

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-742

SUMMARY REVIEW



11/17/07

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: November 17, 2007

FROM: Abraham Karkowsky, M.D., Ph.D., Group-Leader Division of
Cardiovascular and Renal Products HFD-110

TO: Dr. Norman Stockbridge, M.D., Ph.D., Division Director, Division of
Cardiovascular and Renal Products HFD-110

SUBJECT: Approval recommendation for Nebivolol Tablets; NDA 21-742, Mylan
Bertek Pharmaceuticals.

I am recommending approval of nebivolol for use as an antihypertensive. This memo summarizes the information submitted as the sponsor's (Mylan Bertek) complete response on May 30, 2007 and as reviewed by the Division. The efficacy and safety of nebivolol was described by the original set of reviewers and is summarized in my overview document of February 23, 2005. The one outstanding issue that prevented approval of nebivolol during the original review cycle was the observation that male mice developed Leydig cell tumors and hyperplasia during chronic treatment with nebivolol. The letter to the sponsor outlined the criteria that would allow for Nebivolol's approval.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following issues:

A highly statistically significant and dose-related increase in benign and malignant Leydig cell tumors was observed in male mice. The findings appear with exposure only several times the clinically attained blood levels. This effect may be endocrinologically mediated. Other possibly endocrinologically mediated effects were also seen in long-term toxicology studies of rats—reductions in adrenal and ovary weights, dystocia, and interference with cyclicity. If an endocrine mechanism can be established and if this mechanism is not relevant to human use, e.g., because it is not active at clinical doses, the mouse findings may not be of concern. It will therefore be necessary for you to establish the mechanism by which nebivolol is responsible for these findings and demonstrate that these findings are not relevant in humans.

The current submission adequately deals with the question of the Leydig cell tumors. The studies however, raise additional issues regarding the effects of nebivolol on other aspects of the rodent reproductive system. With respect to any correlation with the human experience, Dr. Hicks reviewed the available human data for nebivolol. The exposure to nebivolol that was described in Dr. Hick's review includes several studies whose efficacy has not yet submitted for review as well as post-marketing assessments in countries where nebivolol has been approved. There did not appear to be a suggestion of harm to humans related to the endocrine effects that were observed in rodents.

Consequently, it appears reasonable to include the reproductive and gonadic related effects in the package insert but these issues should not serve as an impediment to nebivolol's approval.

Because of the uncertainty and relevance of the observations in rodents to humans, even though I am recommending approval of nebivolol I also recommend that a waiver to pediatric studies be granted. The drug appears to be a modestly selective beta blocker and offers no particular advantage to other beta blockers currently available to either children or adults. A formulation, (Toprol XL) currently contains labeling for pediatric use. Given the uncertainty of the consequences of nebivolol in altering the reproductive tract in humans and the lack of convincing information that these effects are entirely reversible, there appears to be an unwarranted and unnecessary additional risk to the use of nebivolol in children. Studying nebivolol in a pediatric population appears to be unwarranted.

The TRADENAME for nebivolol is still under review. The cGMP report of the drug substance site has not yet been received. Other concerns raised by the chemist relate to nebivolol's packaging. The latter issue is apparently being discussed in short order with the sponsor and the issue does not appear to be an impediment to nebivolol's approval. Labeling has yet to be finalized. Once these issues are resolved and labeling finalized nebivolol should be approved.

Background:

The initial submission contained four clinical studies that defined the effect of nebivolol on blood pressure. Three of these studies were placebo-controlled, parallel-group dose ranging studies. The fourth study was a dose ranging study on top of other antihypertensive treatments. One of the placebo controlled studies enrolled only blacks. The results of these studies indicate that there is an increase in blood pressure effect of nebivolol in the dose range of 1.25 to 40 mg daily.

The trough sitting blood pressure at the interdosing interval is shown below:

Table 1: LS mean placebo-subtracted effect for trough sitting diastolic blood pressure.

	Nebivolol dose					
	1.25	2.5	5.0	10	20	30-40
Study 302	-5.1*	-5.6*	-5.5*	-6.3*	-6.9*	-8.3*
Study 305			-2.8*	-3.9*	-4.5*	
Study 202 [†]		-2.9 [#]	-4.9*	-6.1*	-6.0*	-5.5*
Study 321 [^]			-3.2*	-3.3*	-4.7*	

P-value reflects trend test or Hochberg adjusted p-values. *P < 0.01; [#] 0.1 < p < 0.05

[†] Study enrolled only African Americans.

[^] Study on top of one or two other antihypertensive medications.

Other measurements of blood pressure including supine systolic blood pressure standing blood pressures (SBP and DBP) and peak measurements (SBP and DBP) also suggest that nebivolol has effects in the dose range of 1.25 to 40 mg daily. These measurements are tabulated in the original review and not reproduce here. Peak

measurements compared to trough measurements suggest that nebivolol may be administered as a once-daily drug.

Nebivolol is a substrate of CYP 2D6. Of the more than 2000 subjects studied during controlled clinical trials (placebo and nebivolol) approximately 6% were genotyped as poor metabolizers. There was therefore some reasonable exposure even at the high dose (30-40 mg, n=13) who were genotyped as poor metabolizers.

With respect to the safety of nebivolol, in the original submission, the signals of adverse events were attributable to its beta-blockade activity.

The current memo is based, in addition, on the following reviews:

- Pharmacology-toxicology review; Elizabeth Hausner, D.V.M. dated October 22, 2007 and November 1, 2007.
- Medical Officer Review by Karen Hicks dated October 19, 2007.
- Chemistry (drug quality assessment) review by Ramasharan D. Mittal, dated November 2, 2007.
- DDMAC review by Lisa Hubbard R. Ph., Regulatory Review Officer dated October 29, 2007.
- DMETS review by Diane C. Smith, PharmD., Safety Evaluator dated September 21, 2007.
- DRUP consult by Harry Handelsman D.O., dated October 11, 2007.
- Toxicology statistical review by Karl K. Lin, Ph.D., dated October 22, 2007 also preliminary review received on November 15, 2007.
- DMEP consult by Valerie S. W. Pratt, M.D., dated October 10, 2007.
- Toxicology consult by Karen Davis-Bruno Ph.D., dated September 21, 2007.
- Clinical statistical review by Sonia Castillo, Ph.D., dated October 17, 2007.

Pharmacology Toxicology:

There were three new pre-clinical studies that were submitted. A re-review of previously performed dog histopathology slides of the reproductive system added no additional data.

Study Tox021-003 was a 28 day study in male mice that were fed nebivolol by gavage. The daily dose of nebivolol was 0 (control), 5, 20 or 80 mg/kg. The key pathology findings after 28 days of treatment were Leydig cell hyperplasia in the 80 mg/kg dose; occasional atrophic tubules in the 20 and 80 mg/kg dose-group and distended seminal vesicles in the in the 80 mg/kg dose group. The mean LH values in the control group (either day 14 or 24) ranged from 0.7 to 5.1 IU. On day 28, the mean control values over the seven measured points during the 24 hour period ranged from 0.9 to 3.1 IU. The high dose nebivolol group LH measurements ranged from 0.8 to 3.8 IU. Although the sponsor suggests that there was an increase in LH values at the 4-6 hour time point the variability of measurements in this study should make the LH increase as likely but not definitive.

Study NEB-TX-02 was a 28 day exposure to mice of either nebivolol at a dose of 80 mg/kg/day or control with or without dihydrotestosterone at a dose of 2 mg/day. The Leydig cell hyperplasia that was observed after treatment with nebivolol alone was abolished when nebivolol and dihydrotestosterone were concomitantly administered. An increase in apoptotic bodies in the seminiferous tubules observed with nebivolol was not abolished when nebivolol was concomitantly administered with dihydrotestosterone (see table below adapted from Dr. Hausner's review). Testosterone treatment either with or without nebivolol provokes in Leydig cell atrophy. The key findings of this study are tabulated below

Table 2: Key reproductive tract findings study NEB-TX=02

Histological finding	Control	Dihydrotestosterone	Nebivolol	Nebivolol with dihydrotestosterone
Number of animals	60	60	57	52
Leydig cell hypertrophy/hyperplasia	0	0	44	0
Seminiferous tubules increased apoptotic-like bodies	1	0	39	36
Leydig cell atrophy	0	60	0	51

With respect to the hormonal changes that were noted in these animals, there was an increase in LH in the nebivolol treated animals relative to control animals. There was no difference in testosterone levels comparing the nebivolol to control treated animals. The increase in LH is consistent with this hormone as the provocative mechanism for the generation of Leydig cell tumors in nebivolol-treated mice. The reason for the LH increase, however, cannot be attributed to an effect of nebivolol in decreasing testosterone levels in mice. The ability of nebivolol to increase LH and the ability of dihydrotestosterone to suppress Leydig cell hyperplasia suggests that if in humans no LH increase is observed, risk of testicular neoplasia in humans appears minimal.

Not all of the effects of nebivolol could be reversed by the concomitant administration of dihydrotestosterone. In particular the changes in the seminiferous tubules were not altered by with concomitant therapy. These results suggest that nebivolol has effects on the rodent reproductive system that differs from a simple effect mediated by its effect on LH.

The third study Tox021-001 explored the effects of nebivolol in both mice and rats. For both rats and mice the daily doses studied were 0 (control), 10, 40 and 160 (later decreased to 80) mg/kg. A positive flutamide group was included for each rodent species. Cohorts of each rodent species were scheduled sacrificed at 2, 4 and 13 weeks of treatment and after a 4 week recovery period (week 17). For the high dose group, in each species, the toxicity of nebivolol at the high dose necessitated some alteration in the dosing schedule. For mice there was no 4 week value but the group that was so scheduled was sacrificed at week 8 because of a 2-week drug hiatus, For rats there was a terminal sacrifice at week 7 (not week 13).

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In addition to genital pathology (including sperm assessments) there were assessments of sex-hormones (LH, estradiol). The effect on rodent sperm parameters is shown below.

Table 3: Effects on sperm Tox021-001 of either nebivolol at daily doses of 10, 20 or 80/160 mg or flutamide

		Parameter mean + SD (approximately 10 animals/assessment)				
		Motile sperm (%)	Progressively motile sperm (%)	Cauda epididymis sperm count (Millions/g)	Right testes sperm count (Millions/g)	Normal sperm (%)
RAT						
Terminal sacrifice (week 7 or 13)	Neb 0	93 ± 4	46 ± 13	525 ± 121	82 ± 25	97 ± 1
	Neb 10	84 ± 8	54 ± 17	564 ± 100	92 ± 27	96 ± 2
	Neb 40	94 ± 4	37 ± 13	552 ± 111	89 ± 12	89 ± 6
	Neb 80	83 ± 14	33 ± 13	485 ± 201	76 ± 25	84 ± 11
	Flutamide	86 ± 8	17 ± 7	391 ± 201	63 ± 31	79 ± 29
Recovery (week 17)	Neb 0	85 ± 24	61 ± 27	671 ± 128	80 ± 23	95 ± 5
	Neb 10	94 ± 5	55 ± 18	613 ± 196	72 ± 24	98 ± 2
	Neb 40	76 ± 29	30 ± 26	295 ± 167	83 ± 27	85 ± 25
	Neb 80	52 ± 30	26 ± 23	293 ± 167	59 ± 32	54 ± 32
	Flutamide	72 ± 37	46 ± 26	463 ± 273	63 ± 29	70 ± 38
MOUSE						
Terminal sacrifice (week 13)	Neb 0	93 ± 6	66 ± 19	1053 ± 207	251 ± 69	76 ± 14
	Neb 10	85 ± 9	56 ± 12	847 ± 261	228 ± 70	82 ± 9
	Neb 40	80 ± 16	55 ± 26	732 ± 244	249 ± 68	52 ± 22
	Neb 80	69 ± 21	17 ± 10	584 ± 360	215 ± 254	50 ± 23
	Flutamide	92 ± 8	53 ± 22	776 ± 142	220 ± 52	80 ± 12
Recovery	Neb 0	76 ± 28	42 ± 30	621 ± 253	167 ± 64	72 ± 8
	Neb 10	84 ± 18	38 ± 24	657 ± 232	172 ± 57	75 ± 8
	Neb 40	92 ± 1	39 ± 27	384 ± 144	143 ± 64	66 ± 25
	Neb 80	96 ± 2	62 ± 19	541 ± 149	164 ± 81	81 ± 14
	Flutamide	84 ± 13	35 ± 29	542 ± 119	176 ± 57	78 ± 8

The flutamide group is shaded in blue. The values that appear to be different in the nebivolol treatment groups compared to control are grey-shaded. In rats there was a decrease in normal sperm, comparing high dose nebivolol to control. Other effects during treatment (13 weeks) were a decrease in motile and highly motile sperm. These effects do not resolve but apparently appears to increase even after a 4 week washout period.

For mice on the other hand there were more obvious effects on sperm during treatment, with reasonably good reversal during the recovery period. Flutamide had only modest effects on some measurements of sperm.

Other observations made during the histology evaluation in rats were: an increase in spermatid retention, exfoliation of germ cells, and degeneration of elongating spermatids in the testes; an increased in sloughed germ cells/cell debris in the epididymis. There were also changes in the prostate (inflammation, distended acini and epithelial thinning); seminal vesicles (distention and epithelial thinning) as well as effects on mammary glands (tubuloalveolar differentiation). These changes were not observed with flutamide. Changes seen with flutamide not observed with nebivolol were related to the seminal vesicles (contracted/epithelial atrophy) and Leydig cell hyperplasia,

In mice additional effects other than Leydig cell hyperplasia, observed at terminal sacrifice were effects on the epididymis (increased vacuolation/apoptosis and sloughed increased germ cells). These effects were seen in 1 or 2 animals at the high dose group.

With respect to hormonal levels, in rats, estradiol levels were consistently elevated only in the flutamide positive-control group with normalization during recovery. LH levels in rats were elevated only in the flutamide control group.

With respect to mouse, there was an inconsistent pattern for estradiol based on dose and treatment duration. Whereas flutamide demonstrated an increase in estradiol at week 2 of treatment by terminal sacrifice (week 8 of treatment), the estradiol levels were equivalent to control. For the nebivolol treated animals there was an increase in LH in the two high dose groups during treatment. Remarkably the highest value for LH was measured after the 4-week recovery measurement.

In summary, there were clear effects caused by nebivolol in mice and rats. The Leydig cell tumors that were noted in mice were abolished with the concomitant treatment with dihydrotestosterone. Not all effects of nebivolol, however, could be explained either by an increase in LH and could not also be entirely reversed by the concomitant treatment with nebivolol. The etiologies of these effects in my mind are not well understood. I am particularly concerned about the lack of reversal of the effect of nebivolol in rats sperm despite a 4-week recovery period. Since, however, the major concern preventing approval was the generation of Leydig cell tumors in mice and the mechanism of these tumors can be attributed to LH increases, not observed in humans (see below), the other effects can be described in labeling and should not serve as an impediment to nebivolol's approval.

Clinical

The sponsor planned Study NEB-PK-03 in order to assess the effect of nebivolol on adrenal function and sex hormone levels in normal males. The study enrolled 157 normal subjects and randomized them to one of three treatments: atenolol, nebivolol or placebo. Subjects received the randomized treatment for a total of 56 days. The first week was at a dose of atenolol of 50 mg daily, nebivolol at 5 mg daily or placebo. Subjects were then treated for an additional 7 weeks at a dose of atenolol of 100 mg daily, nebivolol at 10 mg daily or placebo. Of those enrolled 4 subjects were poor metabolizers and generated concentrations of the isomers of nebivolol at markedly higher levels than the population as a whole.

There were no differences in the nebivolol and either control or atenolol-treated patients with respect to the following parameters: LH and testosterone and mean serum cortisol and serum aldosterone in response to an ACTH stimulation test. To the extent of the sample size of the study allows, the results are sufficient to rule out meaningful changes in these parameters in males during 8 weeks of exposure to nebivolol. Other exposure response analyses by Dr. Wang, did not demonstrate a credible effect relating either d- or l-nebivolol concentrations (which spanned 1.5 to 2 log units) to any effect.

In summary the small study does not demonstrate the same effect of nebivolol on LH levels as being pertinent to humans.

Sildenafil interaction:

There was a single trial (NEB-0398) that assessed the effect of single doses of sildenafil on the kinetics of nebivolol. Normal subjects received 1 dose of sildenafil citrate followed by a two day washout period. Subjects were then started on 10 mg of nebivolol for nine doses. At the 7th dose subjects also received a single 100 mg dose of sildenafil citrate. With the exception of one subject who was an intermediate metabolizer all other subjects were extensive metabolizers. There were small effects of nebivolol on the kinetics of sildenafil (approximately a decrease of 20% in C_{max} and AUC) and a miniscule effect of sildenafil on the kinetics of nebivolol. The effects of concomitant use of sildenafil with nebivolol on vital signs can best be described by the additivity of the individual components effects.

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