

The differences between BiDil and generic ISDN and generic hydralazine

- FDA has confirmed that there are no Generics or Therapeutic Equivalents to BiDil
- The 37.5mg hydralazine capsule used in the V-HeFT I trial and the 37.5mg hydralazine tablet used in the V-HeFT II trial were specially manufactured for those clinical trials. They were never available commercially and are not available commercially today.
- The combinations of the ISDN (Isordil®) and specially manufactured hydralazine used in the V-HeFT trials are **not** bioequivalent to BiDil
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FDA: There are no generics or therapeutic equivalents to BiDil



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

May 3, 2006

Matthew D. Peterson
FoxKiser
750 17th Street, NW
Suite 1100
Washington, DC 20006

Dear Mr. Peterson,

This letter is in response to your letter dated April 28, 2006, requesting that the Food and Drug Administration confirm certain information regarding NitroMed Inc.'s approved drug product, BiDil® Tablets (isosorbide dinitrate and hydralazine hydrochloride), 20 mg/37.5 mg (NDA 20-727).

As reflected in the current *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), FDA has not approved any drug product under section 505 of the Federal Food, Drug, and Cosmetic Act that is designated as therapeutically equivalent (i.e., substitutable) to BiDil. In addition, neither approved labeling for isosorbide dinitrate drug products nor approved labeling for hydralazine hydrochloride drug products contains information regarding the use of these drug products for the treatment of heart failure.

Thank you for contacting the Office of Executive Programs at CDER.

Sincerely,

Christine M. Bechtel RN, MSN
Director, Executive Operations Staff
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

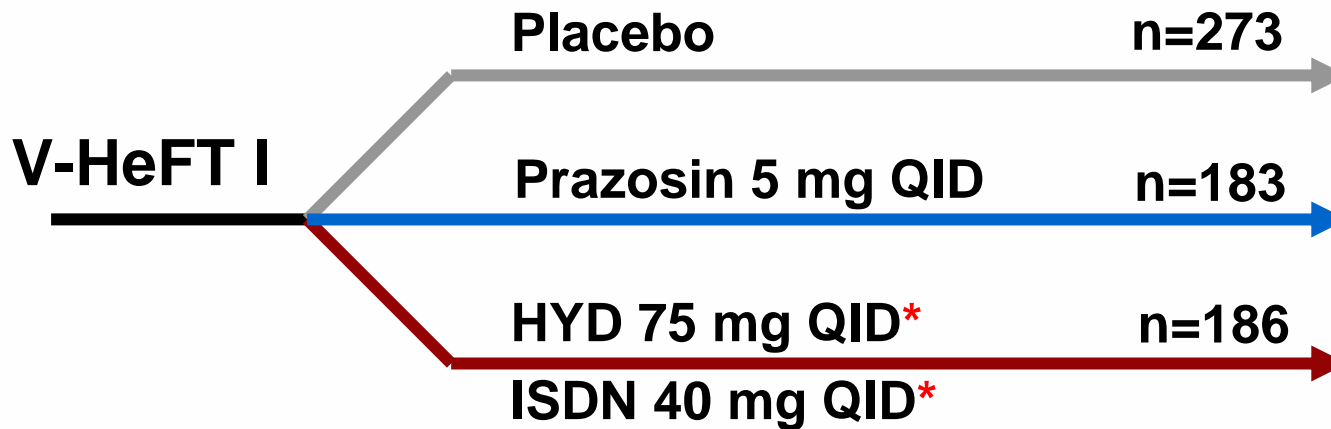
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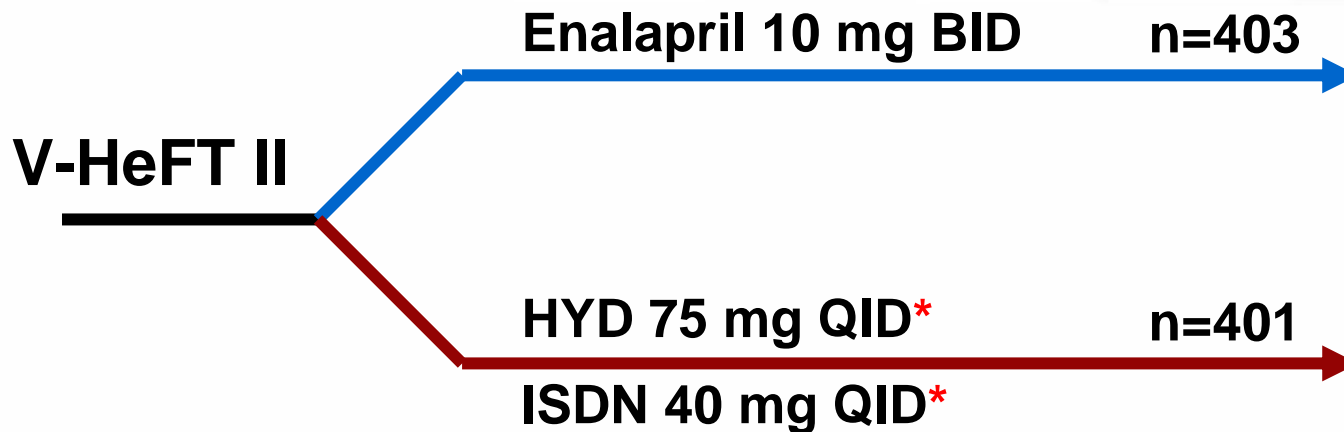
V-HeFT I Study (1980 – 1985)



Objective: To evaluate the effects of ISDN + HYD or prazosin on mortality when compared with placebo among male patients with HF receiving both digoxin and diuretic therapies

***Study Medication:** The hydralazine used in V-HeFT I was a 37.5mg capsule specially manufactured by Pfizer Laboratories for the trial. The ISDN tablet used was a 20mg tablet of Isordil®.

V-HeFT II Study (1986 – 1991)



- **Objective:** The objective of the V-HeFT II trial was to compare the efficacy of ISDN + HYD and the ACE-I, enalapril, for treatment of chronic HF in male patients already receiving digoxin and diuretic therapy

***Study Medication:** The hydralazine used in the V-HeFT II trial was a 37.5mg tablet specially manufactured by Ciba-Geigy for the trial. The ISDN tablet used was a 40mg tablet of Isordil®.

Cohn JN et al. *N Engl J Med.* 1991;325:303-310.

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FDA Definition of Bioequivalence

“..the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses..”

Approved Drug Products with Therapeutic Equivalence Evaluations – 26th Edition
(commonly known as the “Orange Book”), FDA

How is Bioequivalence measured?

“Approval of a generic version of a proprietary drug by the FDA requires demonstration of ...

“bioequivalence” (defined by absorption parameters generally falling between 80% and 125% of those obtained with the proprietary agent under the same testing conditions). The use of the $-20\%/+25\%$ rule is based on a regulatory decision that for most drugs that difference in concentration of the active ingredient in blood will not be clinically significant.”

Issues in Bioequivalence and Generic Substitution for Antiarrhythmic Drugs

Peter R. Kowey, MD – Chief – Division of Cardiovascular Diseases, Lankenau Hospital, Wynnewood, PA

Professor of Medicine – Jefferson Medical College, Philadelphia, PA; Adjunct Professor of Pharmacology at

MCP – Hahnemann School of Medicine, Philadelphia, PA

Accessed at: <http://www.americanheart.org/presenter.jhtml?identifier=3015266>

Why is Bioequivalence important?

- **“This system of assessing bioequivalence of generic products assures that these substitutable products do not deviate substantially in in-vivo performance from the reference product.”**
- ***Therefore*, “have the same clinical effect and safety profile when administered to patients under the conditions specified in labeling.”**
- **“The primary concern from the regulatory point of view is the protection of the patient against approval of products that are not bioequivalent.”**

Approved Drug Products with Therapeutic Equivalence Evaluations – 26th Edition
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The Pharmacokinetics of BiDil tablets vs. ISDN and hydralazine tablets (in combination)

Background

- In 1996 Medco (the previous owner of the BiDil patent) applied to get FDA approval for BiDil based on the results of the V-HeFT trials
- They were required to conduct a pharmacokinetic study to show that BiDil **was** bioequivalent to the ISDN and hydralazine combinations used in the V-HeFT trials
- These results were submitted to FDA as part of the marketing application (which was ultimately denied)

Pharmacokinetic comparison of BiDil tablet and combination of ISDN tablet and hydralazine tablet

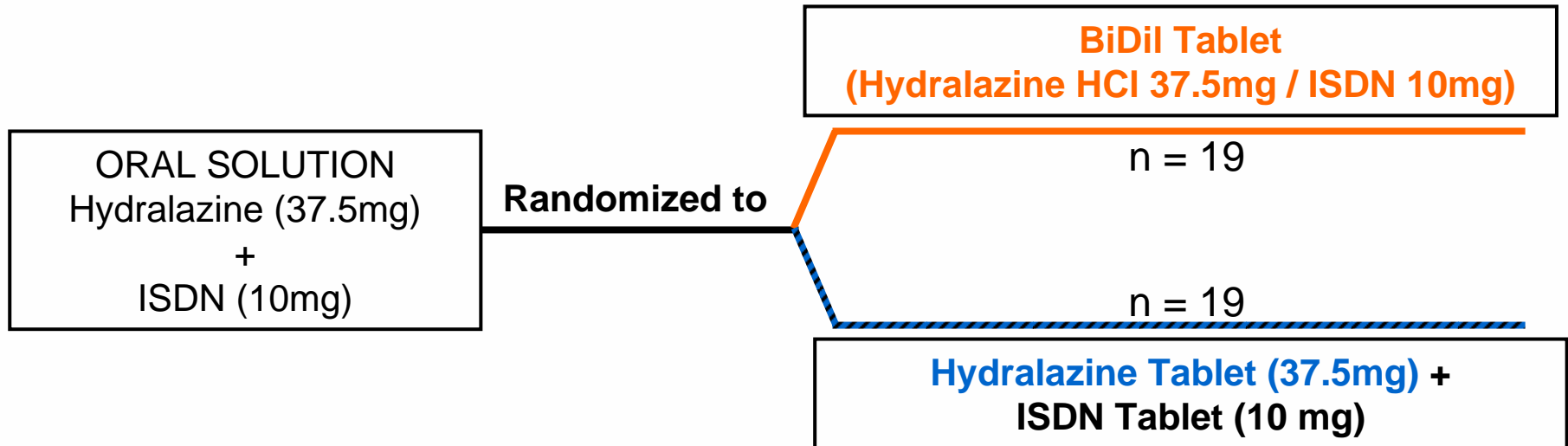
Study Design

- A single-center, open-label, randomized, incomplete crossover study comparing the relative bioavailability of BiDil and a combination of standard formulations of isosorbide dinitrate and hydralazine HCl (in separate tablets) in healthy male and female subjects.
- The study was conducted in 2 phases
 - **Phase A (oral solution) – baseline reference**
 - **Phase B (tablets)**

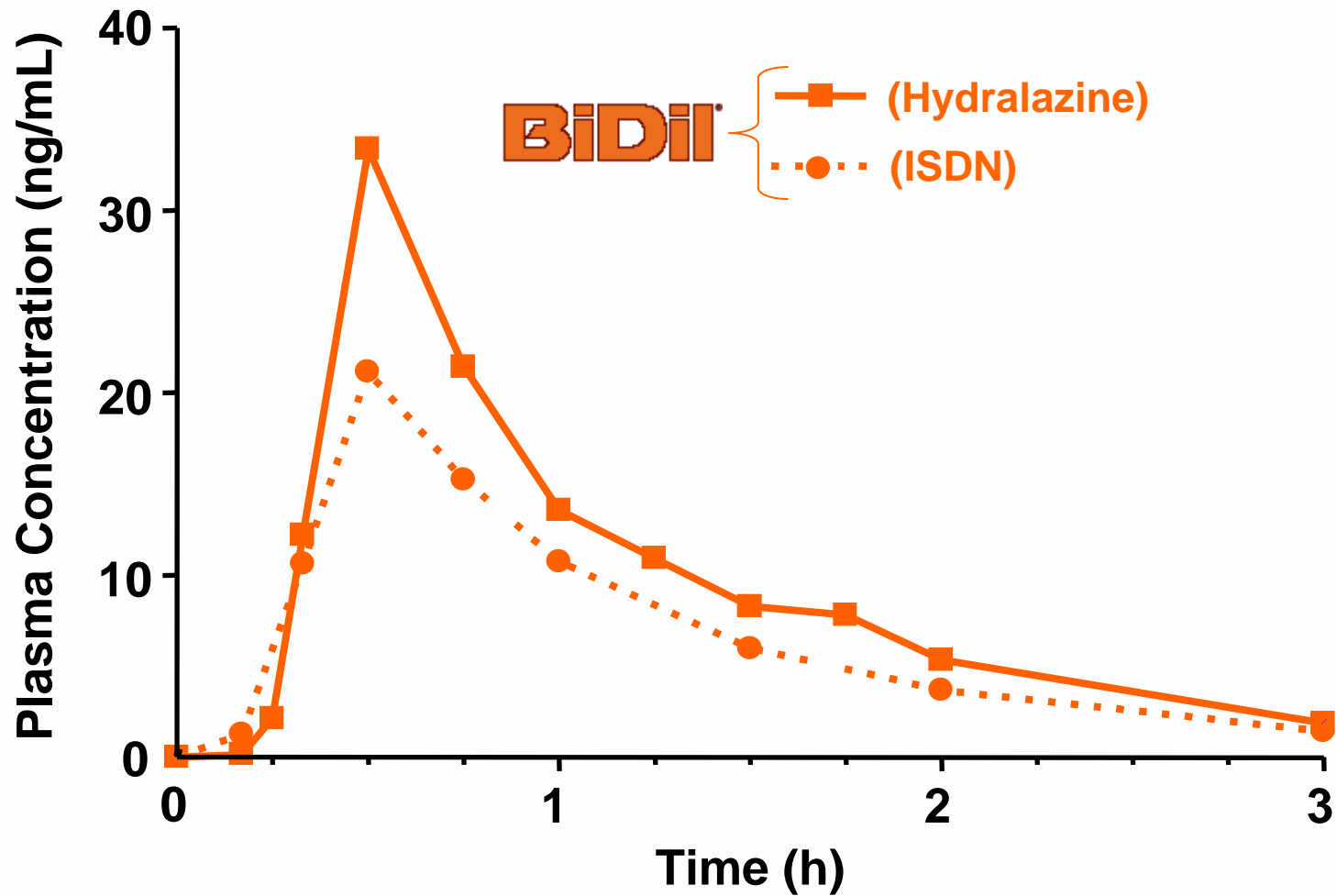
Study Design: Pharmacokinetic comparison of BiDil tablet with combination of ISDN tablet and hydralazine tablet

PHASE A

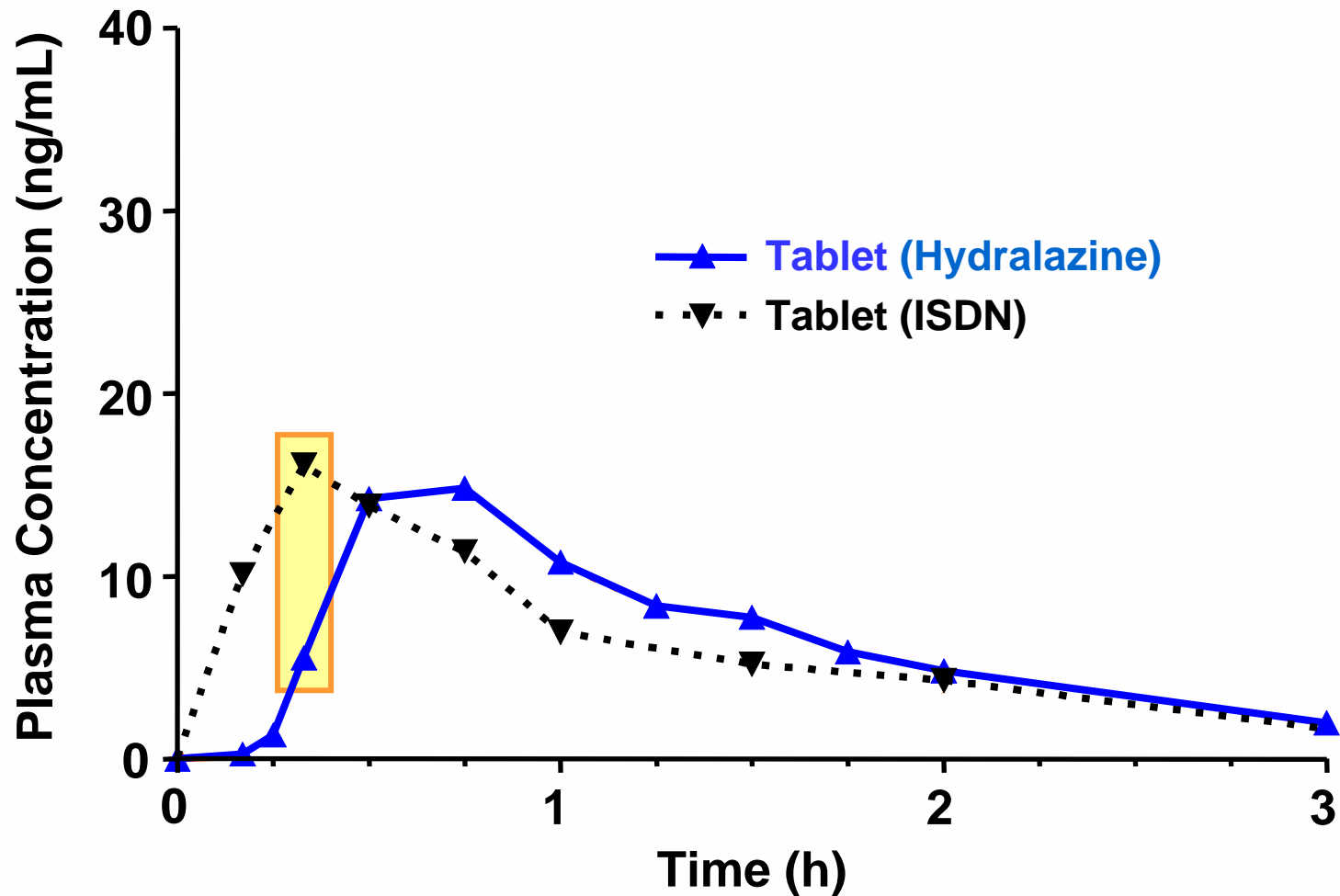
PHASE B



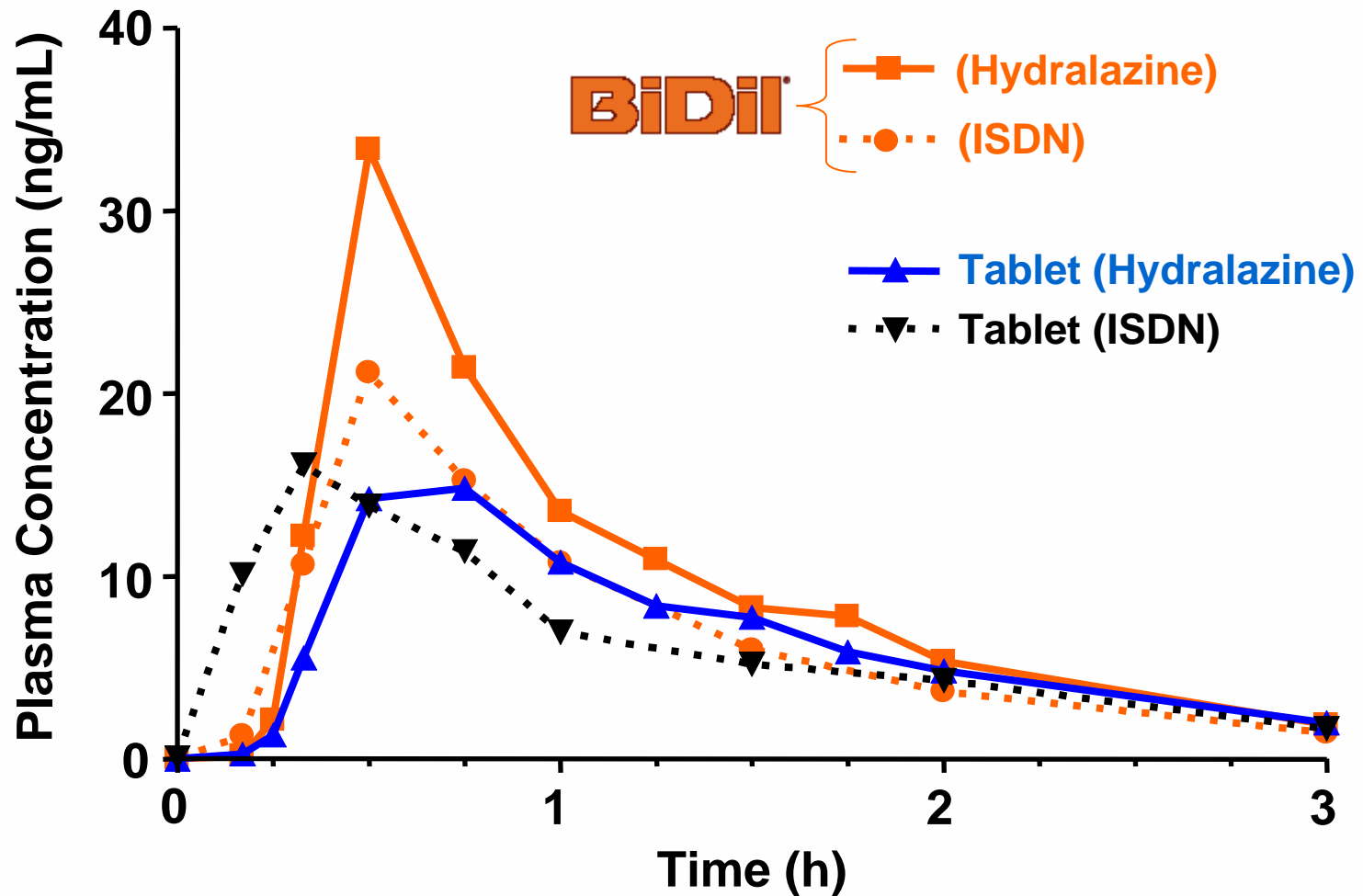
Plasma concentrations of BiDiil[®]



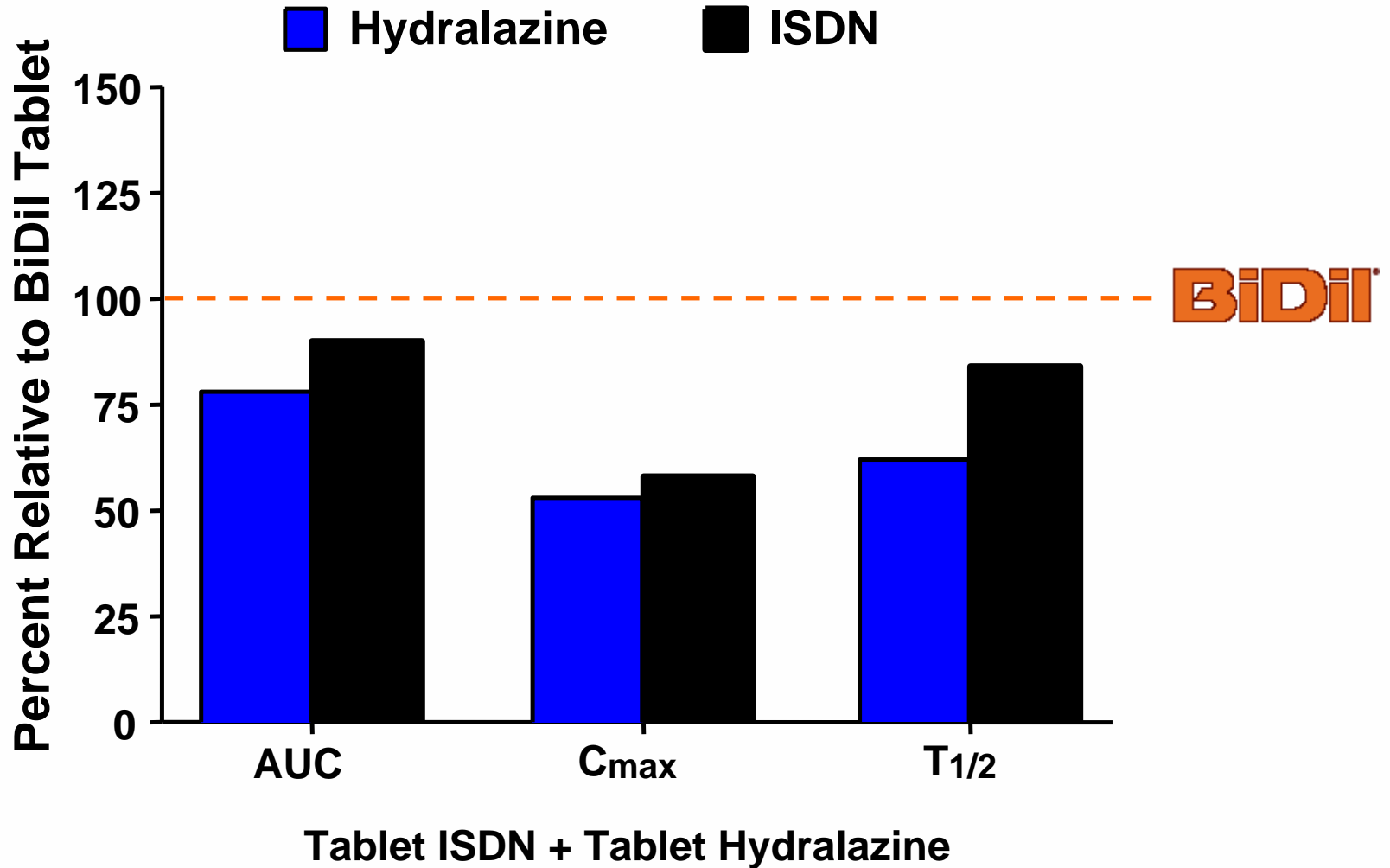
Plasma concentrations of tablet ISDN + tablet hydralazine



Plasma concentrations of BiDiil[®] are different from tablet ISDN + tablet Hydralazine



Tablet ISDN + tablet Hydralazine is NOT bioequivalent to BiDil®



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Conclusions

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Back Up Slides

The hydralazine component in BiDil is NOT bioequivalent to the hydralazine in capsules (V-HeFT I) or tablets (V-HeFT II)

| <u>Hydralazine</u> | C _{MAX} Ratio | C _{MAX} 90% CI | AUCR ¹ Ratio | AUCR 90% CI | AUC Ratio | AUC 90% CI |
|---|------------------------|-------------------------|-------------------------|-------------|-----------|------------|
| BiDil compared to HYD tablet in V-HeFT II | 1.47 | 0.89-2.4 | 1.25 | 0.99-1.58 | 1.56 | 1.11-2.19 |
| BiDil compared to HYD capsule in V-HeFT I | 0.65 | 0.4-1.07 | 0.9 | 0.72-1.44 | 0.94 | 0.67-1.32 |

**NDA 20-727: FDA Clinical Pharmacology / Biopharmaceutics Review:
Submission Date: July 3, 1996²**

1. AUCR = AUC normalized to the AUC of the solution arm in Phase A of the study

2. NitroMed. Data On File - 1996

The ISDN component in BiDil is NOT bioequivalent to the ISDN in V-HeFT I or V-HeFT II

| <u>ISDN</u> | C_{MAX} Ratio | C_{MAX} 90% CI | AUCR¹ Ratio | AUCR 90% CI | AUC Ratio | AUC 90% CI |
|---|----------------------------------|-----------------------------------|-----------------------------------|------------------------|----------------------|-----------------------|
| BiDil compared to ISDN tablet in V-HeFT II | 1.21 | 0.86-1.71 | 1.12 | 0.98-1.27 | 0.97 | 0.82-1.15 |
| BiDil compared to ISDN tablet in V-HeFT I | 1.06 | 0.75-1.5 | 1.04 | 0.92-1.19 | 0.98 | 0.83-1.17 |

NDA 20-727: FDA Clinical Pharmacology / Biopharmaceutics Review: Submission Date: July 3, 1996²

1. AUCR = AUC normalized to the AUC of the solution arm in Phase A of the study

2. NitroMed. Data On File - 1996

FDA Approval of a Generic Requirements

- **Pharmaceutically Equivalent**
 - Same active ingredient
 - Same dose form
 - Same route of administration
 - Same strength or concentration
- **Therapeutically Equivalent**
 - Bioequivalence
- Same conditions of use
- Same labeling

Determining Bioequivalence

- Compare test and reference formulation
 - Single doses of test and reference drug administered
 - Blood or plasma levels are measured over time
- Pharmacokinetic parameters of rate and extent of drug absorption are evaluated statistically
 - Area under the plasma concentration time curve (AUC) for extent of absorption
 - Maximum (peak) drug concentrations (C_{max}) for rate of absorption
 - All data is expressed as a ratio of average response (AUC and C_{max})
 - AUC and C_{max} of test drug must be within 80-125% of the reference drug