridge National Laboratory, 1982, *Methodology for Environmental Risk Analysis*, ORNL/TM-8167

[21] SmithKline Beecham Environmental Research Laboratory, D.R. Orvos, J.L. Brum, A.L.Worthey, study# 96-011, Report No. ERL 9619, "Eprosartan (SK&F 108566): Comparative *Daphnia magna* Toxicity," 19 July 1996

[22] SmithKline Beecham Environmental Research Laboratory, D.R. Orvos, L.C. Hsu, study# 96-014, Report No. ERL 9622, "Eprosartan (SK&F 108566): Comparative *Daphnia Magna* Toxicity of Photolytically-Degraded Solution", 22 July 1996

15 Appendices

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As per separate communication w/ applicant NS 3/11/97

Appendix 15.1 Non-Confidential:

Certifications of Compliance

SmithKline Beecham
Pharmaceuticals

Manufacturing Facility Certification

The undersigned officials at SmithKline Beecham (Manufacturing) Ltd. certify that the SmithKline Beecham (Manufacturing) Ltd. facility at Currabinny , Carrigaline , Co.Cork , Ireland is :

(1) In compliance with all local and national environmental laws

(2) In compliance with, or on an enforceable schedule to be in compliance with , all emission requirements set forth in all permits: and

(3) that approval of the EPROSARTAN New Drug Application and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Name : F. D. [signature]
Title: QA / Regulatory Team Leader.

Date: 14/03/1996.

Name [signature]
Title: Process Team Leader.

Date: 14/03/1996.

SB
SmithKline Beecham
Pharmaceuticals

Manufacturing Facility Certification

The undersigned official(s) at SB Crawley certify that the Crawley, England manufacturing facility is:

1) in compliance with all local and national environmental laws;
2) in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
3) that approval of Eprosartan New Drug Application and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

C E Badman 14 3 96

Name: Clive Badman Date:
Title: Director & Vice President Operations

Dennis Hallifax 11.3.96

Name: Dennis Hallifax Date:
Title: Safety & Environmental Control Department Manager

d:\work\certep.ro

Manor Royal Crawley West Sussex RH10 2CJ Tel 01293 521234 Fax 01293 693200 Telex 87648
SmithKline Beecham plc Registered Number 2339959 Registered Office New Horticulture Court Brentford Middlesex TW8 9EP

Appendix 15.2 Non-Confidential:

Material Safety Data Sheet-Eprosartan

SBMID Material Safety Data Sheet

10000675
Substance/Preparation
EPROSARTAN

SB Number
108566-J (SKF)

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

SUBSTANCE/PREPARATION:
EPROSARTAN
TRADENAMES/SYNONYMS:
(E)-ALPHA-[[2-BUTYL-1-[(4-CARBOXYPHENYL)METHYL)-1H-IMIDAZOL-5-YL]METHY LENE]-2-THIOPHENEPROPANIC ACID MONOMETHANESULFONATE * SK&F 108566-J * 108566-J (SKF) *
(E)-3-[2-BUTYL-1-[(4-CARBOXYPHENYL)METHYL]-1H-IMIDAZOL-5-YL]-2-[(2-THI ENYL)METHYL]PROPENIC ACID METHANESULFONATE
CHEMICAL FAMILY:
Imidazole.
MOLECULAR FORMULA:
C23-H24-N2-O4-S . C-H4-O3-S
MOLECULAR WEIGHT:
520.625
EINECS NUMBER:
Not Assigned
ELINCS NUMBER:
Not Assigned
COMPANY:
SMITHKLINE BEECHAM, CORPORATE ENVIRONMENT & SAFETY
U.S. OFFICE: U.K. OFFICE:
709 SWEDELAND ROAD NORFOLK HOUSE, DOWNSBROOK TRADING ESTATE
KING OF PRUSSIA, PA, 19406 SOUTHDOWNVIEW WAY, WORTHING
U.S.A. WEST SUSSEX, BN14 8NQ, ENGLAND
PHONE NUMBERS:
++1-610-270-7600 ++44-(01)903-822650
EMERGENCY AND AFTER HOURS CONTACT:
++1-800-228-5635 (EXTENSION 221)
++1-800-228-5635, EXTENSION 221 (Toll Free USA/Canada)

2. COMPOSITION/INFORMATION ON INGREDIENTS

EPROSARTAN CAS RN: 144143-96-4 MORE THAN 99 %
CONTAMINANTS:
Not identified.

3. HAZARDS IDENTIFICATION

SKIN CONTACT:
Allergic skin reaction and irritation are not expected following direct contact with this material. However, skin contact should be avoided.
EYE CONTACT:
SEVERE IRRITATION CAN OCCUR. Serious or permanent eye damage is possible.
INHALATION:
This material is a pharmaceutical agent. Effects of breathing dust are not known but might include dizziness and lightheadedness, based upon effects of other drugs that reduce blood pressure.
INGESTION:
This material is a pharmaceutical agent. Symptoms after ingestion might include dizziness and lightheadedness, based upon effects of other agents that reduce blood pressure.
CONDITIONS AGGRAVATED BY EXPOSURE:
Individuals taking medication for low blood pressure might be sensitive to the effects of this material. Over exposure during pregnancy might have an adverse effect on developing offspring.

4. FIRST-AID MEASURES

SKIN CONTACT:
If skin contact occurs, wash contaminated area thoroughly.
NOTE TO PHYSICIAN:
None.
EYE CONTACT:
Flush eyes continuously with water for at least 15 minutes. Do not use a chemical neutraliser. Obtain immediate medical attention.
NOTE TO PHYSICIAN:
Consider further flushing of eyes with large amounts of water or saline. Because of the possibility for permanent eye damage, refer all such cases to an ophthalmologist.
INHALATION:
Move exposed subject to fresh air. Seek medical assistance in case of known or possible overexposure to this material or with symptoms including chest pain, difficulty breathing, loss of consciousness or other adverse effects which may be delayed. IF BREATHING HAS STOPPED, START BASIC LIFE SUPPORT AND SEEK IMMEDIATE MEDICAL ASSISTANCE.
NOTE TO PHYSICIAN:
For combustion products, refer to section number 10. Refer to INGESTION, below.
INGESTION:
In the event of swallowing this material, seek medical assistance. Do not induce vomiting.
NOTE TO PHYSICIAN:
This material is an angiotensin receptor antogonists that can reduce blood pressure. Medical treatment in cases of overexposure should be treated as an overdosage of antihypertensive agents. Refer to current prescribing information or to local poison control information centers. This material is not a corrosive agent.
ANTIDOTES:
No specific antidotes known.

5. FIRE-FIGHTING MEASURES

FIRE CONTROL:
This material is expected to be combustible. Water, dry powder or foam extinguishers are recommended. Carbon dioxide extinguishers may be ineffective.
SPECIAL FIREFIGHTING PROCEDURES:
Since toxic, corrosive or flammable vapours might be evolved from fires involving this material, self contained breathing apparatus and full protective equipment are recommended for firefighters. Move containers from the fire area if possible without increased personal risk. If possible, contain and collect firefighting water for later disposal.

6. ACCIDENTAL RELEASE MEASURES

SPILLS:
Eliminate all sources of ignition (no smoking, sparks or flames). Prevent entry into waterways, sewers, and surface drainage systems. If spill is outdoors, cover with plastic sheet to minimise spreading or contact with rain. Fence or cordon the affected area and do not allow individuals to touch or walk through the spilled material unless wearing appropriate protective clothing. Avoid dust generation. Collect material and place it in a suitable, properly labelled container for recovery or disposal. Following removal of spillage, wash down spillage area with copious amounts of water only if waste water can be directed to an on-site waste water treatment system.
DECONTAMINATION PROCEDURES:
Detergent solutions can be used for clean-up and decontamination operations. No specific detoxification procedures have been identified for this substance.

7. HANDLING AND STORAGE

HANDLING:
Depending upon scale of operation, a fume cupboard or other type of exhaust ventilation is recommended to routinely control exposure to this material. Assess operations based upon available dust explosion information to determine the suitability of preventive or protective systems as precautionary measures against possible dust explosions. If prevention is not possible, consider protection by use of containment, venting or suppression of dust handling equipment. Bond and earth (ground) all plant and equipment to ensure that no isolated conductors are present. All personnel dealing with dusty operations must be earthed (grounded). Minimise the use of plastics when handling this material. This material should be handled in conductive or anti- static liners (bags). This material should not be allowed to come into contact with any surface temperature greater than 327 C.
STORAGE:
Keep in tightly closed containers or packages away from moisture and away from sources of ignition. Store at room temperature (15 to 30 degrees C; 59 to 86 degrees F).

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:
EPROSARTAN:
SmithKline Beecham(PEL):
0.1 MG/M3 (8 HR TWA)
INDUSTRIAL HYGIENE METHOD:
For SmithKline Beecham operations, contact the site Occupational or Industrial Hygienist or regional Corporate health and safety group, as appropriate, for advice on suitable monitoring methods.
For other operations, industrial hygiene monitoring advice may be obtained from the health and safety group identified in section 1.

PERSONAL PROTECTION:
RESPIRATORS:
If dust is present, a laboratory fume hood, local exhaust ventilation or an appropriate respirator should be used. The specific type used will be determined by air concentrations present. Follow local regulations for respirator use in the workplace.
GLOVES:
Wear impervious gloves.
EYE PROTECTION:
Wear safety glasses with sideshields when handling this material.
HYGIENE PRACTICES:
Wash hands and arms thoroughly after handling this material. Clean up spills immediately.
OTHER PROTECTIVE EQUIPMENT:
Wear lab coat or other protective clothing with long sleeves. An eye wash station should be available.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE:
White/off-white. Solid.
FLASH POINT:•
AUTOIGNITION TEMP:
LOWER EXPLOSIVE LIMIT:
UPPER EXPLOSIVE LIMIT:
MELTING POINT:
251 degrees C.
BOILING POINT:
Not determined.
PH OF AQUEOUS SOLUTIONS:
Not determined.
WATER SOLUBILITY:
This material is insoluble in water.
OTHER SOLUBILITY:
This material is soluble in: methyl alcohol, ethyl alcohol.
OXYGEN BALANCE:
This material is considered to be of low energy hazard potential based on its oxygen balance. Oxygen balance calculated as minus 169.
TRAIN FIRE:
This material has not been train fire tested. Therefore, it should be assumed to burn in bulk quantities.
DUST EXPLOSION:
Classification A.

Minimum Ignition Temperature - Cloud (degrees C): 490.
Minimum Ignition Temperature : Ignition did not occur.
Minimum Explosion Pressure - Pmax (bar): 8.6.
Maximum Rate of Pressure Change - dP/dTmax (bar/second): 797.
Explosion Constant - Kst (bar metre/second): 216.
Explosion Severity - St (Class): 2.

DUST ELECTROSTATIC PROPERTIES:

Minimum Ignition Energy (mJ): Less than 5.
Resistivity at Ambient Humidity (ohm metre): 1.4x10e12.
Charge Relaxation Time at Ambient Humidity (seconds): 167.
Resistivity at Low Humidity (ohm metre): 1.8x10e12.
Charge Relaxation Time at Low Humidity (seconds): 552.

10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:

Avoid direct sunlight, conditions that might generate heat and dispersion as a dust cloud.

INCOMPATIBILITY:

Strong oxidisers.

STABILITY:

This material is expected to be stable.

THERMAL STABILITY:

Not determined.

HAZARDOUS POLYMERISATION:

Not expected under normal conditions.

HAZARDOUS DECOMPOSITION PRODUCTS:

Toxic, corrosive or flammable thermal decomposition products are expected when the material is exposed to fire.

FIRE AND EXPLOSION HAZARDS:

Ignition of a dust cloud produces a strong dust explosion. High pressure between 8 and 10 bar is produced during a dust explosion. Dust clouds are potentially very highly sensitive to ignition from incendive electrostatic discharges.

11. TOXICOLOGICAL INFORMATION

ORAL TOXICITY:

No lethality or signs of toxicity occurred up to 14 days after rats were given a single oral dose of 1000 mg/kg.

INHALATION TOXICITY:

No studies have been conducted.

SKIN TOXICITY:

This material was classified as a non irritant to intact and a mild irritant to abraded rabbit skin after direct application for 4 hours.

EYE EFFECTS:

No studies have been conducted. Severe Irritation might occur based on the pH of this material.

SENSITISATION:

This material was classified as a non-sensitiser to guinea pig skin. No allergic skin reactions occurred in the maximisation test.

GENETIC TOXICITY:

This material was not genotoxic in laboratory studies with cultured cells or in animals.

CARCINOGENICITY:
Studies have not been conducted with this material and it is not listed as a carcinogen by SB, IARC, NTP or US OSHA.
REPRODUCTIVE EFFECTS:
This material is categorised according to SB criteria as follows:
Known or presumed to cause developmental toxicity in humans (category 1D). Adverse effect on the fetus might occur during mid or late stages of pregnancy.
OTHER TOXICOLOGIC OR ADVERSE EFFECTS:
None known for this material.

12. ECOLOGICAL INFORMATION

ACUTE AQUATIC EFFECTS:
Not determined.
BIODEGRADATION:
Not determined.
ACTIVATED SLUDGE RESPIRATION INHIBITION (OECD 209 PROTOCOL):
Not determined.
SOIL ADSORPTION:
Not determined.
OTHER EFFECTS:
Not determined.

13. DISPOSAL CONSIDERATIONS

Collect for recycling or recovery, if possible. Dispose of material on site in a licensed chemical incinerator if allowed by the incinerator license or permit. If no on-site incinerator is available, dispose of material in a licensed commercial chemical incinerator. For SmithKline Beecham operations, refer to SB Standard E-7 and associated guidance G-E-7 on hazardous waste disposal for selection of the most appropriate waste disposal option. All local and national requirements must be observed when disposing of this material.

14. TRANSPORT INFORMATION

TRANSPORT CLASSIFICATION AND LABELLING:
Technical Name: Eprosartan
AIR TRANSPORT (IATA REQUIREMENTS):
Proper Shipping Name: Other Regulated Substance (Eprosartan)
ID Number: 8027
Class/Division: 9 (danger sign - black vertical stripes in upper half of white diamond with figure 9 in bottom corner)
Subsidiary Risk: None
Packing Group: Not applicable (use packing instruction 906)
Exceptions: None.
MARITIME TRANSPORT (IMDG REQUIREMENTS):
Classification: Not classified for marine transport.
Although the hazards of this material are not regulated according to IMDG requirements, hazard label information in section 16 of the MSDS must be shown on the container.
UNITED STATES GROUND TRANSPORT (DOT REQUIREMENTS):
Proper Shipping Name: Other Regulated Substance, solid, nos

(Eprosartan)
NA Number: 3077
Class/Division: 9
Subsidiary Risk: None
Packing Group: III
Marine Pollutant: Not listed
US Emergency Response Guide Number: 31
Exceptions: Quantities equal to or less than 5 kg are not subject to the full packaging and labelling requirements, although the appropriate shipping papers will be required.

EUROPEAN GROUND TRANSPORT (ADR/RID REQUIREMENTS):
Classification: Not classified for European ground transport.
Although the hazards of this material are not regulated according to ADR/RID requirements, hazard label information in section 16 of the MSDS must be shown on the container.

15. REGULATORY INFORMATION

EUROPEAN UNION CLASSIFICATION AND LABELLING REQUIREMENTS:

FIRE:
Not classified as a significant fire hazard
HEALTH:
Toxic Irritant

ENVIRONMENTAL:
(Leave blank)
RISK PHRASES:
Risk of serious damage to eyes. (R41)
May cause harm to unborn child.(R61)
SAFETY PHRASES:
Avoid exposure - obtain special instruction before use. (S53)
Avoid contact with eyes. (S25)
In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. (S26)
Wear suitable protective clothing and gloves. (S36/37)
SYMBOL:
Skull and cross bones.(T) & Saint Andrew's Cross.(Xi)

16. OTHER INFORMATION

INFORMATION ON HAZARD
**** NOT CLASSIFIED AS A SIGNIFICANT FIRE HAZARD ****
**** TOXIC & IRRITANT ****
**** CAUTION - ENVIRONMENTAL HAZARD NOT FULLY IDENTIFIED ****
** RISK OF SERIOUS DAMAGE TO EYES.
** MAY CAUSE HARM TO UNBORN CHILD.
** AVOID CONTACT WITH EYES.
** IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE.
** WEAR SUITABLE PROTECTIVE CLOTHING AND GLOVES.
** AVOID EXPOSURE - OBTAIN SPECIAL INSTRUCTION BEFORE USE.
** TARGET ORGAN- PHARMACEUTICAL AGENT- MAY REDUCE BLOOD PRESSURE.

** SYMBOL: SKULL AND CROSS BONES.(T) & SAINT ANDREW'S CROSS.(XI)

REFERENCES:
SB HAZARD DETERMINATION

OTHER INFORMATION:
IF HMIS RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:
HEALTH = 1 FIRE= U REACTIVITY = U
IF NFPA RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:
HEALTH = 1 FIRE= U REACTIVITY = 0

DATE REVISED: 15 May 96

Appendix 15.5 : Data Summary Table - Eprosartan (SK&F 108566)

PHYSICAL/CHEMICAL CHARACTERIZATION

Water Solubility (mg/L)

pH 1 610

pH 2 84

pH 3 14

pH 4 7

pH 5 9

pH 6 240

pH 7 910

pH 7.5 >20000

Dissociation Constants - $pKa_1 = 4.11$

$pKa_2 = 5.68$

$pKa_3 = 6.89$

Octanol/Water Partition/Distribution Coefficients - QSAR ClogP = 4.52.

Experiment Octanol/Water Distribution Coefficients

Aqueous Phase	Mean D_{ow}	Log Mean D_{ow}
pH 4.84 buffer	33.3	1.52
pH 6.83 buffer	0.243	-0.614
pH 9.03 buffer	0.00284	-2.55
water (pH 6.65)	0.696	-0.157

Henry's Law Constant/Vapor Pressure

QSAR estimated Henry's Law constant = 3.4×10^{-12} atm·m^3/mol.

Activated Sludge Adsorption - mean $K_d = 24.3 \pm 9.7$ mL/g

DEPLETION MECHANISMS

Hydrolysis - extensive solution degradation is acetate buffer catalyzed at pH 4.5.

Aquatic Biodegradation - no biodegradation observed in batch activated sludge test.

Soil Biodegradation - not investigated.

Photolysis - rapid conversion to SB 206328 (Z isomer of eprosartan) in pH 7 phosphate buffer solution under normal sunlight exposure conditions. Half-life of eprosartan under these conditions is less than 20 minutes.

Metabolism - excreted, primarily in feces, as parent compound.

ENVIRONMENTAL EFFECTS

Microbial Inhibition

OECD 209 activated sludge respiration inhibition - no inhibition observed up to the highest test concentration (EC50 > 140 mg/L).

Microbics Microtox assay with *Vibrio fischeri* - no inhibition up to the highest test concentration (15-min EC50 > 36 mg/L).

Acute Toxicity

Daphnia magna 48-hour acute - no effects were observed relative to controls up to the eprosartan test matrix solubility limit (EC50 > 120 mg/L as zwitterion).

Lepomis macrochirus (bluegill sunfish) 96-hour acute - eprosartan did not cause increased fish mortality, relative to the controls, at eprosartan zwitterion concentrations up to and including 88 mg/L. The eprosartan no-observed-effect-concentration (NOEC) was determined to be 16 mg/L as the zwitterion.