CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200796Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	200-796
Applicant Name	Takeda Pharmaceuticals North America, Inc.
Date of Submission	April 22, 2010
PDUFA Goal Date	February 27, 2011
Proprietary Name / **Established (USAN) Name**	Edarbi/azilsartan medoxomil
Dosage Forms / Strength	40 mg & 80mg Tablets
Proposed Indication(s)	Treatment of hypertension
Action:	Approve

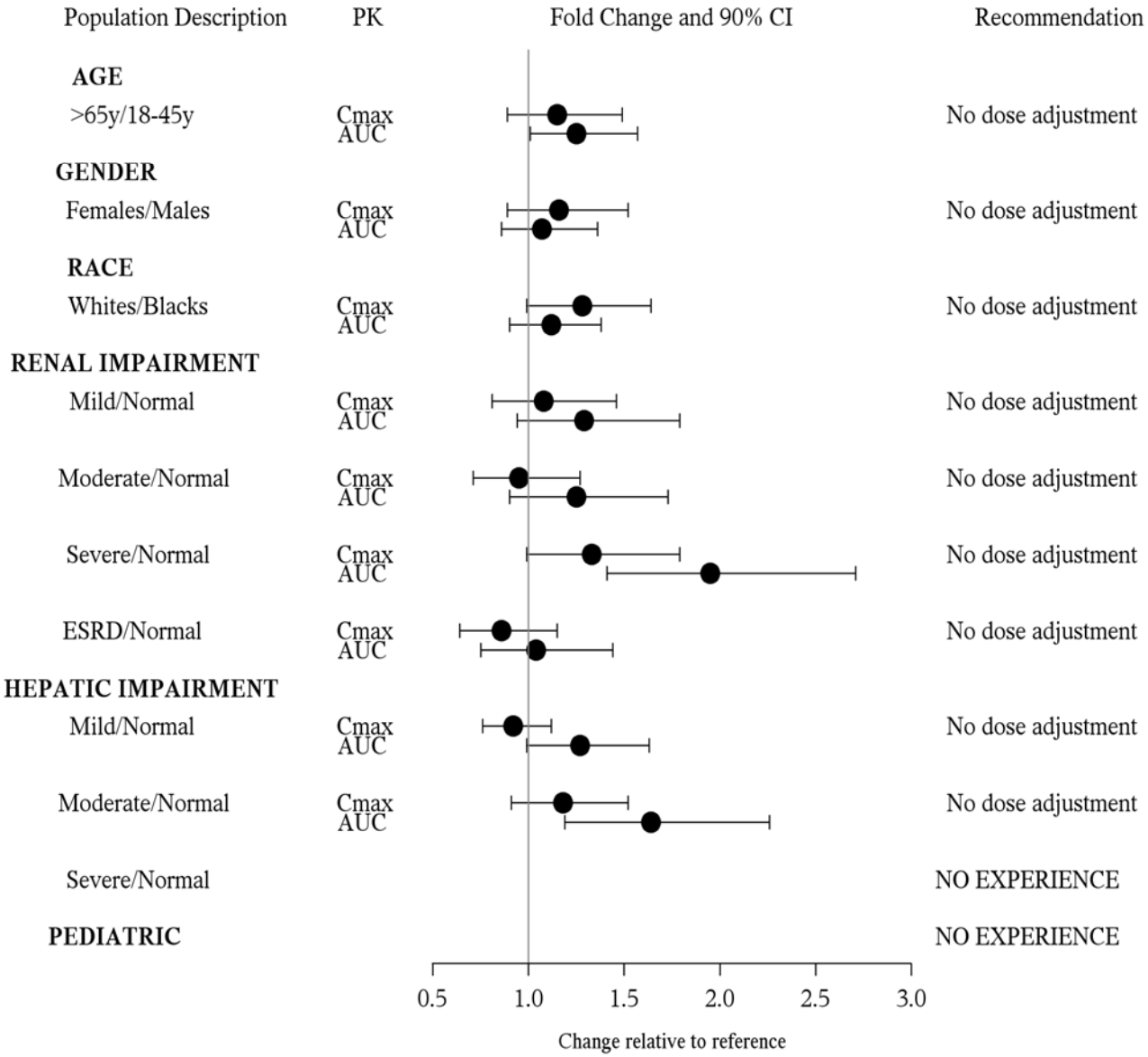
Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer/Statistical Review	Maryann Gordon/ John Lawrence
Pharmacology Toxicology Review	Philip Gatti/William Link
CMC Review/OBP Review	Charles Jewell/Shiroman Prafull
Clinical Pharmacology Review	Divya Menon-Anderson
CDTL Review	Shari Targum
Div Dir Review	Norman Stockbridge

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader

I. Introduction

As explained in Dr. Stockbridge's Division Director memo and Dr. Targum's CDTL memo, consideration of azilsartan, a new member of a well-established anti-hypertensive drug class, angiotension II receptor blockers (ARBs) is relatively straightforward. Azilsartan has no significant chemistry or pharm-tox issues. It is given as the medoxomil ester (TAK-491; azilsartan itself is TAK-536) is converted to the active moiety on absorption, and has a terminal half life at about 12 hours. It has no significant drug-drug interactions or effects of abnormal excretory function. The small effects that do exist are shown in the pharmacokinetics (12.3) section of labeling in an innovative forest plot format that presents an uncluttered and straightforward description of what, if any, effect on blood levels (AUC or Cmax) might be of concern.

Impact of intrinsic factors on the pharmacokinetics of azilsartan



None of these factors has a more than 50% effect on blood levels, so there is little chance of a favorable or adverse effect, given the relatively flat dose-response curve of azilsartan for both effectiveness and safety.

All reviewers and supervisors recommended that azilsartan be approved, but there were several areas of discussion. The principal issues for azilsartan have been:

1. Dose: 40 mg vs. 80 mg, with some interest in still lower doses, especially in volume-contracted patients.
2. Effects compared to valsartan and olmesartan, two well-established ARB's.
3. Effects on serum creatinine (small, reversible increases are known to occur with ARB's and ACEI's, but there can be larger effects in patients who are fluid-depleted (on higher doses of diuretics) and there are possible interactions with diuretics (more effect with chlorthalidone than with HCTZ).

II. Dose-Response

In the well-established tradition for anti-hypertensive agents, azilsartan was the subject of very extensive dose-response studies in phase 2 and 3, assessing both clinic BP and 24 hour ABPM BP (the 24 hour data was far more extensive than usual). In a controlled trial database of almost 6000 patients, over 3500 were given azilsartan at doses of 2.5 to 80 mg. Most dose-response data came from 6 week placebo-controlled studies, but 6 month active control studies using ABPM were also informative, even without placebo groups, because there is little effect in ABPM measures on placebo [The "placebo effect" in clinic BP is generally thought to be largely the result of a reader bias, the desire to find a blood pressure meeting entry criteria; the effect appears at the first post-randomization measurement, does not increase over time, and is not a "regression to the mean phenomenon or a true placebo-response]. There is also a placebo-controlled randomized withdrawal study in patients on 6 months of open-label azilsartan, futher confirming long-term effectiveness.

The dose-response studies are described in Drs. Gordon's and Targum's reviews.
As noted in Dr. Targum's January 21, 2011 review, the relatively small (60-75 patients per group) dose-finding studies 001, 002 and 005, which studied doses from 5 mg to 80 mg, clearly showed a greater effect of doses of 10-80 mg compared to 5 mg, but a clear advantage of 80 mg (or 40 mg) was not consistently seen. The larger (280-290 patients per group) phase 3 studies (019, 008) do, however, show a reasonably consistent larger effect of 80 mg than 40 mg by both clinical and ABPM measures. These results are shown in Table 1 of labeling (section 14), with study #1 being study 019, and # 2 being 008.

Placebo Corrected Mean Change from Baseline in
Systolic / Diastolic Blood Pressure at 6 Weeks (mm Hg)

	Study 1 N=1285		Study 2 N=989	
	Clinic Blood Pressure (Mean Baseline 157.4 / 92.5)	24 Hour Mean by ABPM (Mean Baseline 144.9 / 88.7)	Clinic Blood Pressure (Mean Baseline 159.0 / 91.8)	24 Hour Mean by ABPM (Mean Baseline 146.2 / 87.6)
Edarbi 40 mg	-14.6 / -6.2	-13.2 / -8.6	-12.4 / -7.1	-12.1 / -7.7
Edarbi 80 mg	-14.9 / -7.5	-14.3 / -9.4	-15.5 / -8.6	-13.2 / -7.9
Olmesartan 40 mg	-11.4 / -5.3	-11.7 / -7.7	-12.8 / -7.1	-11.2 / -7.0
Valsartan 320 mg	-9.5 / -4.4	-10.0 / -7.0		

The increased effect of 80 mg compared to 40 mg is small, just 1-2 mm Hg, but as noted appears in both clinic pressures and ABPM measures. If 80 mg had a side effect cost, the value of the added 1-2 mm Hg would have to be carefully weighed. There is no doubt, however, that epidemiologically, even 1-2 mm Hg greater BP has an adverse CV effect, and there is reason to seek the full effect of any antihypertensive modality in the absence of adverse effects. Like previous ARBs, azilsartan has little in the way of dose-related toxicity. I therefore believe the recommended dose should be 80 mg.

I should note one further element of support for this view. Dr. Gordon describes a pooled analysis of studies 008 and 019 that looked at subgroups by baseline blood pressure.

Placebo – corrected change in Systolic Blood Pressure (SBP)

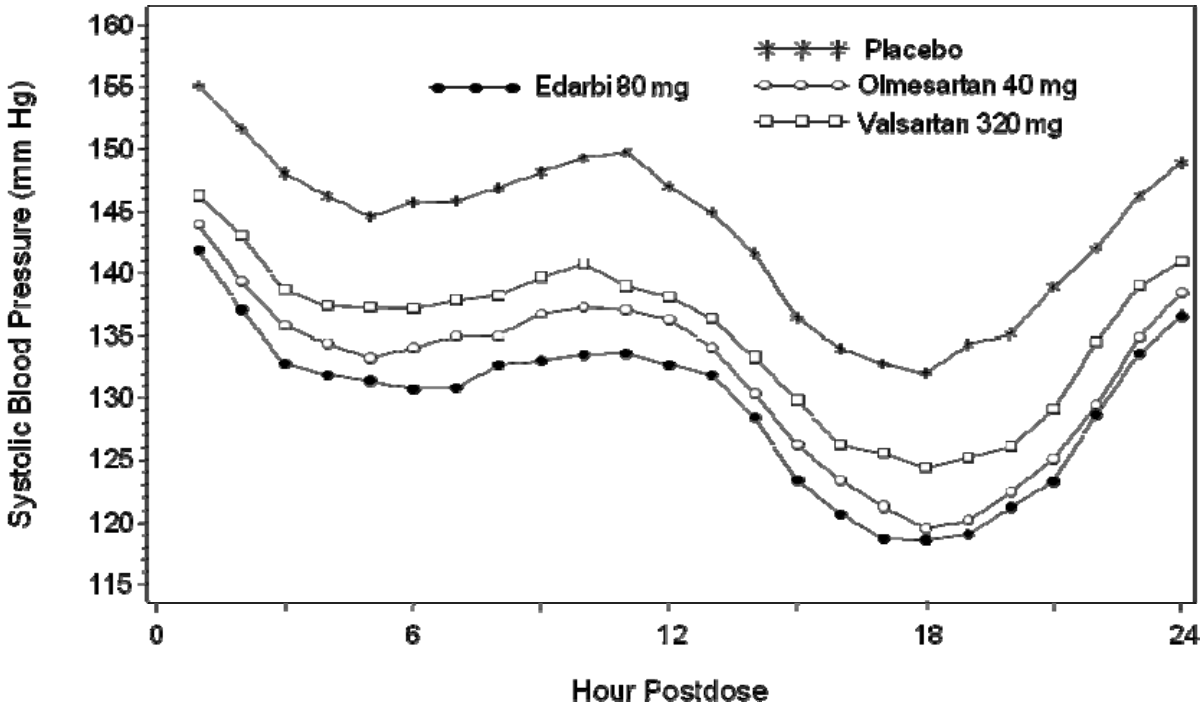
	> 140 to < 160		> 160 to < 180	
	40 mg	80 mg	40 mg	80 mg
n	250	230	176	203
24 hour	-12.3	-12.8	-12.5	-15.0
clinic	-14.1	-14.9	-12.3	-15.6

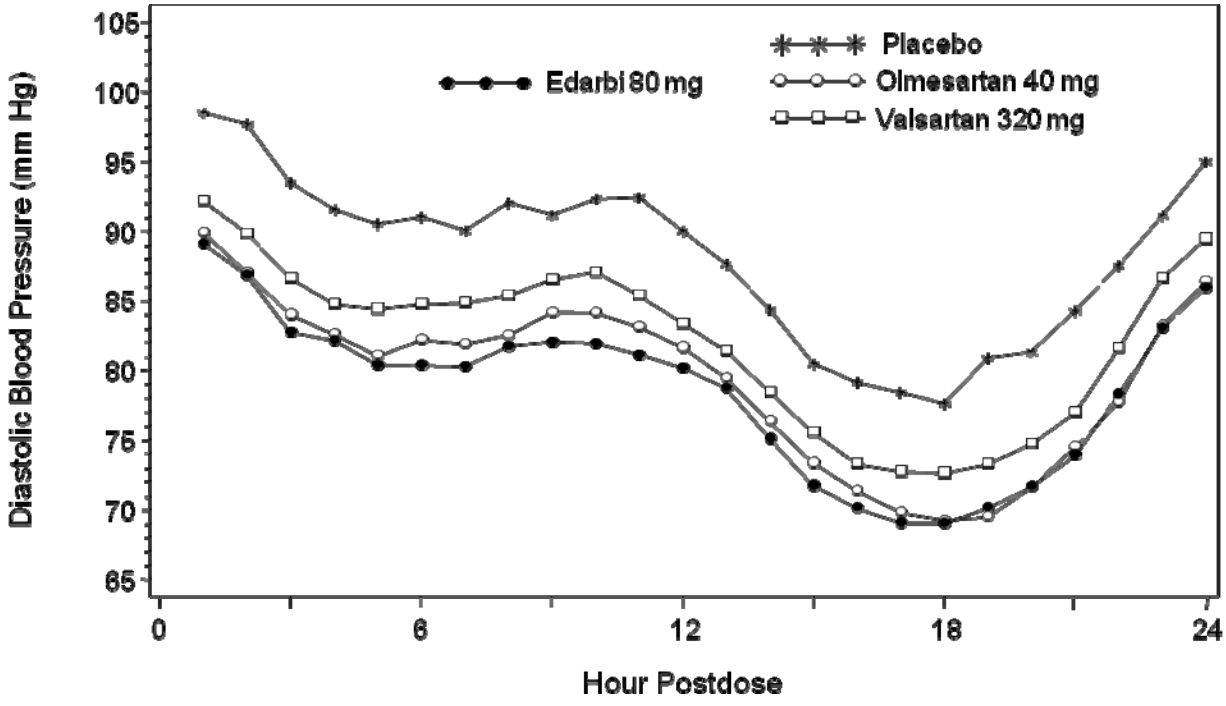
The larger effect of 80 mg is most prominent in patients with higher initial blood pressure (there were only a small number of patients with still higher pressure).

III. Comparison with other ARBs

In the studies shown in labeling, azilsartan was more effective by 2-3 mmHg than maximum labeled doses of valsartan and olmesartan, as measured by both clinic and ABPM measures. The differences in Table 1 of labeling are all statistically significant (both clinic and ABPM) for both comparator drugs for systolic pressure, the primary study endpoint, and for most measures of diastolic pressure.

The 24 hour results for study 1 (study 019) were shown in labeling.


Placebo
Edarbi 80 mg
Olmesartan 40 mg
Valsartan 320 mg
Systolic Blood Pressure (mm Hg)
160
155
150
145
140
135
130
125
120
115
0
6
12
18
24
Hour Postdose


Placebo
Edarbi 80 mg
Olmesartan 40 mg
Valsartan 320 mg
Diastolic Blood Pressure (mm Hg)
105
100
95
90
85
80
75
70
65
0
6
12
18
24
Hour Postdose

There was also a 6 month comparative study of azilsartan 40 mg, azilsartan 80 mg, and valsartan 320 mg (each drug was titrated to the aforementioned doses). Effects at week 24 were for ABPM

Systolic Blood Pressure (mm Hg)

	Azilsartan 40 mg n = 327	Azilsartan 80 mg n = 329	Valsartan 320 mg n = 326
Change from baseline	14.9	15.3	11.3
Difference from valsartan	-3.6	-4.0	_

The results were reasonably constant over the 24 weeks of the study.

In general, FDA grants a comparative claim only with a strong and consistent showing of advantage, usually with two supporting studies, and that standard was met here, although differences were modest in size. The difference versus valsartan appeared somewhat larger but we concluded that a greater effect was also shown consistently in two studies with olmesartan.

IV. Effects on serum creatinine

ARBs (and ACEIs) cause small reversible increases in serum creatinine. In these trials, azilsartan 80 mg caused such increases (>30 % from baseline), only slightly more often than placebo (1.3% vs. 0.9%), but less often than olmesartan (about 2.5%). The rate of increases of ≥ 30% was clearly greater, however; in patients also on chlorthalidone, reaching almost 10% (for 40 mg) vs. 1.7% on placebo. Labeling suggests use of the 40 mg dose in patients on high doses of diuretics.

V. Conclusions

Azilsartan should be approved at a recommended dose of 80 mg (40 mg for people volume-depleted). It has few adverse effects other than the potential for hypotension (hypotension was the adverse effect most likely to lead to drug discontinuation [0.4% on azilsartan 80 mg vs. none on placebo], small reversible increases in serum creatinine, and diarrhea (2% of azilsartan 80 mg vs. 0.5% of patients on placebo).

In a vigorous effort at assessing comparative effectiveness, azilsartan was shown to have a modestly greater antihypertensive effect than two standard ARBs, valsartan and olmesartan.

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/s/

ALEXIS T CHILDERS
02/25/2011

ROBERT TEMPLE
02/25/2011