CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-012

PHARMACOLOGY REVIEW(S)

NDA 22-012

PHARMACOLOGY/TOXICOLOGY REVIEW OF NDA

SUBMISSION (serial No. 000) DATE: 21-Dec-2005
CENTER RECEIPT DATE: 21-Dec-2005
REVIEW COMPLETION DATE: 27- Sept - 2006

REVIEWER: Albert DeFelice, Ph.D.
Supervisory Pharmacologist
Division of CardioVascular and Renal Drug Products (HFD-110)

SPONSOR: SB Pharmaco Puerto Rico, Inc. d/b/a GlaxoSmithKline
One Franklin Plaza, 200 N. 16th Street
Philadelphia, PA, 19102

DRUG PRODUCT: Coreg ® (carvedilol phosphate) Extended-release Capsules, 10, 20, 40, and 80 mg (containing carvedilol phosphate hemi-hydrate).

RELATED INDs and NDAs: IND 70, 154MR tablets; NDA 20-297 Coreg ® tablets.

REFERENCE LISTED PROPRIETARY DRUG PRODUCTS: NDA 20-297 Coreg® (carvedilol) Tablets

DRUG SUBSTANCES:

PHARMACOLOGIC CATEGORIES: Non-specific β-, and α_1- adrenoceptor antagonist.

PROPOSED INDICATION: essential hypertension; mild to severe CHF; promote survival post – acute MI.

FORMULATION AND ROUTE OF ADMINISTRATION: This is an extended release gelatin capsule formulation of a new salt form of carvedilol (free-base) for once-daily oral administration. Excipients are comprised of magnesium stearate; Hydrogenated castor Oil ; Methacrylic Acid Co-polymers and Hydrogenated Vegetable Oil

PROPOSED DOSAGE REGIMEN: OD
NONCLINICAL PHARMACOLOGY/TOXICOLOGY DATA: No new data are provided. Sponsor cross-references proprietary NDA 20-297 Coreg® (carvedilol) Tablets

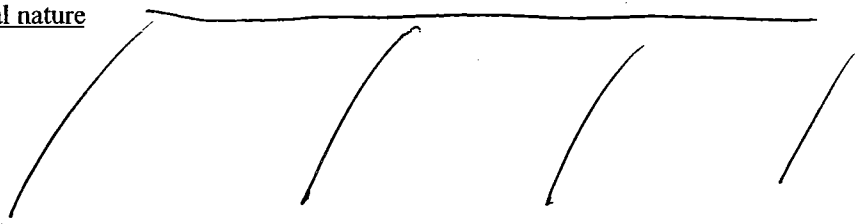
EVALUATION:

Sponsor provided no new *in vitro* or *in vivo* preclinical data related to safety of this new formulation, and typically no such ancillary studies would be required since it is a marketed product, and an adequate battery of pre-clinical safety studies were performed to support NDA 20-297 for the immediate release formulation of carvedilol.
However, two potential safety issues with the subject controlled-release formulation derive from the component - . The latter is associated with "hypersensitivity" clinically i.e., releases histamine with expected sequelae (symptomatic bronchoconstriction, hypotension etc. alleviated by pre-treatment with antihistamine and

dexamethasone) and observed in the context of an [redacted] Moreover, according to the chemist's review of the subject formulation, [redacted] promotes formation of the degradant [redacted] (especially in the context of accelerated stability testing) which, furthermore, is a potentially genotoxic impurity.

A. [redacted] ıssue:

Chemical nature [redacted]



Dosage: The 80 mg (MRHD) strength capsule contains approx. [redacted] of the ds) of [redacted] which would provide approx [redacted] .ng/Kg/day to a 60 Kg patient receiving one such capsule OD.

Pharmacology: According to the [redacted] hydrogenated castor oil is claimed to be devoid of pharmacologic activity at the doses at which it is employed as an excipient i.e., a maximum of [redacted] by the im, sc, topical, and po routes.

Toxicity studies (Literature): Cardiotoxicity, nephrotoxicity, and neurotoxicity of unknown pathogenesis, as well as anaphylactoid (i.e., "histamine-like") reactions, have been observed in humans and animals following parenteral administration of formulations containing [redacted] hydrogenated castor oil [redacted] However, oral toxicity is reportedly much less i.e., tolerated at up [redacted] of the diet when fed to dogs and rats, respectively, for 6 months; and at levels up to [redacted] ed to dogs for 4 weeks [redacted] Oral tolerability of these [redacted] is also asserted by the [redacted] who reported no excess gross or microscopic lesions in 3-month feeding studies in rats and dogs at up to [redacted] of the diet [redacted] Furthermore no evidence of developmental toxicity was reported in mice and rat feeding studies (at up to [redacted] respectively) where gravid rodents were exposed during fetal organogenesis i.e., gd day [redacted] mice) or [redacted] at) (ibid). Of relevance to oral safety risk assessment – and the expectation that gastric mucosa will be directly exposed to the highest concentrations of [redacted] - is the absence of effect *in vitro* on epithelial integrity (intracellular enzyme activity; morphology; permeability) using monolayers of human intestinal mucosal cells, and at up to approx [redacted] Chemically analogous, if not homologous, [redacted] is reportedly devoid of genotoxicity in a variety of in vitro and oral in vivo bioassays [redacted]. The [redacted] judged it to be safe at a human oral dose level of [redacted] based on tolerability in rat and dog safety studies of 13 and 26 weeks, respectively ([redacted] As noted above, one 80 mg strength capsule daily affords patients approx. [redacted] ng/Kg of [redacted]

Approved Drug products containing [redacted]

The FDA inactive ingredient database cites 3 oral formulations containing [redacted] g of this excipient., and one where it comprises [redacted] of the oral [redacted] The subject carvedilol formulation affords [redacted] at the highest strength (80 mg carvedilol). As of 1995, there were also 268 topical cosmetic product formulations containing [redacted]

B. **issue:**

Excipient - Drug substance compatability studies (at 45 deg.; at 25 deg/60% RH)) revealed that the is causing approx degradation of the drug substance - primarily to , a potentially genotoxic impurity. The current specification is up to , after accelerated stability testing.

A consult was requested of CDER's Informatics and Computational Safety Analysis Staff (ICSAS) to assess carcinogenic and mutagenic potential of based on quantitative structure-activity relationship afforded by results of toxicity studies in the FDA/CDER, NIEHS, NCI, and L Gold CPD databases.

Based on *multiCASE MC4PC* and *MDL-QSAR*- derived computational toxicology estimations ((ICSAS, 2006), neither carvedilol nor the were predicted to be carcinogenic in rodents, or mutagenic in Salmonella. In contrast, all three compounds are predicted to be genotoxic in two or more other *in vitro* and *in vivo* genotoxicity assays. Findings in actual laboratory toxicology testing of carvedilol under NDA 20-297 were consistent with the predictions of negative carcinogenicity and salmonella mutagenicity findings, but, contrary to prediction, carvedilol was also negative in all other in vitro and in vivo assays of genotoxicity (CHO /HGPRT assay for mutagenicity; *in vitro* Hamster micronucleus and *in vivo* human lymphocyte tests for clastogenicity).

In conclusion, based on a) their assay evaluation criteria for interpreting combined results of the six rodent carcinogenicity database modules; b) actual empirical findings in in vitro and in vivo testing of intact carvedilol vis a vis predictions of such, and c.) the fact that all three compounds had adequate "coverage" in this MC4PC test, CDER's ICSAS deemed all three compounds inactive in the MC4PC rodent carcinogenicity test, and not expected to be *trans*-gender and/or *trans* species rodent carcinogens. *MDL-QSAR* non-parametric discriminant analysis modeling classified all three compounds possessing a low potential for being rodent carcinogens. Reportedly, the statistical confidence in the prediction was excellent with a probability of membership in the low carcinogenic risk potential class in the mouse and rat carcinogenicity database of 83% or greater. See Appendix for details on *MC4PC* and *MDL-QSAR* –based computational toxicology as performed by CDER's ICSAS.

RECOMMENDATIONS:

Reviewer agrees with the conclusion of CDER's ICSAS resource that - since all three compounds tested negative for salmonella mutagenicity and carcinogenicity in MCASE and MDLQSAR models - the prediction, per MCASE, of the possibly being positive in the hgprt and mouse micronucleus *in vivo* endpoints assays is insufficient signal to require additional testing of the by sponsor. Furthermore, the prediction that intact carvedilol would be also be positive in the latter two genotoxicity assays was not borne out by the negative results when actually (and adequately) tested in the latter two assays.

Reviewer does not see the need for any further assessment of oral toxicity in view of the absence of oral toxicity of this and chemically very closely related analogues in rat and dog dietary studies at up to of the feed vs. the ng/Kg afforded by the 80 mg strength capsule; and the absence of genotoxicity, carcinogenicity, and reproductive toxicity of closely-related structural analogues, including intact carvedilol

The Hydrogenated Castor Oils s. Although not all have been studied, it is considered acceptable to extrapolate the results of those that have been studied to all analogues in the family Accordingly, I am not concerned that per se has not been exhaustively tested in all relevant assays, especially given

the relative exposures afforded by an 80 mg strength capsules vs. that provided by the diet in feeding studies of it and other members of the chemical class. FDAs AVDAC considers the analogous , if not homologous. ——— , to be safe at — Kg/ po/ day based on tolerability in 13 and 26 week oral studies in rats and dogs, respectively

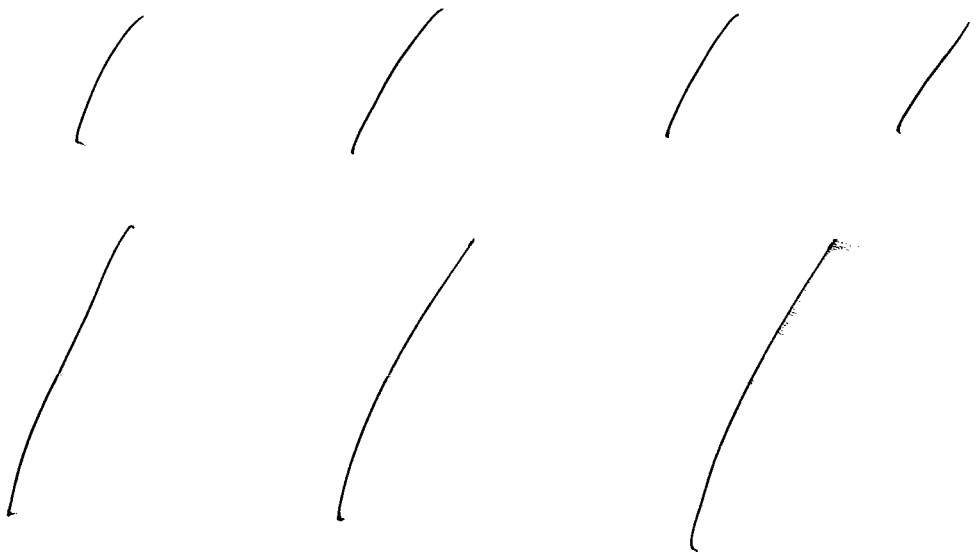
It is noted that the FDA inactive ingredient database cites 3 oral formulations containing — — of this excipient., and one where it comprises — of the oral — The subject carvedilol formulation affords — , at the highest strength (80 mg carvedilol).

Appendix:

MC4PC and *MDL-QSAR* software modules were developed per CRADAs between FDA/CDER and Multi CASE, Inc., and MDL, Inc., respectively. The materials and methods and the results of a validation tests have been described elsewhere (Matthews, and Contrera, 1998; Contrera et al, 2005). Both modules reportedly have high coverage (>85%) for FDA-regulated substances (pharmacophoric and/or functional groups in food additives; pharmaceuticals). FDA's ICSAS group optimized predictive performance of *MC4PC* and *MDL-QSAR* software to provide useful specificity and sensitivity (>70% for MDL-*QSAR;* approx. 60% for carcinogenicity and salmonella mutagenicity per *MC4PC).* Modules used for predicting genotoxicity are empirically based on experimental data acquired from industry, PHARMA, scientific literature; Zeiger database, and NIH/NLM GENETOX database.

Results obtained from the twenty-one MC4PC genetic toxicity modules showed that all thee compounds (carvedilol, ') are predicted to be positive in the hgprt (mutagenicity) and micronucleus (clastogenicity) assays and, for , in Drosophila as well. However, no test compound was expected to be positive in the cardinal Ames (salmonella) test as borne out, partially, by negative results with carvedilol in this mutagenicity assay. This reviewer considers the positive predictions of genotoxicity of — in the hgprt and micronucleus assays as suspect since carvedilol was similarly indicted but proved unequivocally negative in both assays - as well as in human lymphocytes cell test for clastogenicity.

References:



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/s/

Albert Defelice
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PHARMACOLOGIST