DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Mary Ellen Evanich
Regulatory Affairs
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

RE: **IND** [redacted]
Vardenafil
MACMIS ID #10099

Dear Ms. Evanich:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified certain promotional activities by Bayer Corporation (Bayer) that are in violation of the Federal Food, Drug, and Cosmetic Act (Act). Specifically, Bayer is promoting its investigational new drug, vardenafil, as safe or effective for erectile dysfunction at its promotional exhibit booth at the 96th annual meeting of the American Urological Association (AUA) in Anaheim.

Section 21 CFR 312.7 states, among other things, that an investigational new drug may not be promoted as being safe or effective for the uses under investigation. Your exhibit booth at AUA includes posters describing the safety or effectiveness of vardenafil, an investigational treatment for erectile dysfunction. For example, you present claims including, but not limited to, "[v]ardenafil was generally safe and well tolerated and had no clinically significant influence on physical examination, vital signs, or electrocardiogram and laboratory parameters," "...investigators concluded that there was convincing evidence that the clinical activity of vardenafil was consistent with its high selectivity and had a favorable adverse event profile," "[v]ardenafil is a potent and selective inhibitor of PDE5," and "...compared with placebo, oral treatment with 20 or 40 milligrams of vardenafil resulted in earlier, longer-lasting erections with better rigidity and tumescence following visual stimulation." These claims concerning the safety or effectiveness of your investigational product are violative.

Moreover, your representatives are disseminating a poster book and an audiocassette at your exhibit booth that include the same or similar violative claims and representations.

In order to address these objections, DDMAC requests that Bayer immediately discontinue the use of these, and all promotional materials and activities for vardenafil that contain the same or similar violations. Bayer's written response, indicating its intent to comply with this request, should be received on or before June 20, 2001. This response should include a list of all similarly violative promotional materials and your method for discontinuing their use.

If you have any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #10099 in addition to the IND number.

Sincerely,

{See appended electronic signature page}

Mark W. Askine
Branch Chief
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mark Askine
6/6/01 08:54:06 AM

IMPAIRED ERECTILE FUNCTION IN THE NEW MILLENNIUM

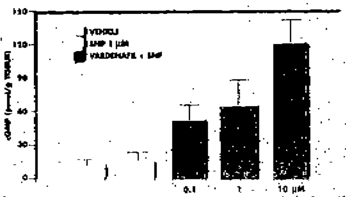
Vardenafil preclinical data

Selectivity Profile of Vardenafil for the Different PDE Isoenzymes[1]

	VARDENAFIL IC_{50} (nM)	VARDENAFIL Ratio to PDE5
PDE5	0.7	1
PDE6	157	224
PDE1	180	257
PDE3	2,500	3,600
PDE4	4,000	5,700
PDE2	>10,000	>10,000

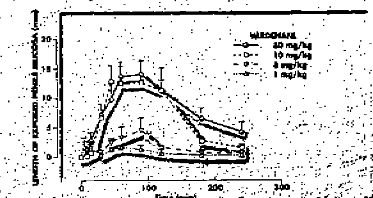
- PDE isoenzymes from different sources were isolated and characterized and the inhibitory potency of vardenafil was determined with a scintillation proximity assay.
- Vardenafil is a potent and selective inhibitor of PDE5.
- Other PDE isoenzymes required markedly higher concentrations of vardenafil for inhibition.

Effect of Vardenafil on cGMP Levels[1]



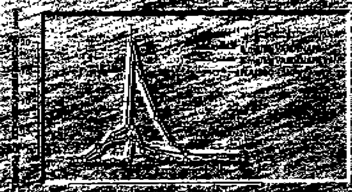
- Vardenafil produced dose-dependent increases in cGMP levels in rabbit corpus cavernosum.
- This effect was enhanced by the NO donor sodium nitroprusside (SNP).
- At all concentrations, vardenafil had no effect on cAMP levels, which is consistent with its profile as a potent and selective inhibitor of PDE5.

Efficacy of Oral Vardenafil[2]



- Vardenafil (1–30 mg/kg) reproducibly induced dose-dependent penile erections in conscious rabbits after oral administration.
  - maximal response: [illegible] 10 mg/kg
  - onset of action: [illegible] 20 minutes postadministration
  - maximal effect: [illegible] minutes postadministration
  - duration of erection: [illegible] to [illegible] hours

Potentiation of the Effect of Vardenafil on Penile Erection in the Presence of the NO Donor SNP[2]



- [illegible]

* In vitro activity does not necessarily imply clinical effectiveness.

1. Bischoff E, Niewoehner U, Haning H, et al. Vardenafil [illegible] cavernosum. Int J Impot Res. 2000;12(suppl 3):[illegible] Perth, Western Australia. 2. Bischoff E, Niewoehner U, [illegible] rabbit model. J Urol. 2001;165:[illegible]

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Pharmaceutical Division

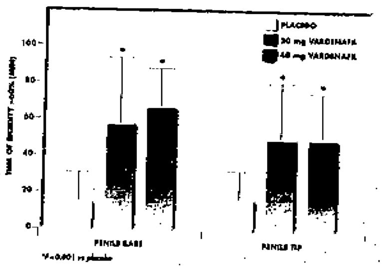
IMPAIRED ERECTILE FUNCTION IN THE NEW MILLENNIUM

Vardenafil clinical data (phase I and II)

In a randomized, double-blind, safety study, 12 subjects aged 18 to 45 years received once-daily oral doses of 40 mg vardenafil or placebo for 14 days.

Vardenafil was generally safe and well tolerated and had no clinically significant influence on physical examination, vital signs, or electrocardiogram and laboratory parameters.[1]

Mean Duration of Penile Rigidity (>60%) at Base and Tip in Response to Placebo and to 20- and 40-mg Doses of Vardenafil[2]

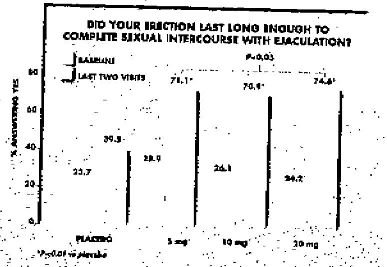


In a randomized, double-blind, placebo-controlled, three-way crossover design study, 21 patients with impaired erectile function received 20 or 40 mg oral doses of vardenafil or placebo.

RigiScan™ measurements of erectile response on visual sexual stimulation showed that erections started earlier, lasted longer, and showed better rigidity and tumescence in the vardenafil treatment group.

Both doses of vardenafil produced statistically significant ($P<0.001$) increases in duration of penile rigidity compared with placebo.

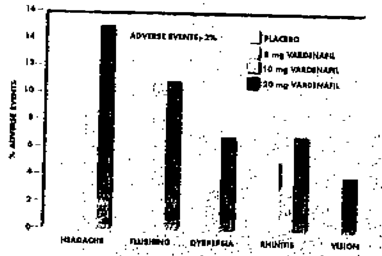
Percentage of Successful Attempts at Sexual Intercourse During 4-Week Baseline Period and the Last 4 Weeks of Treatment[3]



In a 12-week, double-blind, randomized, placebo-controlled, fixed-dose study, 601 men with impaired erectile function of various etiologies were treated with 5, 10, or 20 mg of vardenafil or placebo, once daily as needed.

The proportion of successful attempts at sexual intercourse, the hardness of erection and the overall level of [illegible] were also significantly increased with vardenafil ($P<0.05$).

Safety Results: Adverse Events[3]



In the 12-week study, no serious drug-related adverse events were observed.

1. Sachse R, Rohde G. Safety, tolerability and pharmacokinetics of multiple dose treatment with the new PDE5-inhibitor BAY 38-9456. *Eur Urol.* 2000;37(suppl 2):81. Abstract 321. Paper presented at: XVth Congress of the European Association of Urology; April 12-15, 2000; Brussels, Belgium. **2.** Stark S, Sachse R, Stark A, et al. Erectile response on visual sexual stimulation after 20 mg or 40 mg BAY 38-9456 or placebo. *Eur Urol.* 2000;37(suppl 2):4. Abstract 15. Paper presented at: XVth Congress of the European Association of Urology; April 12-15, 2000; Brussels, Belgium. **3.** [illegible]

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