

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**ANDA 90-790**

**Name:** Losartan Potassium Tablets USP,  
25 mg, 50 mg, and 100 mg

**Sponsor:** Apotex Corp.

**Approval Date:** October 6, 2010

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**ANDA 90-790**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**ANDA 90-790**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Rockville, MD 20857

ANDA 090790

Apotex Corp.  
Attention: Kiran Krishnan  
Associate Director, Regulatory Affairs  
2400 N. Commerce Parkway, Suite 400  
Weston, FL 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated August 27, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Losartan Potassium Tablets USP, 25 mg, 50 mg and 100 mg.

Reference is also made to the tentative approval letter issued by this office on August 11, 2010, and to your amendments dated February 1, August 12, September 21, September 24, September 27, September 28, and October 4, 2010.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is approved effective on the date of this letter. The Division of Bioequivalence has determined your Losartan Potassium Tablets USP, 25 mg, 50 mg and 100 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Cozaar Tablets, 25 mg, 50 mg, 100 mg, respectively, of Merck Research Laboratories. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The reference listed drug (RLD) upon which you have based your ANDA, Cozaar Tablets, 25 mg, 50 mg, and 100 mg, of Merck Research Laboratories, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 5,210,079 (the '079 patent) is scheduled to expire on November 11, 2010 (with pediatric exclusivity extension).

Your ANDA contains a statement under section 505(j)(2)(A)(viii) of the Act that the '079 patent is a method-of-use patent, and that this patent does not claim any indication for which you are seeking approval.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Amundson Road  
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance

for industry titled "SPL Standard for Content of Labeling  
Technical Qs and As" at  
<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible via publicly available labeling  
repositories.

Sincerely yours,

*{See appended electronic signature page}*

Keith Webber, Ph.D.  
Deputy Director  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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

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/s/

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ROBERT L WEST

10/06/2010

Deputy Director, Office of Generic Drugs  
for Keith Webber, Ph.D.

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 90-790**

**TENTATIVE APPROVAL LETTER**



ANDA 090790

Apotex Corp.  
U.S. Agent for: Apotex, Inc.  
Attention: Kiran Krishnan  
Associate Director, Regulatory Affairs  
2400 North Commerce Parkway, Suite 400  
Weston, FL 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated August 27, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Losartan Potassium Tablets USP, 25 mg, 50 mg, and 100 mg.

Reference is also made to your amendments dated March 5, July 7, September 8, and September 14, 2009; and January 15, January 20, January 25, February 1, February 18, February 19, February 23, March 5 and March 15, 2010.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the exclusivity issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug (RLD) upon which you have based your ANDA, Cozaar Tablets, 25 mg, 50 mg, and 100 mg, of Merck Research Laboratories, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 5,210,079 (the '079 patent) is scheduled to expire on November 11, 2010, and U.S. Patent No.

5,608,075 (the '075 patent) expired on September 4, 2009 (both with pediatric exclusivity added).

With respect to the '079 patent, your ANDA contains a statement under section 505(j)(2)(A)(viii) of the Act that this is a method of use patent, and that your ANDA does not claim any indication protected by this patent.

Your ANDA also contains a paragraph IV certification to the '075 patent under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Losartan Potassium Tablets USP, 25 mg, 50 mg, and 100 mg, under this ANDA. You have notified the agency that Apotex, Inc. (Apotex) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Apotex within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

However, we are unable at this time to grant final approval to your ANDA. Prior to the submission of your ANDA, another applicant submitted an ANDA for Losartan Potassium Tablets USP, 25 mg, 50 mg, and 100 mg, which contained a paragraph IV certification to the '075 patent. Your ANDA will be eligible for final approval upon the expiration of the other applicant's 180-day exclusivity identified in section 505(j)(5)(B)(iv) of the Act, or that exclusivity is otherwise resolved.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" upon receipt of this letter. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

For further information on the status of this application, or prior to submitting additional amendments, please contact Dat Doan, Project Manager, at (240) 276-9336.

Sincerely yours,

*{See appended electronic signature page}*

Keith Webber, Ph.D.  
Deputy Director  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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

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/s/

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ROBERT L WEST

08/11/2010

Deputy Director, Office of Generic Drugs  
for Keith Webber, Ph.D.

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**ANDA 90-790**

**LABELING**

Material Code: TBD	ECL Common Text#: N/A	Description: ARPL USA FOIL BS LOSARTAN POTASSIUM FCT 50MG
Material Code REF: N/A		
QA Rev#: 0	QA Change: N/A	C of A: PKGP-CA-PAD
Previous Code: N/A	Pre or Post Commercial Change: NEW FINISHED GOOD	CCP#: REFER TO TRACKWISE
Pantone Colours: <span style="display: inline-block; width: 15px; height: 15px; background-color: black; margin-right: 5px;"></span> BLACK <span style="display: inline-block; width: 15px; height: 15px; background-color: magenta; margin-left: 20px; margin-right: 5px;"></span> DIELINE		
Dimensions/Dieline#: FE23N 62.3 mm x 116 mm	Minimum Font Size: 5 PT	Prepared by: (b) (6) Date: FEB 19, 2010

NOTE: LOT & EXP. ARE FOR POSITION ONLY (UNIQUE TO EACH ORDER)

PAGE 1 OF 1

(LAYOUT FOR SUBMISSION PURPOSES ONLY)

**PERF. & DIELINE  
DO NOT PRINT**

 <small>Losartan Potassium Tablet, USP 50 mg MFD. FOR APOTEX CORP. WESTON, FL 33326 MADE IN INDIA 01)00360505316106 (L) GEXXXX EXP. XX XXXX</small>	 <small>Losartan Potassium Tablet, USP 50 mg MFD. FOR APOTEX CORP. WESTON, FL 33326 MADE IN INDIA 01)00360505316106 (L) GEXXXX EXP. XX XXXX</small>	 <small>Losartan Potassium Tablet, USP 50 mg MFD. FOR APOTEX CORP. WESTON, FL 33326 MADE IN INDIA 01)00360505316106 (L) GEXXXX EXP. XX XXXX</small>	 <small>Losartan Potassium Tablet, USP 50 mg MFD. FOR APOTEX CORP. WESTON, FL 33326 MADE IN INDIA 01)00360505316106 (L) GEXXXX EXP. XX XXXX</small>	 <small>Losartan Potassium Tablet, USP 50 mg MFD. FOR APOTEX CORP. WESTON, FL 33326 MADE IN INDIA 01)00360505316106 (L) GEXXXX EXP. XX XXXX</small>	 <small>Losartan Potassium Tablet, USP 50 mg MFD. FOR APOTEX CORP. WESTON, FL 33326 MADE IN INDIA 01)00360505316106 (L) GEXXXX EXP. XX XXXX</small>
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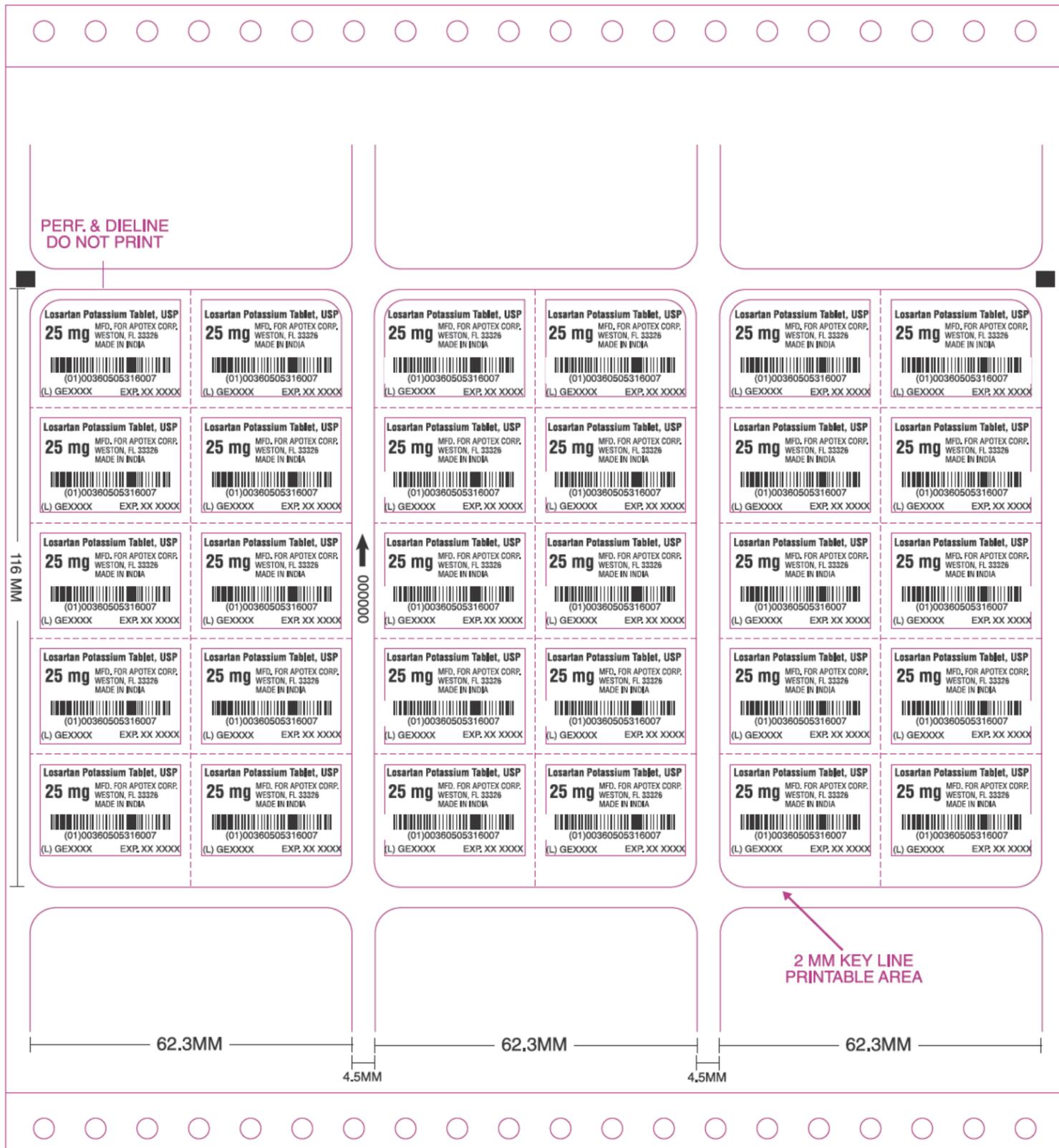
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Previous Code: N/A	Pre or Post Commercial Change: NEW FINISHED GOOD	CCP#: REFER TO TRACKWISE
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PAGE 1 OF 1

(LAYOUT FOR SUBMISSION PURPOSES ONLY)

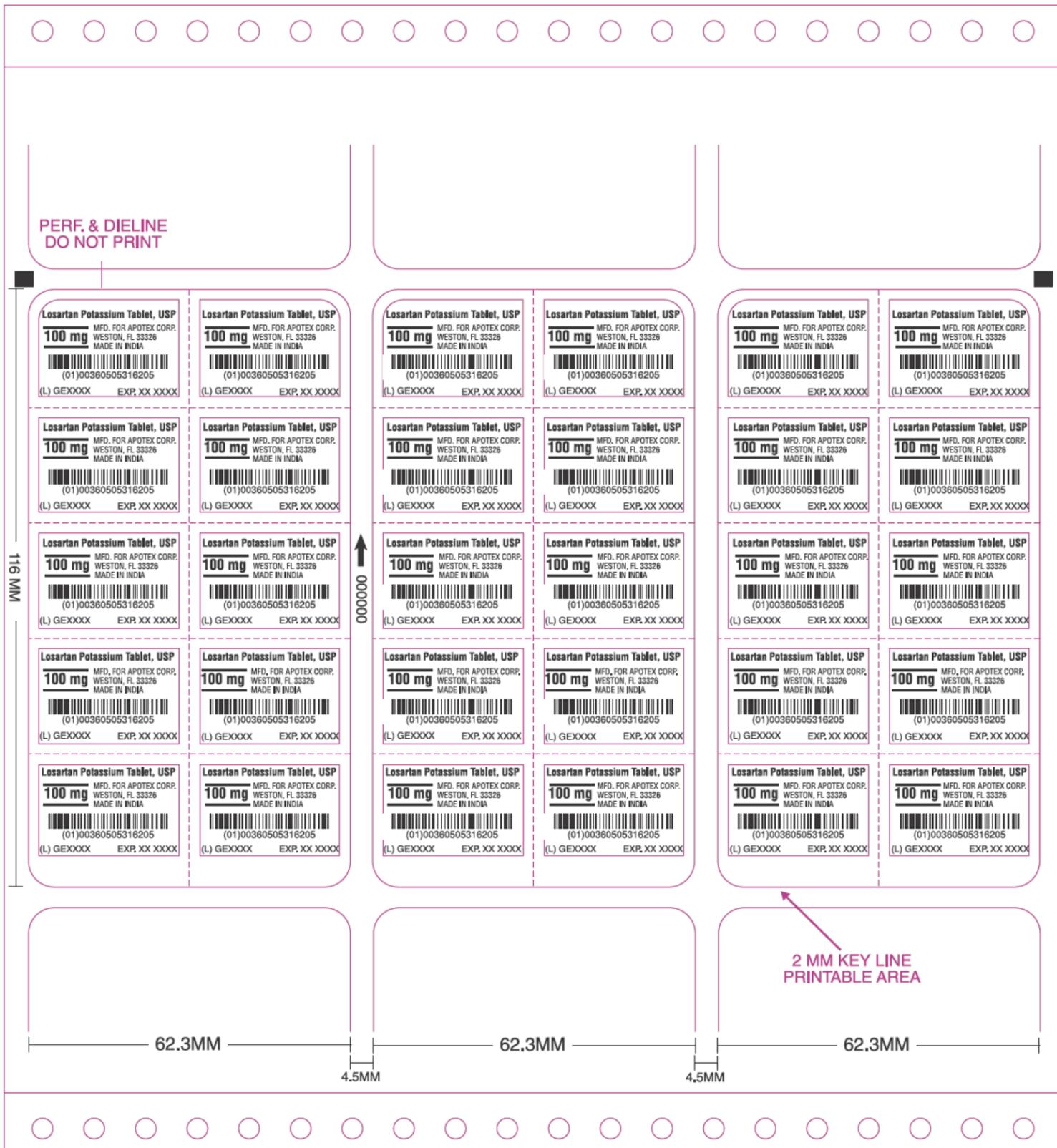


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Material Code REF: N/A		
QA Rev#: 0	QA Change: N/A	C of A: PKGP-CA-PAD
Previous Code: N/A	Pre or Post Commercial Change: NEW FINISHED GOOD	CCP#: REFER TO TRACKWISE
Pantone Colours: <span style="display: inline-block; width: 15px; height: 15px; background-color: black; border: 1px solid black;"></span> BLACK <span style="display: inline-block; width: 15px; height: 15px; background-color: magenta; border: 1px solid black;"></span> DIELINE		
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PAGE 1 OF 1

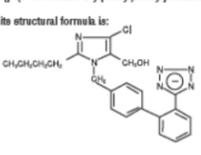
(LAYOUT FOR SUBMISSION PURPOSES ONLY)



Material Code: N/A	ECL Common Text#: 287286	Description: ECL LOSARTAN K ARPL USA
Material Code REF: 286313 / 286340 / 286351 / 286352 / 286353 / 286354 / 286355 / 286356		
QA Rev#: 0	QA Change: N/A	C of A: PKGP-CA-LBL-PIL
Previous Code: N/A	Pre or Post Commercial Change: NEW FINISHED GOOD	CCP#: REFER TO TRACKWISE
Pantone Colours: <span style="display: inline-block; width: 15px; height: 15px; background-color: black; margin-right: 5px;"></span> BLACK <span style="display: inline-block; width: 15px; height: 15px; background-color: gray; margin-left: 20px; margin-right: 5px;"></span> DIELINE		
Dimensions/Dieline#: 50.8 mm x 138.125 mm PULLOUT - 50.8 mm x 349.25 mm	Minimum Font Size: 4 PT	Prepared by: (b) (6) Date: JAN 22, 2010

WHEN A PULL-OUT IS BEING UTILIZED IN A BOOKLET, IT IS TO BE INSERTED IN THE CENTER COUNT AND ONCE FOR ALL OTHER SIZE COUNTS (b) (4) SIZE

**INSIDE SINGLE PAGES**

2"	<p><b>INSIDE PAGES</b> 3.5625"</p> <p style="text-align: center;">Lesartan Potassium Tablets USP 25 mg, 50 mg, 100 mg 3 Only</p> <p style="text-align: center;"><b>USE IN PREGNANCY</b> When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, losartan potassium tablets should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.</p> <p><b>DESCRIPTION</b> Losartan Potassium Tablets USP is an angiotensin II receptor (type AT<sub>1</sub>) antagonist. Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(6-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.</p> <p>Its empirical formula is C<sub>22</sub>H<sub>27</sub>ClN<sub>4</sub>O and its structural formula is:</p>  <p style="text-align: right;">1</p>	<p><b>INSIDE PAGES</b> 3.5625"</p> <p>Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetone/nitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.</p> <p>Losartan potassium is available as tablets for oral administration containing either 25 mg, 50 mg or 100 mg of losartan potassium and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, magnesium stearate, hypromellose 6 cp, hydroxy propyl cellulose, titanium dioxide and carnauba wax.</p> <p>Losartan potassium 25 mg, 50 mg and 100 mg tablets contain potassium in the following amounts: 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq) and 8.48 mg (0.216 mEq), respectively.</p> <p style="text-align: center;"><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Mechanism of Action</b> Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, Kininase II)], is a potent vasoconstrictor; the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT<sub>2</sub> receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT<sub>1</sub> receptor and have much greater affinity (about 1000-fold) for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor. <i>In vitro</i> binding studies indicate that losartan is a reversible, competitive inhibitor of the AT<sub>1</sub> receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT<sub>1</sub> receptor.</p> <p style="text-align: right;">2</p>	2"																																				
NON PRINTING DIE LINE	ALL COPY SHOULD BE .125" AWAY FROM EDGE OF DIE LINE	NON PRINTING DIE LINE	ALL COPY SHOULD BE .1652" AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE																																				
2"	<p><b>INSIDE PAGES</b> 3.5625"</p> <p>Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.</p> <p style="text-align: center;"><b>Pharmacokinetics</b></p> <p><b>General</b> Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of <sup>14</sup>C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. <i>In vitro</i> studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.</p> <p>The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours.</p> <p>The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulates in plasma upon repeated once-daily dosing.</p> <p>Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal.</p> <p style="text-align: right;">3</p>	2"	<p><b>INSIDE PAGES</b> 3.5625"</p> <p>the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C<sub>max</sub> but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).</p> <p>The pharmacokinetics of losartan and its active metabolite were also determined after IV doses of each component separately in healthy volunteers. The volume of distribution of losartan and the active metabolite is about 34 liters and 12 liters, respectively. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. After single doses of losartan administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral <sup>14</sup>C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of <sup>14</sup>C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.</p> <p>Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.</p> <p style="text-align: center;"><b>Special Populations</b></p> <p><b>Pediatric:</b> Pharmacokinetic parameters after multiple doses of losartan (average dose 0.7 mg/kg, range 0.36 to 0.97 mg/kg) as a tablet to 25 hypertensive patients aged 6 to 16 years are shown in Table 1 below. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and similar to historical pharmacokinetic data in adults. The principal pharmacokinetic parameters in adults and children are shown in the table below.</p> <p style="text-align: right;">4</p>	NON PRINTING DIE LINE	ALL COPY SHOULD BE .125" AWAY FROM EDGE OF DIE LINE																																		
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2"	<p><b>INSIDE PAGES</b> 3.5625"</p> <table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">Adults given 50mg once daily for 7 days N=12</th> <th colspan="2">Age 6-16 given 0.7mg/kg once daily for 7 days N=25</th> </tr> <tr> <th>Parent</th> <th>Active Metabolite</th> <th>Parent</th> <th>Active Metabolite</th> </tr> </thead> <tbody> <tr> <td>AUC<sub>0-24</sub> (ng·h/mL)</td> <td>442± 173</td> <td>168± 452</td> <td>368± 169</td> <td>186± 1076</td> </tr> <tr> <td>C<sub>max</sub> (ng/mL)<sup>a</sup></td> <td>224± 82</td> <td>212± 73</td> <td>141± 88</td> <td>222± 127</td> </tr> <tr> <td>T<sub>1/2</sub> (h)<sup>b</sup></td> <td>2.1± 0.70</td> <td>7.4± 2.4</td> <td>2.3± 0.8</td> <td>5.6± 1.2</td> </tr> <tr> <td>T<sub>peak</sub> (h)<sup>c</sup></td> <td>0.9</td> <td>3.5</td> <td>2.0</td> <td>4.1</td> </tr> <tr> <td>CL<sub>CR</sub> (mL/min)<sup>d</sup></td> <td>56± 23</td> <td>20± 3</td> <td>53± 33</td> <td>17± 8</td> </tr> </tbody> </table> <p><sup>a</sup>Mean ± standard deviation <sup>b</sup>Harmonic mean and standard deviation <sup>c</sup>Median <sup>d</sup>Median</p> <p>The bioavailability of the suspension formulation was compared with losartan tablets in healthy adults. The suspension and tablet are similar in their bioavailability with respect to both losartan and the active metabolite (see DOSAGE AND ADMINISTRATION, Preparation of Suspension)</p> <p><b>Geriatric and Gender:</b> Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).</p> <p><b>Race:</b> Pharmacokinetic differences due to race have not been studied (see also PRECAUTIONS, Race and CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke, Race).</p> <p style="text-align: right;">5</p>		Adults given 50mg once daily for 7 days N=12		Age 6-16 given 0.7mg/kg once daily for 7 days N=25		Parent	Active Metabolite	Parent	Active Metabolite	AUC <sub>0-24</sub> (ng·h/mL)	442± 173	168± 452	368± 169	186± 1076	C <sub>max</sub> (ng/mL) <sup>a</sup>	224± 82	212± 73	141± 88	222± 127	T <sub>1/2</sub> (h) <sup>b</sup>	2.1± 0.70	7.4± 2.4	2.3± 0.8	5.6± 1.2	T <sub>peak</sub> (h) <sup>c</sup>	0.9	3.5	2.0	4.1	CL <sub>CR</sub> (mL/min) <sup>d</sup>	56± 23	20± 3	53± 33	17± 8	2"	<p><b>INSIDE PAGES</b> 3.5625"</p> <p><b>Renal Insufficiency:</b> Following oral administration, plasma concentrations and AUCs of losartan and its active metabolite are increased by 50-90% in patients with mild (creatinine clearance of 50 to 74 mL/min) or moderate (creatinine clearance 30 to 49 mL/min) renal insufficiency. In this study, renal clearance was reduced by 55-85% for both losartan and its active metabolite in patients with mild or moderate renal insufficiency. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted (see WARNINGS, Hypotension - Volume-Depleted Patients and DOSAGE AND ADMINISTRATION).</p> <p><b>Hepatic Insufficiency:</b> Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-times and about 1.7-times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2-times higher. A lower starting dose is recommended for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).</p> <p><b>Drug Interactions</b> Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide. Co-administration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Co-administration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. A somewhat greater interaction (approximately 40% reduction in the AUC of active metabolite and approximately 30% reduction in the AUC of losartan) has been reported with rifampin. Fluconazole, an inhibitor of cytochrome P450 2C9, decreased the AUC of the active metabolite by approximately 40%, but increased the AUC of losartan by approximately 70% following multiple doses. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. The AUC of active metabolite following oral losartan was not affected by erythromycin, another inhibitor of P450 3A4, but the AUC of losartan was increased by 30%.</p> <p style="text-align: right;">6</p>	NON PRINTING DIE LINE	ALL COPY SHOULD BE .125" AWAY FROM EDGE OF DIE LINE
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2"	<p><b>INSIDE PAGES</b> 3.5625"</p> <p><b>Pharmacodynamics and Clinical Effects</b> <b>Adult Hypertension</b> Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.</p> <p>In a single-dose study in normal volunteers, losartan had no effects on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple-dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uterine effect leading to a minimal decrease in serum uric acid (mean decrease &lt; 0.4 mg/dL) during chronic oral administration.</p> <p>The antihypertensive effects of losartan potassium tablets were demonstrated principally in 4 placebo-controlled, 6- to 12-week trials of dosage from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50-100 mg/day) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.</p> <p>The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10- and 25-mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100 and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure, compared to placebo in the range of 5.5-10.5/5.5-7.5 mmHg, with the 150-mg dose giving no greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once-daily dosing at the same total dose. Peak (6 hour) effects were uniformly but moderately larger than trough effects, with the trough-to-peak ratio for systolic and diastolic responses 50-95% and 60-90%, respectively.</p> <p style="text-align: right;">7</p>	2"	<p><b>INSIDE PAGES</b> 3.5625"</p> <p>Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo-adjusted blood pressure reductions of 15.5/9.2 mmHg.</p> <p>Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Losartan potassium was effective in reducing blood pressure regardless of race, although the effect was somewhat less in Black patients (usually a low-rain population).</p> <p>The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.</p> <p><b>Pediatric Hypertension</b> The antihypertensive effect of losartan was studied in one trial enrolling 177 hypertensive pediatric patients aged 6 to 16 years old. Children who weighed &lt; 50 kg received 2.5, 25 or 50 mg of losartan daily and patients who weighed ≥ 50 kg received 5, 50 or 100 mg of losartan daily. Children in the lowest dose group were given losartan in a suspension formulation (see DOSAGE AND ADMINISTRATION, Preparation of Suspension). The majority of the children had hypertension associated with renal and urogenital diseases. The sitting diastolic blood pressure (SDBP) on entry into the study was higher than the 95th percentile level for the patient's age, gender, and height. At the end of three weeks, losartan reduced systolic and diastolic blood pressure, measured at trough, in a dose-dependent manner. Overall, the two higher doses (25 to 50 mg in patients &lt; 50 kg; 50 to 100 mg in patients ≥ 50 kg) reduced diastolic blood pressure by 5 to 6 mmHg more than the lowest dose used (2.5 mg in patients &lt; 50 kg; 5 mg in patients ≥ 50 kg). The lowest dose, corresponding to an average daily dose of 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy. When patients were randomized to continue losartan at the two higher doses or to placebo after 3 weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7 mmHg more than patients randomized to continuing losartan. When the low dose of losartan was randomly withdrawn, the rise in trough diastolic blood pressure was the same in patients receiving placebo</p> <p style="text-align: right;">8</p>	NON PRINTING DIE LINE	ALL COPY SHOULD BE .125" AWAY FROM EDGE OF DIE LINE																																		
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**INSIDE SINGLE PAGES**

<p>2"</p> <p>NON PRINTING DIE LINE</p>	<p>INSIDE PAGES</p> <p>3.5625"</p>	<p>2"</p> <p>ALL COPY SHOULD BE .1562" AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE</p>	<table border="1" style="width: 100%;"> <tr> <td style="width: 25%;">Study 1†</td> <td style="width: 15%;">HCTZ</td> <td style="width: 15%;">Losartan</td> <td style="width: 45%;">Lisinopril</td> </tr> <tr> <td>Cough</td> <td>25%</td> <td>17%</td> <td>69%</td> </tr> <tr> <td>Study 2††</td> <td>Placebo</td> <td>Losartan</td> <td>Lisinopril</td> </tr> <tr> <td>Cough</td> <td>35%</td> <td>29%</td> <td>62%</td> </tr> </table> <p>† Demographics = (89% caucasian, 64% female) †† Demographics = (90% caucasian, 51% female)</p> <p>These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE-inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.</p> <p>Cases of cough, including positive re-challenges, have been reported with the use of losartan in post-marketing experience. <b>Pediatric Patients:</b> No relevant differences between the adverse experience profile for pediatric patients and that previously reported for adult patients were identified.</p> <p style="text-align: right;">25</p>	Study 1†	HCTZ	Losartan	Lisinopril	Cough	25%	17%	69%	Study 2††	Placebo	Losartan	Lisinopril	Cough	35%	29%	62%	<p>2"</p> <p>NON PRINTING DIE LINE</p>	<p><b>Hypertensive Patients with Left Ventricular Hypertrophy</b> In the LIFE study, adverse events with losartan potassium were similar to those reported previously for patients with hypertension.</p> <p><b>Post-Marketing Experience</b> The following additional adverse reactions have been reported in post-marketing experience: <b>Digestive:</b> Hepatitis (reported rarely). <b>General Disorders and Administration Site Conditions:</b> Malaise. <b>Hemic:</b> Thrombocytopenia (reported rarely). <b>Hypersensitivity:</b> Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schönlein purpura, has been reported. Anaphylactic reactions have been reported. <b>Metabolic and Nutrition:</b> Hyperkalemia, hyponatremia have been reported with losartan. <b>Musculoskeletal:</b> Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers. <b>Nervous system disorders:</b> Dysgeusia</p> <p style="text-align: right;">26</p>	<p>2"</p> <p>ALL COPY SHOULD BE .1562" AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE</p>
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<p>ALL COPY SHOULD BE .125" AWAY FROM EDGE OF DIE LINE</p> <p>INSIDE PAGES</p> <p>3.5625"</p>	<p>ALL COPY SHOULD BE .125" AWAY FROM EDGE OF DIE LINE</p> <p>INSIDE PAGES</p> <p>3.5625"</p>	<p>2"</p> <p>NON PRINTING DIE LINE</p>	<p>No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.</p> <p><b>Pediatric Hypertensive Patients ≥6 years of age</b> The usual recommended starting dose is 0.7 mg/kg once daily (up to 50 mg total) administered as a tablet or a suspension (see Preparation of Suspension). Dosage should be adjusted according to blood pressure response. Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied in pediatric patients. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Pharmacodynamics and Clinical Effects, and WARNINGS, Hypotension - Volume-Depleted Patients.) Losartan potassium is not recommended in pediatric patients &lt;6 years of age or in pediatric patients with glomerular filtration rate &lt;30 mL/min/1.73 m<sup>2</sup> (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Pharmacodynamics and Clinical Effects, and PRECAUTIONS). <b>Preparation of Suspension (for 200 mL of a 2.5 mg/mL suspension)</b> Add 10 mL of Purified Water USP to an 8 ounce (240 mL) amber polyethylene terephthalate (PET) bottle containing ten 50 mg losartan potassium tablets. Immediately shake for at least 2 minutes. Let the concentrate stand for 1 hour and then shake for 1 minute to disperse the tablet contents. Separately prepare a 50/50 volumetric mixture of Ora-Plus™ and Ora-Sweet SF™. Add 100 mL of the 50/50 Ora-Plus™/Ora-Sweet SF™ mixture to the tablet and water slurry in the PET bottle and shake for 1 minute to disperse the ingredients. The suspension should be refrigerated at 2-8°C (36-46°F) and can be stored for up to 4 weeks. Shake the suspension prior to each use and return promptly to the refrigerator. <b>Hypertensive Patients with Left Ventricular Hypertrophy</b> The usual starting dose is 50 mg of losartan potassium tablets once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of losartan potassium should be increased to 100 mg once daily followed by an increase in hydrochlorothiazide</p> <p style="text-align: right;">29</p>	<p>2"</p> <p>NON PRINTING DIE LINE</p>	<p>to 25 mg once daily based on blood pressure response (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke).</p> <p style="text-align: center;"><b>HOW SUPPLIED</b></p> <p style="text-align: center;"><b>Losartan Potassium Tablets USP 25 mg</b></p> <p>White, Round -shaped, biconvex tablets with "APO" debossed on one side and "LS" over "25" on the other side. Supplied in the following presentations: Bottles of 30 (NDC 60505-3160-3) Bottles of 90 (NDC 60505-3160-9) Bottles of 1000 (NDC 60505-3160-8) Unit dose Blisters of 100 (10x10s) (NDC 60505-3160-0)</p> <p style="text-align: center;"><b>Losartan Potassium Tablets USP 50 mg</b></p> <p>White, Round -shaped, biconvex tablets with "APO" debossed on one side and "LS" over "50" on the other side. Supplied in the following presentations: Bottles of 30 (NDC 60505-3161-3) Bottles of 90 (NDC 60505-3161-9) Bottles of 1000 (NDC 60505-3161-8) Unit dose Blisters of 100 (10x10s) (NDC 60505-3161-0)</p> <p style="text-align: right;">30</p>	<p>2"</p> <p>NON PRINTING DIE LINE</p>																
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## FRONT LEAFLET

FRONT PANEL # 1

ALL COPY BE 0.125" (3.175mm) AWAY FROM EDGE OF DIELINE ON THE LEFT & RIGHT SIDES

2.0"

**PATIENT INFORMATION**  
**Losartan Potassium Tablets USP**  
**25 mg, 50 mg, 100 mg**  
**ⓘ Only**

Read the Patient Information that comes with Losartan Potassium Tablets before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition and treatment.

**What is the most important information I should know about Losartan Potassium Tablets?**

**Do not take Losartan Potassium Tablets if you are pregnant or plan to become pregnant. Losartan Potassium Tablets can harm your unborn baby causing injury and even death. Stop taking Losartan Potassium Tablets if you become pregnant and call your doctor right away.** If you plan to become pregnant, talk to your doctor about other treatment options before taking Losartan Potassium Tablets.

**What is Losartan Potassium Tablets?**

Losartan Potassium Tablets is a prescription medicine called an angiotensin receptor blocker (ARB). It is used:

- Alone or with other blood pressure medicines to lower high blood pressure (hypertension).
- To lower the chance of stroke in patients with high blood pressure and a heart problem called left ventricular hypertrophy. Losartan Potassium Tablets may not help Black patients with this problem.

Losartan Potassium Tablets has not been studied in children less than 6 years old or in children with certain kidney problems.

**High Blood Pressure (hypertension).** Blood pressure is the force in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. Losartan Potassium Tablets can help your blood vessels relax so your blood pressure is lower.

**Left Ventricular Hypertrophy (LVH)** is an enlargement of the walls of the left chamber of the heart (the heart's main pumping chamber). LVH can happen from several things. High blood pressure is the most common cause of LVH.

**Who should not take Losartan Potassium Tablets?**

- Do not take Losartan Potassium Tablets if you are allergic to any of the ingredients in Losartan Potassium Tablets. See the end of this leaflet for a complete list of ingredients in Losartan Potassium Tablets.

**What should I tell my doctor before taking Losartan Potassium Tablets?**

Tell your doctor about all of your medical conditions including if you:

- Are pregnant or planning to become pregnant. See "What is the most important information I should know about Losartan Potassium Tablets?"
- Are breast-feeding. It is not known if Losartan Potassium Tablets passes into your breast milk. You should choose either to take Losartan Potassium Tablets or breast-feed, but not both.

- are vomiting a lot or having a lot of diarrhea
- have liver problems
- have kidney problems

**Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.**

Losartan Potassium Tablets and certain other medicines may interact with each other. Especially tell your doctor if you are taking:

- potassium supplements
- salt substitutes containing potassium
- water pills (diuretics)
- Medicines used to treat pain and arthritis, called non-steroidal anti-inflammatory drugs NSAIDS.

**How should I take Losartan Potassium Tablets?**

- Take Losartan Potassium Tablets exactly as prescribed by your doctor. Your doctor may change your dose if needed.

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BACK OF FRONT PANEL #1

ALL COPY BE 0.125" (3.175mm) AWAY FROM EDGE OF DIELINE ON THE LEFT & RIGHT SIDES

2.0"

- Losartan Potassium Tablets can be taken with or without food.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Just take the next dose at your regular time.
- If you take too much Losartan Potassium Tablets, call your doctor or Poison Control Center, or go to the nearest hospital emergency room right away.

**What are the possible side effects of Losartan Potassium Tablets?**

Losartan Potassium Tablets may cause the following side effects that may be serious:

- Injury or death of unborn babies.** See "What is the most important information I should know about Losartan Potassium Tablets?"
- Low blood pressure (hypotension).** Low blood pressure may cause you to feel faint or dizzy. Lie down if you feel faint or dizzy. Call your doctor right away.
- Allergic reaction.** Symptoms of an allergic reaction are swelling of the face, lips, throat or tongue. Get emergency medical help right away and stop taking Losartan Potassium Tablets
- For people who already have kidney problems, you may see a worsening in how well your kidneys work.** Call your doctor if you get swelling in your feet, ankles, or hands, or unexplained weight gain.

The most common side effects of Losartan Potassium Tablets in people with high blood pressure are:

- "colds" (upper respiratory infection)
- dizziness
- stuffy nose
- back pain

Tell your doctor if you get any side effect that bothers you or that won't go away. This is **not** a complete list of side effects. For a complete list, ask your doctor or pharmacist.

**How do I store Losartan Potassium Tablets?**

- Store Losartan Potassium Tablets at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature], Dispense in a tight, light – resistant container (see USP).
- Keep Losartan Potassium Tablets in a tightly closed container that protects the medicine from light.
- Keep Losartan Potassium Tablets and all medicines out of the reach of children.

**General information about Losartan Potassium Tablets**

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Losartan Potassium Tablets for a condition for which it was not prescribed. Do not give Losartan Potassium Tablets to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about Losartan Potassium Tablets. If you would like more information,

talk with your doctor. You can ask your pharmacist or doctor for information about Losartan Potassium Tablets that is written for health professionals.

**What are the ingredients in Losartan Potassium Tablets?**

**Active ingredients:** Losartan potassium  
**Inactive ingredients:** Lactose monohydrate, microcrystalline cellulose, pregelatinised starch, magnesium stearate, hypromellose 6 cp, hydroxy propyl cellulose, titanium dioxide and carnauba wax.

**ⓘ Only**

**APOTEX CORP.**

**Losartan Potassium Tablets USP 25 mg, 50 mg and 100 mg**

Manufactured by: Apotex Research Pvt. Ltd. Bangalore - 560 099, India  
Manufactured for: Weston Corp. Weston, Florida 33326

Revised: January 2010

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Pantone Colours:		Previous Code:	N/A		
Dimensions/Dieline#:	66 mm x 287 mm (2.598" X 11.299") Flat 66 mm x 145 mm (2.598" x 5.709") Folded			Prepared by:	 @
				Date:	JAN 22, 2010

PAGE 1 OF 1

**FRONT PPI PAD**



**PATIENT INFORMATION**  
**Losartan Potassium Tablets USP**  
**25 mg, 50 mg, 100 mg**  
**R Only**

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**NON PRINTING AREA**

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Losartan Potassium Tablets and certain other medicines may interact with each other. Especially tell your doctor if you are taking:

- potassium supplements
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- Medicines used to treat pain and arthritis, called non-steroidal anti-inflammatory drugs NSAIDS.



FRONT PANEL #1

FRONT PPI PAD

FRONT PANEL #2



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- If you take too much Losartan Potassium Tablets, call your doctor or Poison Control Center, or go to the nearest hospital emergency room right away.

**What are the possible side effects of Losartan Potassium Tablets?**

Losartan Potassium Tablets may cause the following side effects that may be serious:

- **Injury or death of unborn babies.** See "What is the most important information I should know about Losartan Potassium Tablets?"
- **Low blood pressure (hypotension).** Low blood pressure may cause you to feel faint or dizzy. Lie down if you feel faint or dizzy. Call your doctor right away.
- **Allergic reaction.** Symptoms of an allergic reaction are swelling of the face, lips, throat or tongue. Get emergency medical help right away and stop taking Losartan Potassium Tablets.
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- Keep Losartan Potassium Tablets away from children out of the reach of children.

**General information about Losartan Potassium Tablets**

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**R Only**

**APOTEX CORP.**  
**Losartan Potassium Tablets USP 25 mg, 50 mg and 100 mg**

Manufactured by:  
Apotex Research Pvt. Ltd.  
Apotex Corp.  
Weston,  
Florida 33226  
India

Revised: January 2010

P P P D

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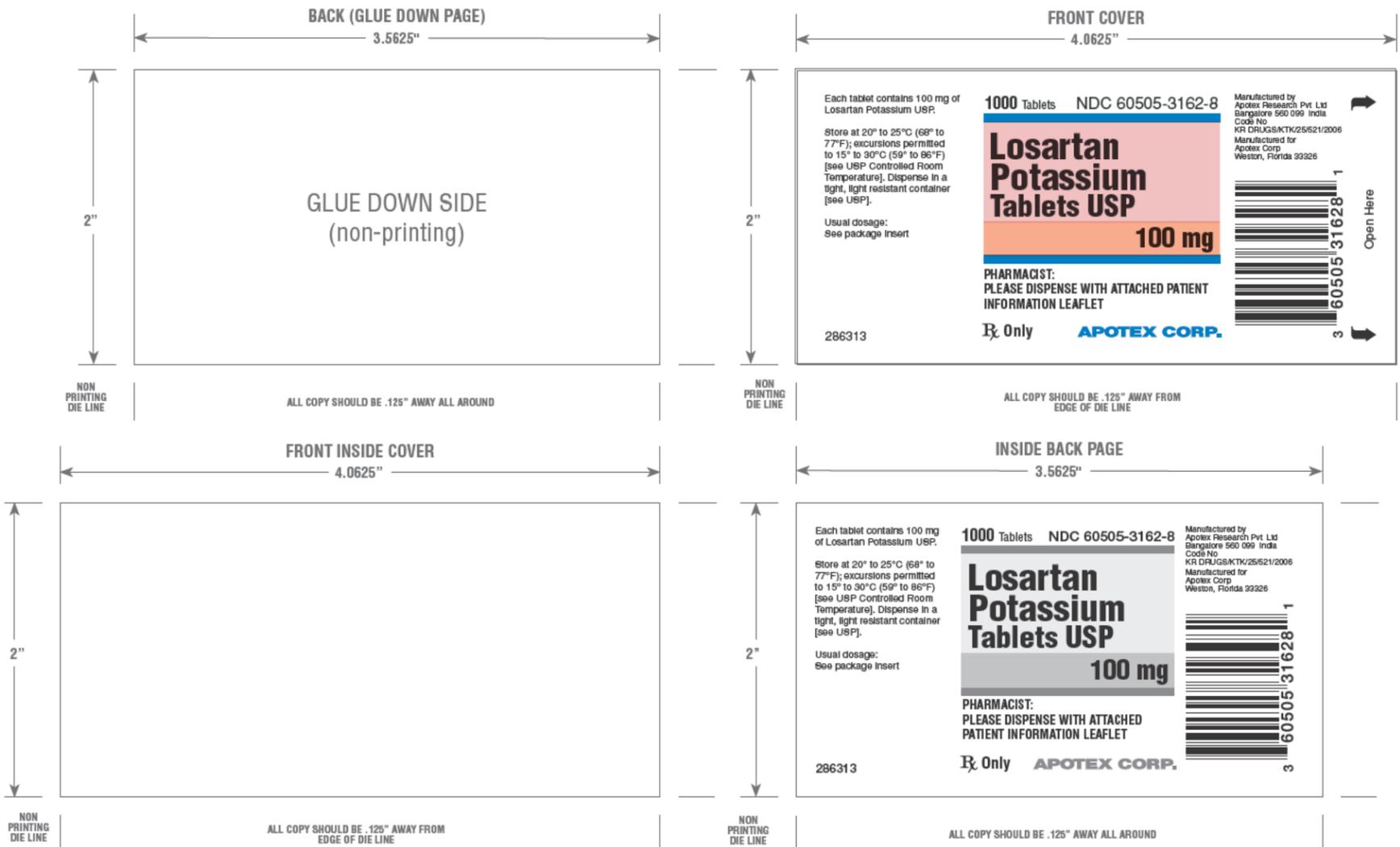
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WHEN A PULL-OUT IS BEING UTILIZED IN A BOOKLET, IT IS TO BE INSERTED IN THE CENTER (b) (4) SIZE COUNT AND ONCE FOR ALL OTHER SIZE COUNTS

**COMPOSITE**



**COVER**





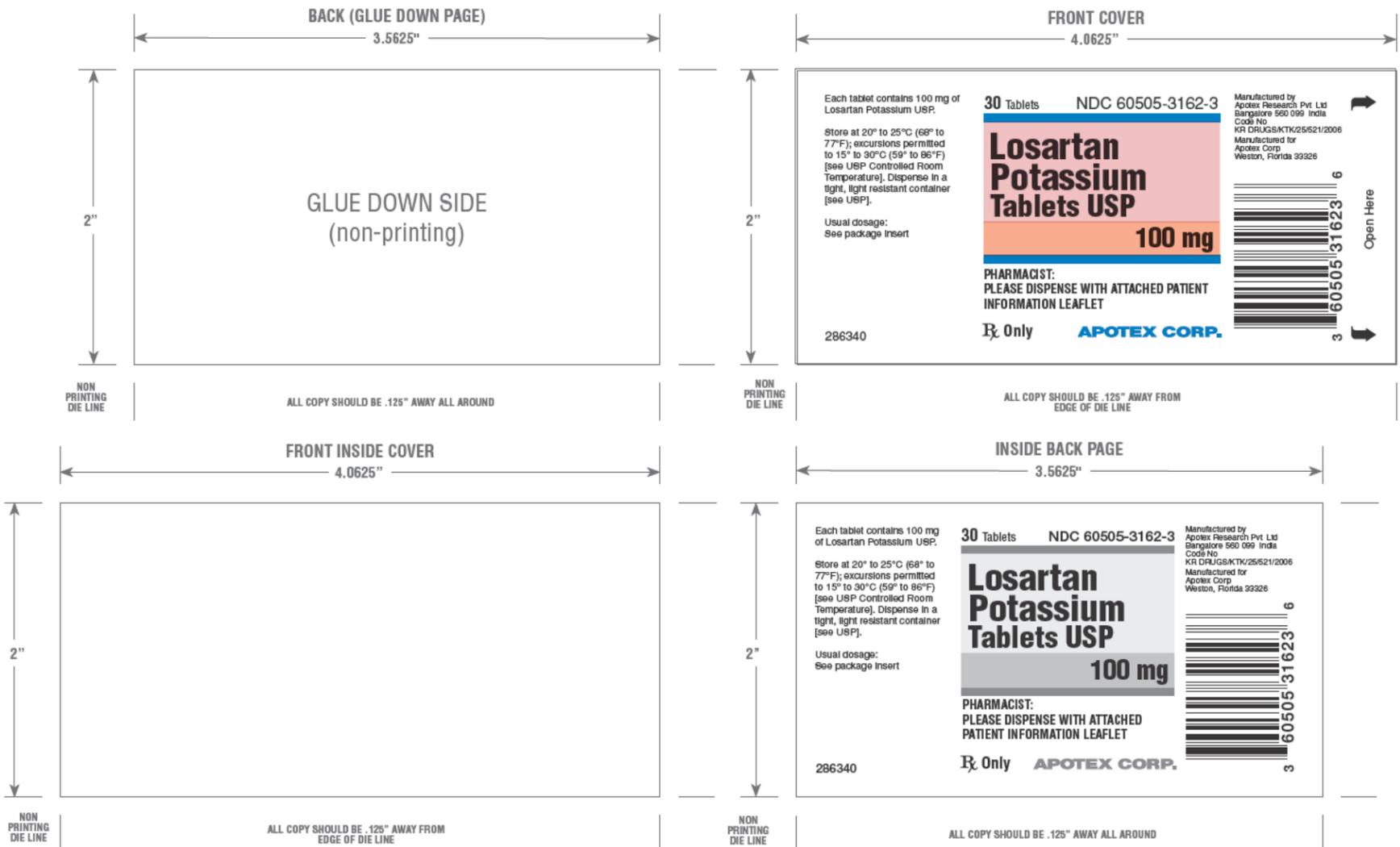
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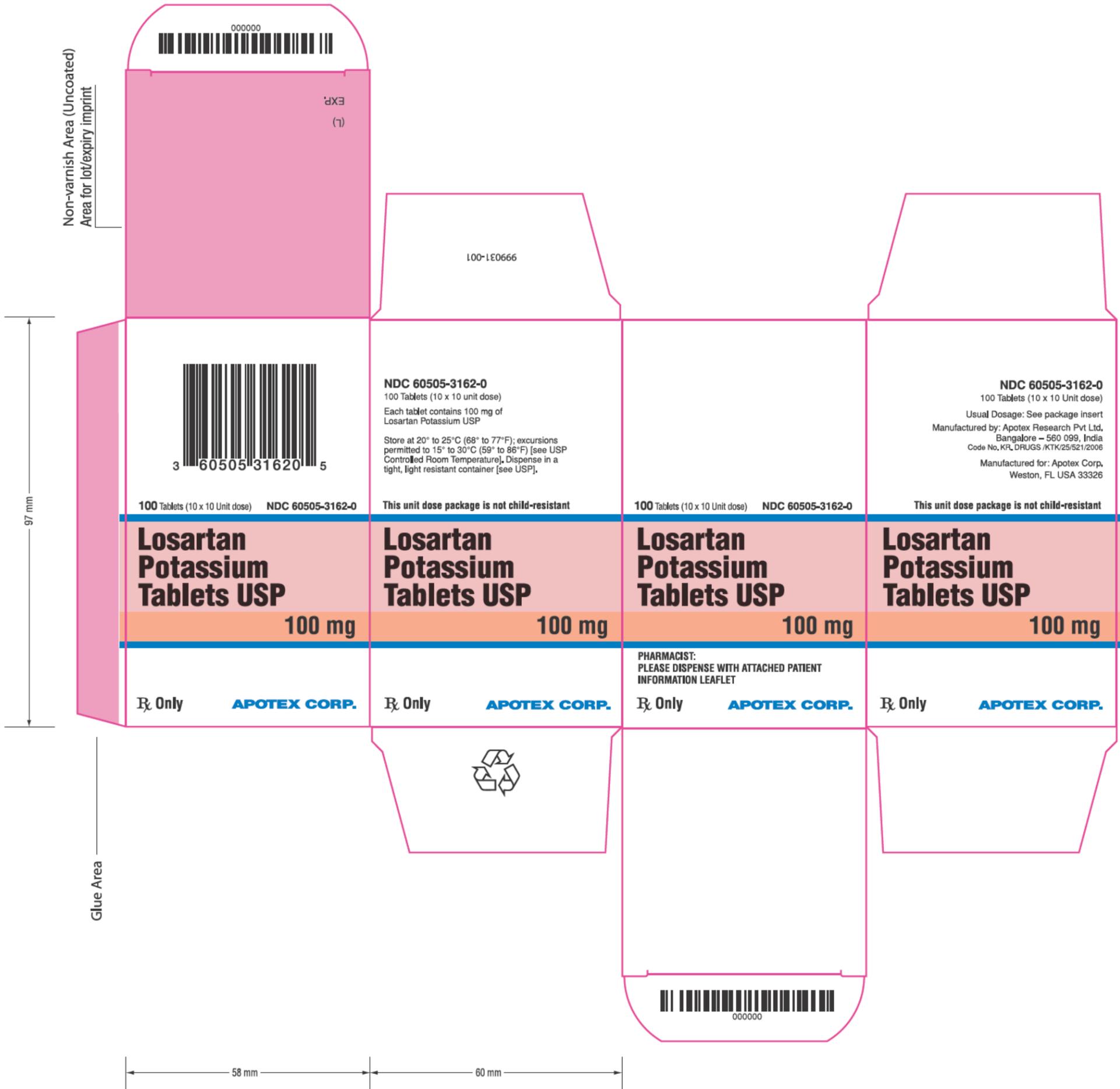
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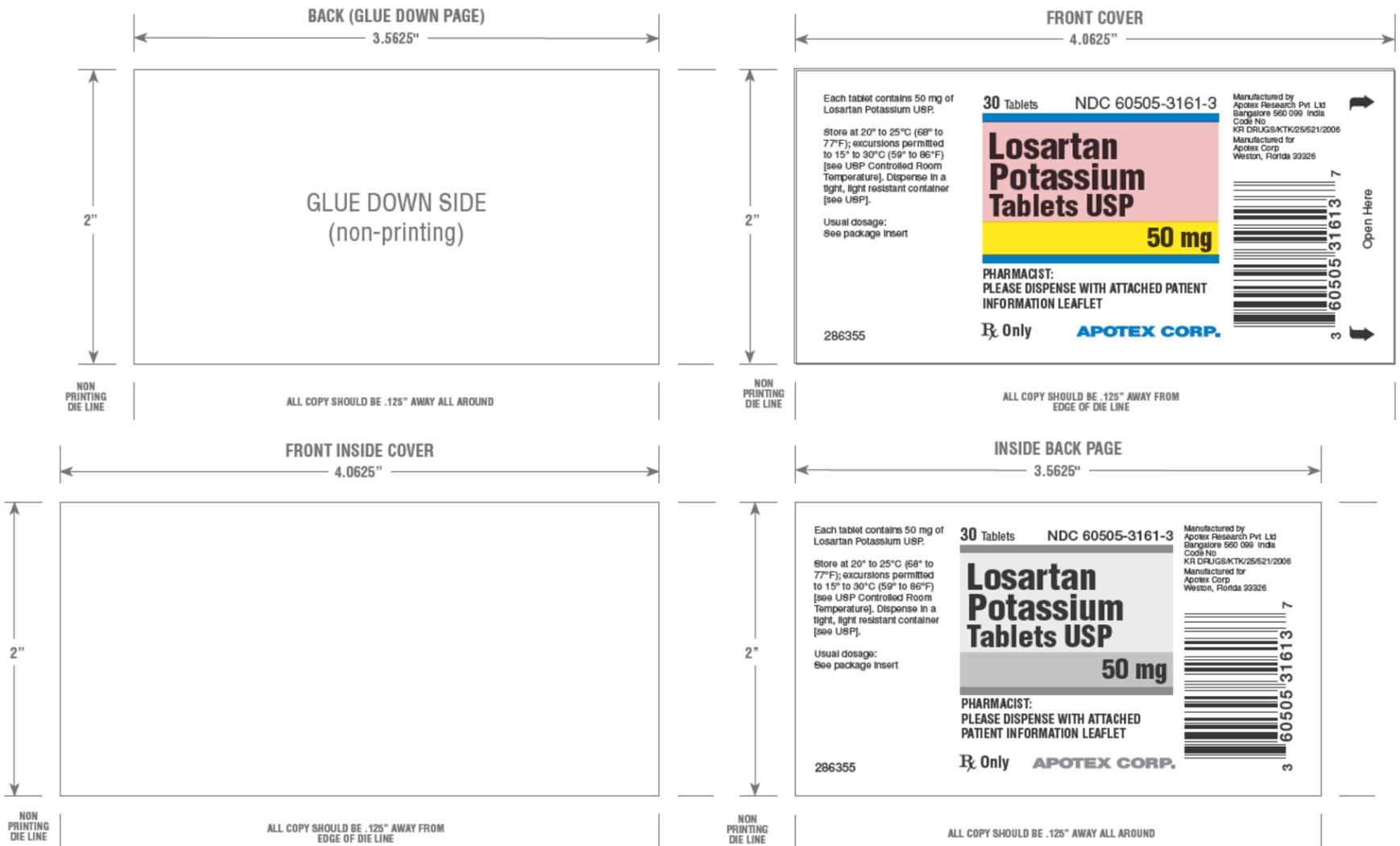
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WHEN A PULL-OUT IS BEING UTILIZED IN A BOOKLET, IT IS TO BE INSERTED IN THE CENTER (b) (4) SIZE COUNT AND ONCE FOR ALL OTHER SIZE COUNTS

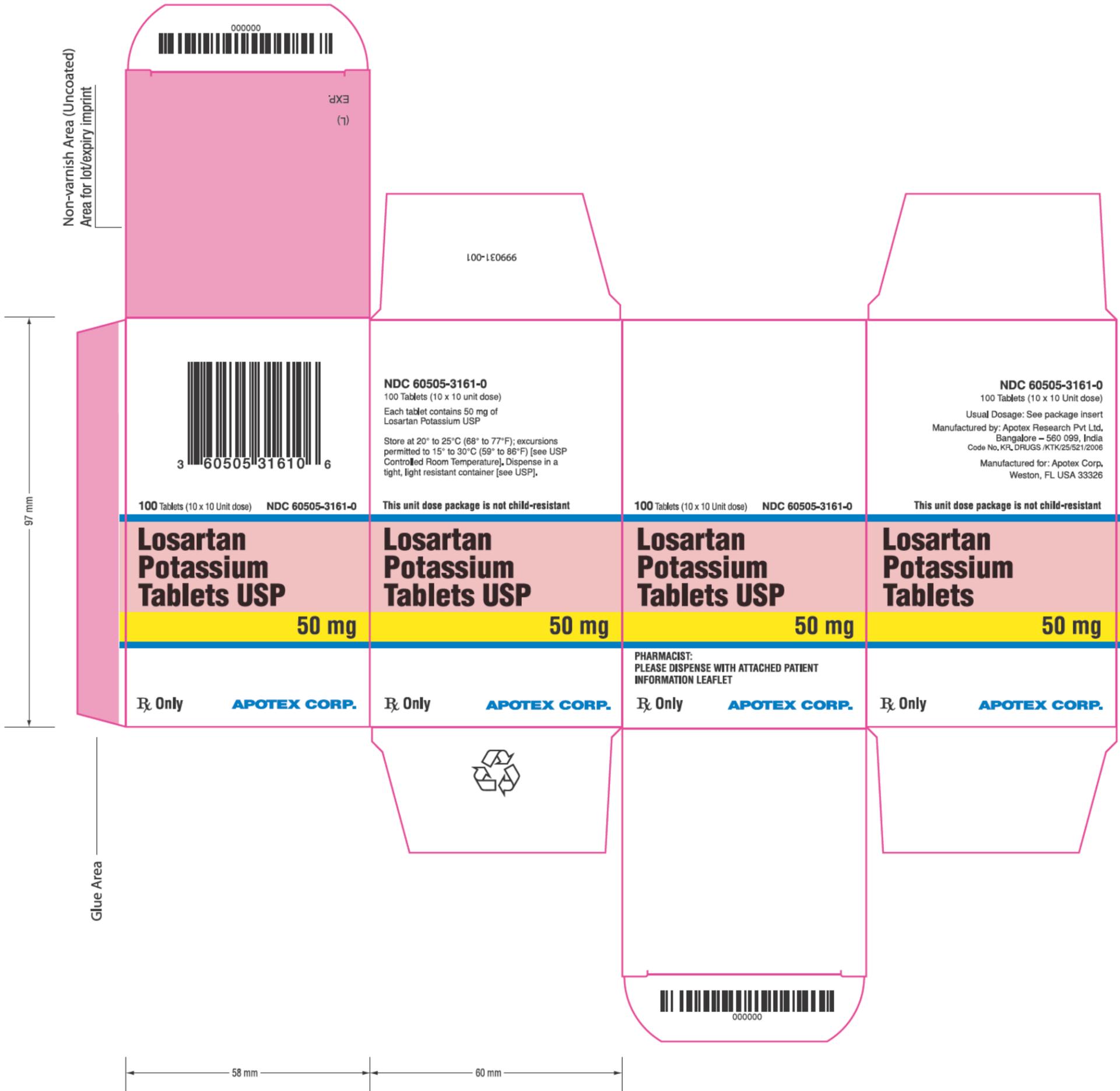
**COMPOSITE**



**COVER**



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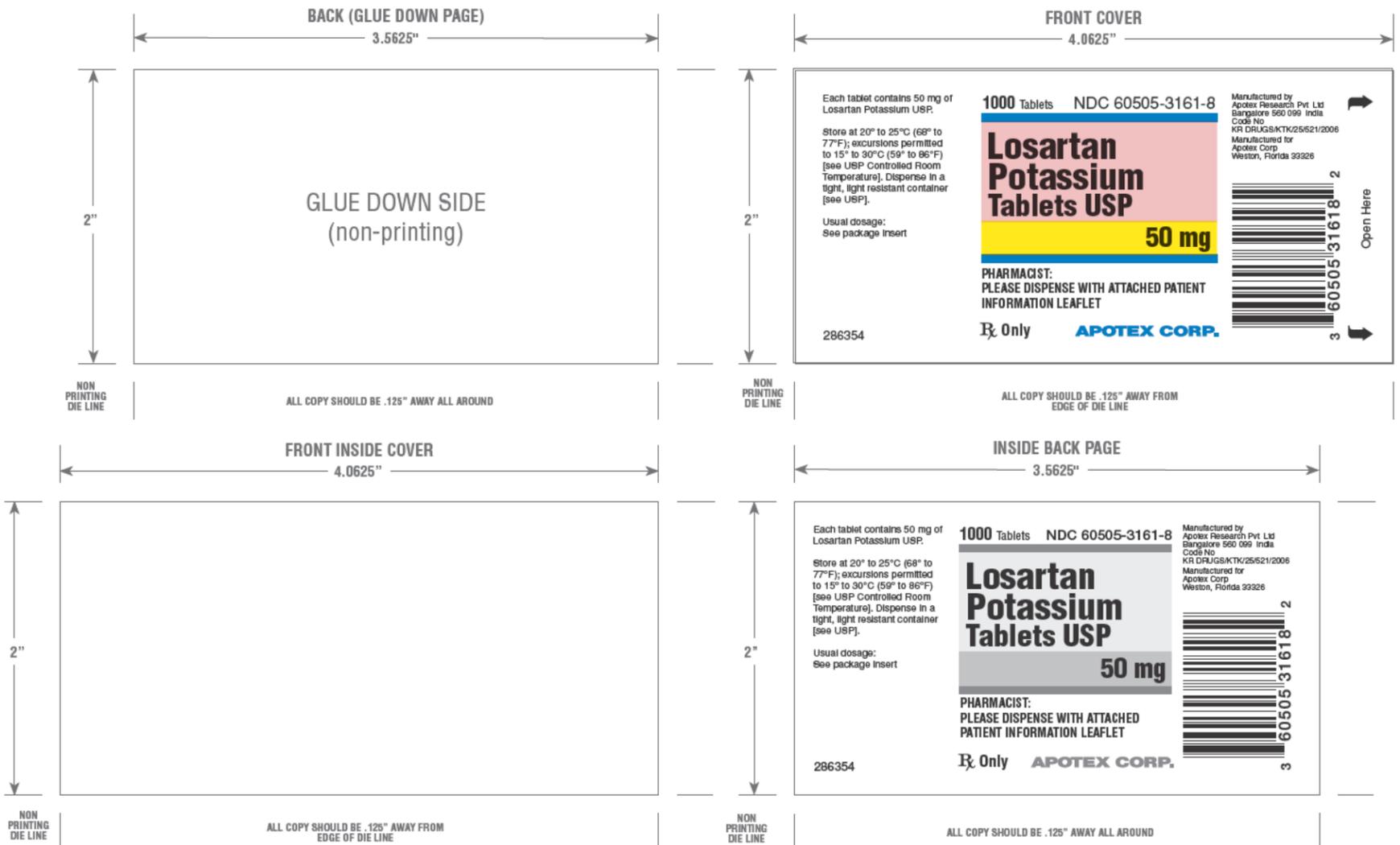
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**COVER**



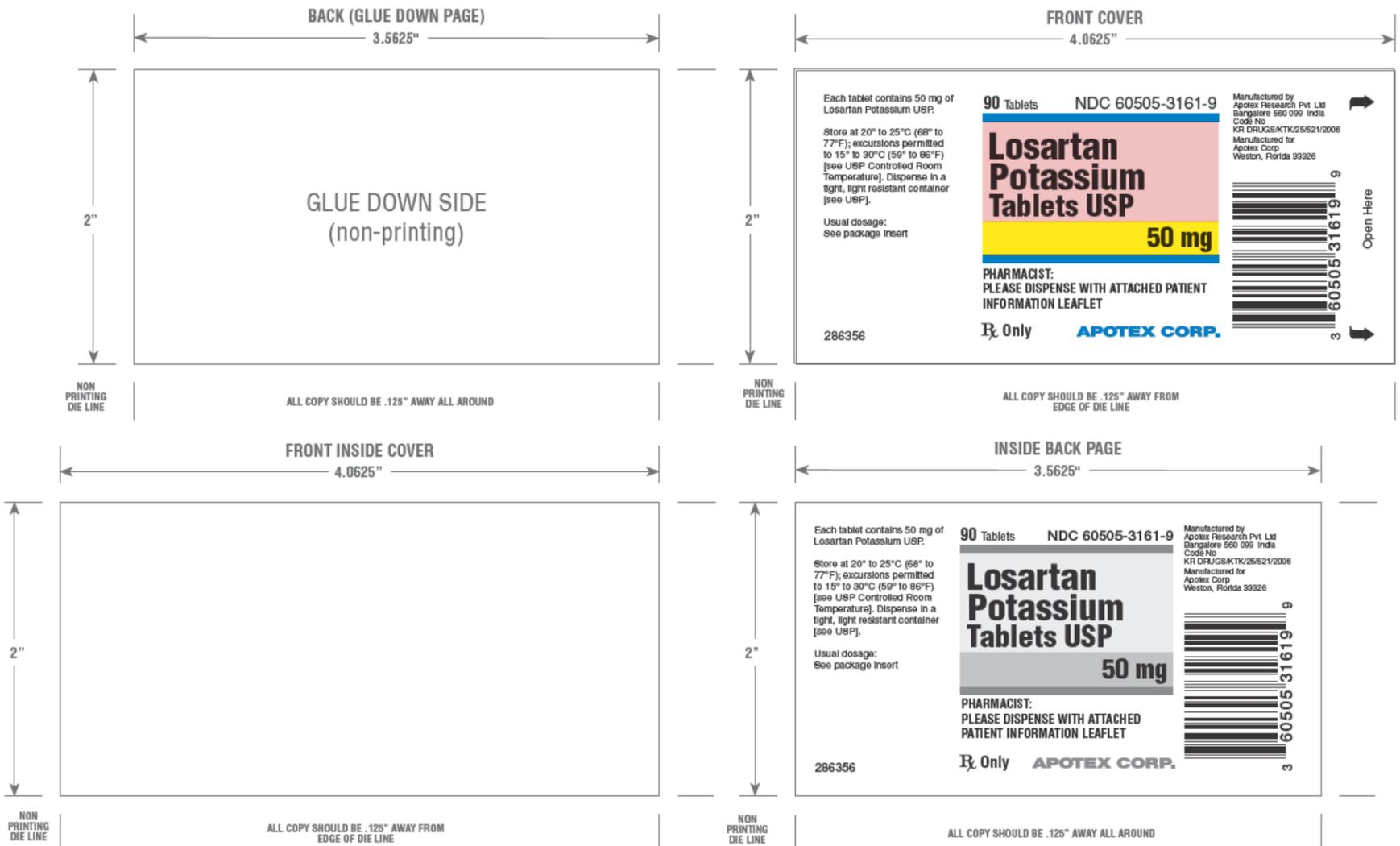
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**COMPOSITE**



**COVER**



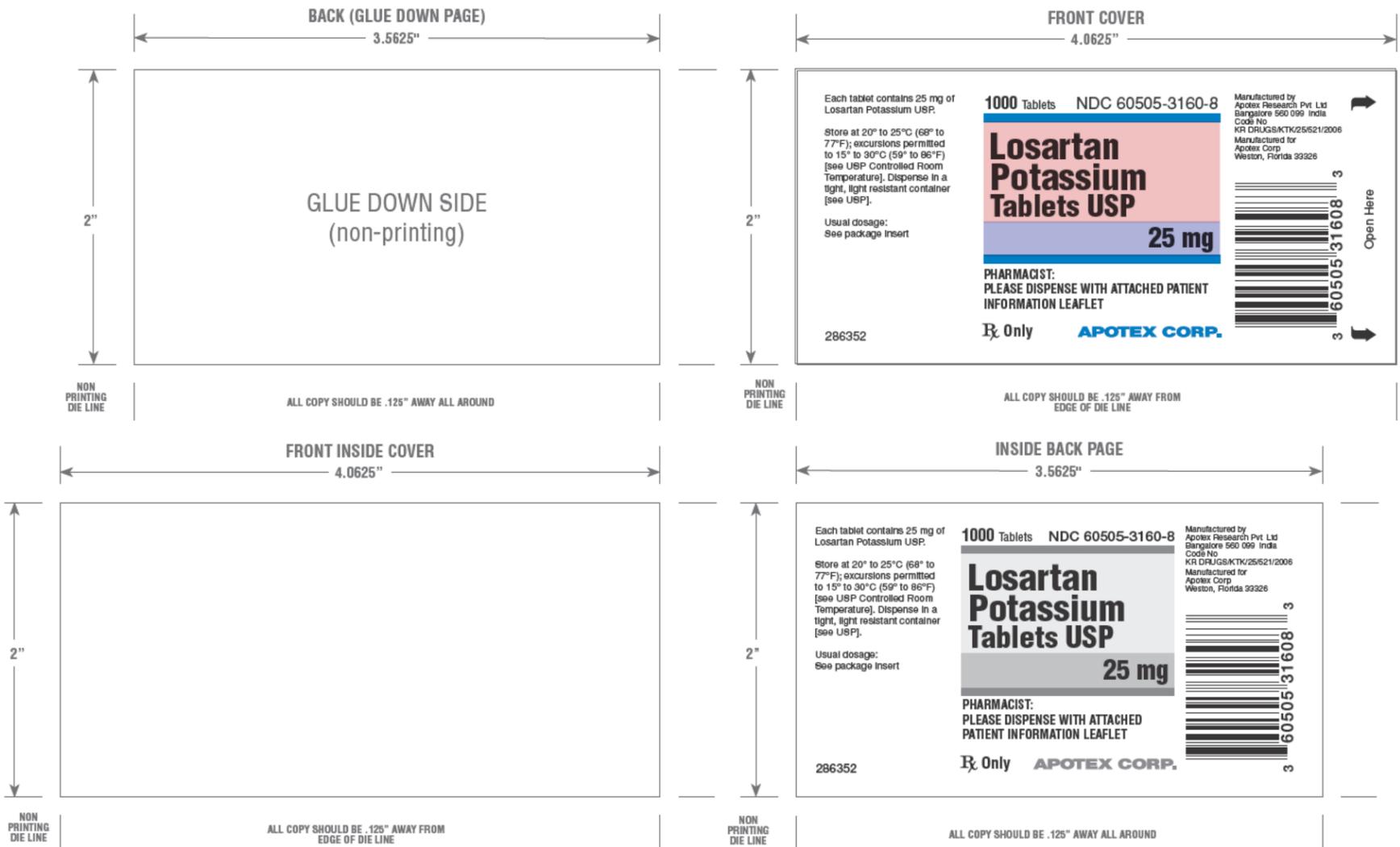
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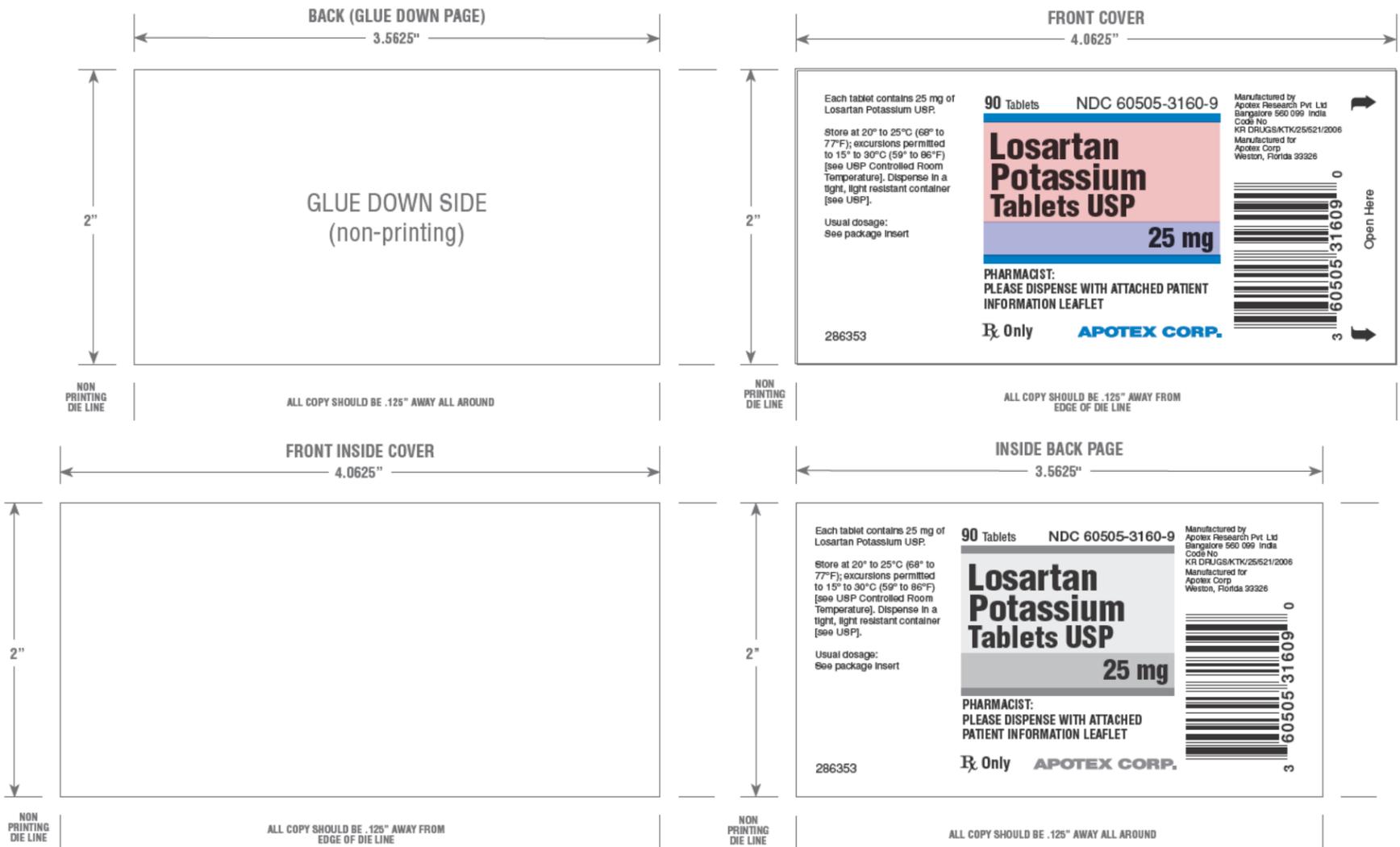
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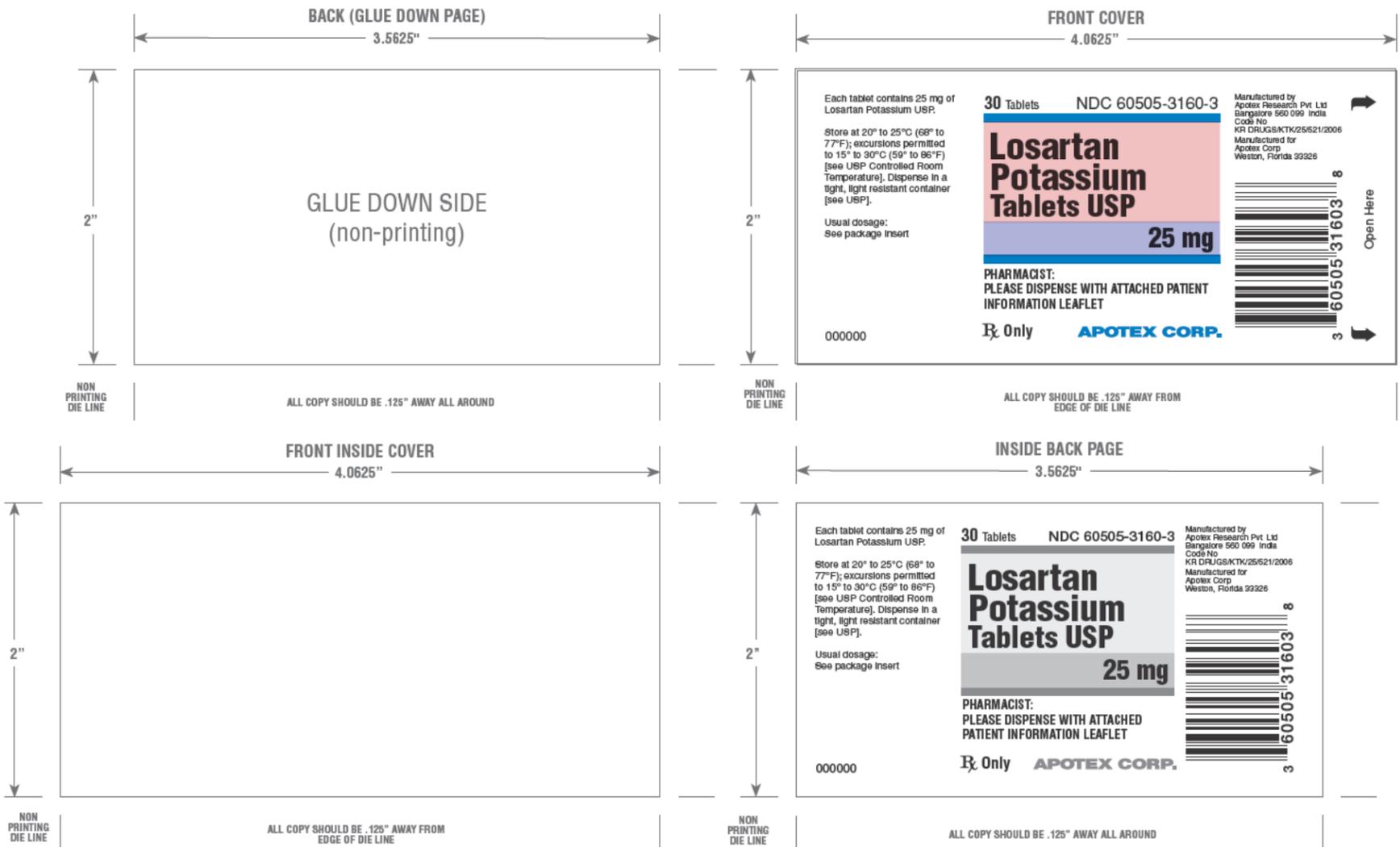
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WHEN A PULL-OUT IS BEING UTILIZED IN A BOOKLET, IT IS TO BE INSERTED IN THE CENTER **(b) (4)** SIZE COUNT AND ONCE FOR ALL OTHER SIZE COUNTS

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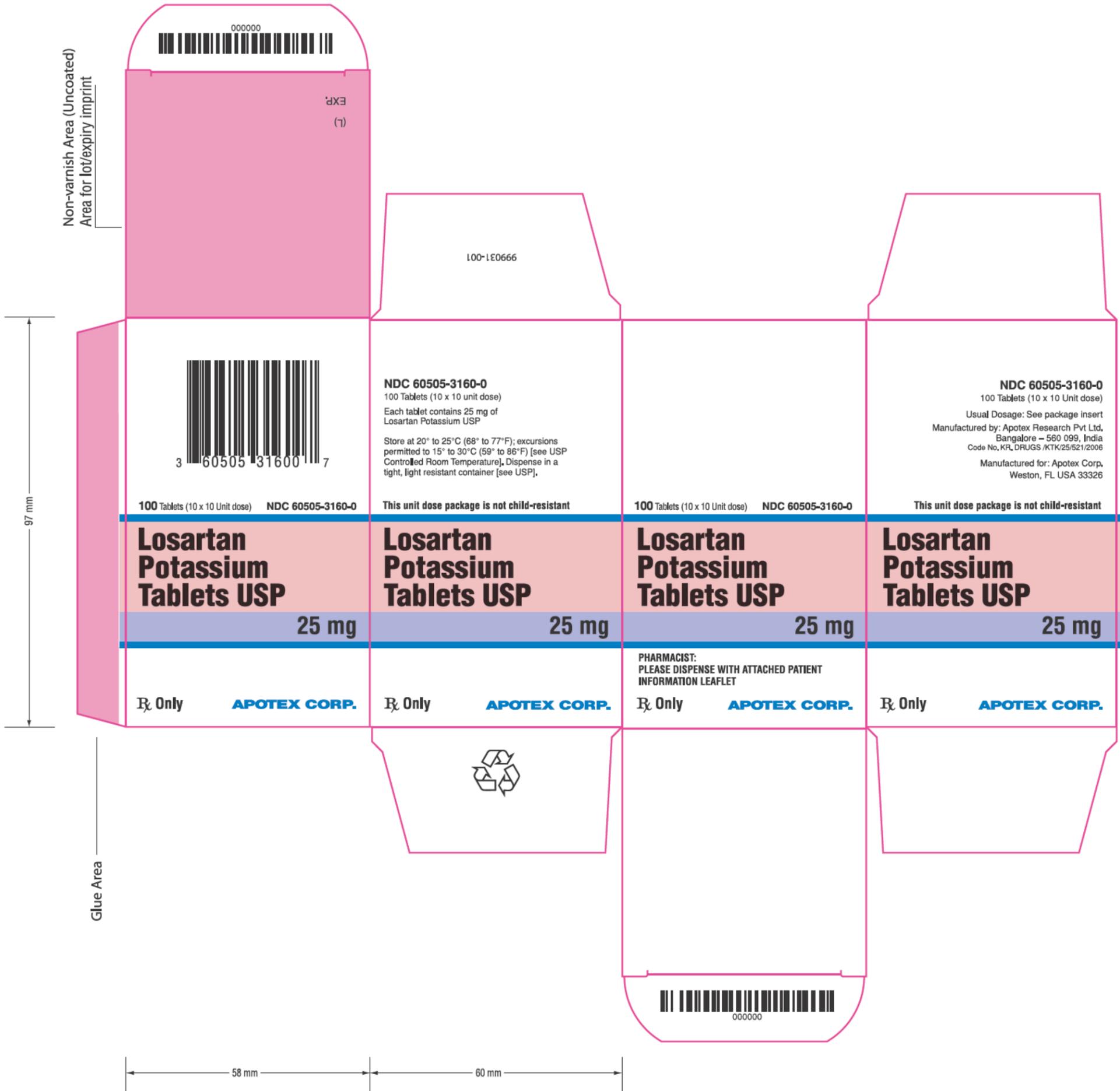


**COVER**



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Pantone Colours		
Dimensions/Dieline#: 999031-001 58mm x 60mm x 97mm	Minimum Font Size:	Prepared by: (b) (6) Date: JAN 8, 2010

NON VARNISH AREA



**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 90-790**

**LABELING REVIEWS**

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

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ANDA Number: 90-790  
Date of Submission: August 27, 2008  
Applicant's Name: Apotex Corporation  
Established Name: Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg tablets

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**Labeling Deficiencies:**

**1. GENERAL COMMENTS**

- a. Referring to the [REDACTED] <sup>(b) (4)</sup> proposed count bottles, **the Agency does NOT approve bulk labeling.** Please delete this count bottle from your HOW SUPPLIED section.
- b. We note that you did NOT include information related to the "Preparation of the suspension" and/or the suspension in the labeling. This is not protected information. Please revise and/or comment.

**2. CONTAINER – Bottles of 30s, 90s and 1000s**

Side Panel: Revise to read

Each tablet contains:  
xx mg Losartan Potassium USP

**3. CARTON – 100 (10X10 unit-dose blisters)**

**See comment above.**

**4. Unit-Dose Blisters – 10s**

Satisfactory in **draft** as of the August 27, 2008 electronic submission

**5. PACKAGE INSERT and PATIENT INFORMATION LEAFLET**

- a. Please revise your labeling to be in accord with the most recently approved labeling for the reference listed drug, Cozaar® Tablets (NDA 20-386/S-049; June 4, 2009).
- b. See comment under CONTAINER above

Submit your revised labels and labeling electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - [http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_17](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

**6. Revisions needed post-approval: None**

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No  
What is the RLD on the 356(h) form: Cozaar® Tablets  
NDA Number: 20-386/S-049  
NDA Drug Name: Cozaar® Tablets  
NDA Firm: Merck & Co. Inc.  
Date of Approval of NDA Insert and supplement: NDA 20-386/S-049; June 4, 2009  
Has this been verified by the MIS system for the NDA? Yes  
Was this approval based upon an OGD labeling guidance? No  
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Cozaar® Tablets.

**FOR THE RECORD**

1. The model labeling **was based** on the most recently approved labeling for this drug product, Cozaar® (NDA 20-386/S-049; approved June 4, 2009).
2. Storage/Dispensing Conditions:  
NDA: Store at 25°C (77°F), excursions permitted to 15 – 30°C (59 – 86°F)[See USP Controlled Room temperature].  
ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]. (b) (4)  
USP: NOT USP and NOT PF.  
NDA: Dispense in a well-closed container as defined in the USP.  
ANDA: Dispense in a tight, light resistant container.
3. **In July of 2007, this decision (below) was reversed by Peter Rickman and John Grace. (Previous submission) This applies to this application even though different patent certifications filed, they are the same pertaining to this Indication**  
After further review on 1/23/2006, Peter Rickman and John Grace decided that the exclusivity “Treatment of Type II Diabetic Neuropathy” (Use code I-383), should be included in the labeling. It was to loosely associated with patent #5210079\*PED “(U-496- Method for Treating Chronic Renal Failure).
4. Product Line:  
The innovator markets their product in three strengths (25 mg, 50 mg and 100 mg). They are packaged in bottles of 30, 90, 100 and 1000 tablets and unit-dose cartons of 100 tablets  
The applicant proposes to market their product in bottles of 30s, 90s and 1000s as well as unit-dose cartons of 100 tablets for all strengths.

**5. Patent/ Exclusivities:**

**NDA: 20-386**

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5138069*PED	<i>Feb. 11, 2010</i>			Paragraph III	None
5153197*PED	<i>April 6, 2010</i>	U-3	Treatment of Hypertension	Paragraph III	None
5210079*PED	<i>November 11, 2010</i>	U-496	Method for Treating Chronic Renal Failure	MOU	None
5608075*PED	<i>Sept 4, 2014</i>			Paragraph IV	

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**Exclusivity Data– NDA 20-386**

Code	Reference	Expiration	Labeling Impact
I-383	Treatment of Type II Diabetic Nephropathy	Sept. 17, 2005	Needs to be carved out of the labeling U-496 listed in FTR as per Peter Rickman

6. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, (no tablets are scored as is the RLD not scored)

Dosage Strength	Tablet Description
25 mg	White, round, biconvex tablets with 'APO' debossed on one side and 'LS' over '25' on the other side.
50 mg	White, round, biconvex tablets with 'APO' debossed on one side and 'LS' over '50' on the other side.
100 mg	White, oval shaped, biconvex tablets with 'APO' debossed on one side and 'LS 100' on the other side.

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and The components and quantitative composition of Losartan Potassium Tablets 25 mg, 50 mg and 100 mg is summarized below:

**Composition and compositions: Not satisfactory per chemistry**

**What are the components and composition of the final product? What is the function of each excipient?**

The quantitative composition of each component in the Losartan Potassium Tablets is listed below:

Components	Function	%w/w	mg/25 mg Tablet	mg/50 mg Tablet	mg/100 mg Tablet
Losartan Potassium USP (b) (4)	Active Ingredient	27.23	25.00	50.00	100.00
(b) (4)					

(b) (4)				
Coated Tablet weight	100%	91.80	183.60	367.20

(b) (4)

**The drug substance Losartan Potassium consist of 27.33% of the weight of the tablets.**

The composition of Film coating material ( (b) (4) ) is in the table below.

Ingredients	(b) (4)		
	mg/tablet		
	25 ma*	50 ma**	100mg***

(b) (4)

**c) Description of Accompanying Reconstitution Diluent(s): N/A**

**d) Type of Container and Enclosure used for Dosage Form:**

As indicated by stability studies the proposed Losartan Potassium Tablets 25 mg, 50 mg and 100 mg are packed into HDPE bottles and closures.

These container/closure systems meet all current established acceptance criteria including USP General Chapter <661> and USP General Chapter <671> and have been approved for use with the firm's other products.

8. All manufacturing will be done by:  
 Apotex Research Pvt Ltd.  
 Plot No 1, Bommasandra Industrial Area, 4th Phase  
 Bommasandra Industrial Estate  
 Bangalore, India- 560 099

9. Container/Closure -

The Losartan Potassium Tablets 25 mg, 50 mg and 100 mg are packaged in the container and closure systems as described in the below table.

Count	Strength	Container Closure System
30's	25 mg	75 cc round, white, opaque, HDPE bottle with 38mm polypropylene blue CRC cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	
	100 mg	
90's	25 mg	?
	50 mg	
	100 mg	
(b) (4)		
1000's	25 mg	250 cc round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	400 cc round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
	100 mg	(b) (4) (625 cc for commercial batches) round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) (b) (4) liner and Lift and Peel induction seal. (b) (4) (625 cc for commercial batches) round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
100 U/D Blisters	25 mg 50 mg 100 mg	Blister packs comprising of white opaque (b) (4) film and aluminium foil. The blister packs will be packed in cartons containing 10 strips of 10 tablets.

Blister packaging of the exhibit and stability batch presented in this ANDA is 10 strips of 10 tablets.

(b) (4)  
The opaque container should be adequate enough to protect the drug product from light damage.

**Chemistry Deficiency:** (b) (4)

Date of Review: 8/19/09  
Primary Reviewer: Jim Barlow

Date of Submission: August 27, 2008  
Date:

Team Leader: Koung Lee

Date:

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- ANDA 90790	----- ORIG 1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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

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/s/

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JAMES T BARLOW  
08/20/2009

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

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ANDA Number: 090790  
Date of Submission: September 8, 2009  
Applicant's Name: Apotex Inc.  
Established Name: Losartan Potassium Tablets USP, 25 mg, 50 mg and 100 mg tablets

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**Labeling Deficiencies:**

**1. GENERAL COMMENTS**

- a. Did your firm submit stability data supporting this suspension storage in your Chemistry data? Please comment. (Also, please note that this information (suspension) cannot be carved out of your labeling since it is not protected.)
- b. Please note that Losartan Potassium Tablets are now subject to a "USP" monograph. Please revise to include this designation in your labeling where appropriate.

**2. CONTAINER – Bottles of 30s, 90s and 1000s**

See comment 1.(b.) above.

**3. CARTON – 100 (10X10 unit-dose blisters)**

See comment 1.(b.) above.

**4. Unit-Dose Blisters – 10s**

Satisfactory in **draft** as of the August 27, 2008 electronic submission

**5. PACKAGE INSERT**

**PRECAUTIONS**

Revise the following subsection to read as follows –

***Electrolyte Imbalance***

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed.

***Information for Patients***

*Pregnancy:* Female patients.....

**6. PATIENT INFORMATION LEAFLET**

We note that a Patient Information Leaflet was never submitted for review. Note that a PIL was approved for the reference listed drug on April 13 and September 21, 2006. Please address this and/or comment.

Submit your revised labels and labeling electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - [http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_17](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

7. Revisions needed post-approval: None

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No  
What is the RLD on the 356(h) form: Cozaar® Tablets  
NDA Number: 20-386/S-049  
NDA Drug Name: Cozaar® Tablets  
NDA Firm: Merck & Co. Inc.  
Date of Approval of NDA Insert and supplement: NDA 20-386/S-049; June 4, 2009  
Has this been verified by the MIS system for the NDA? Yes  
Was this approval based upon an OGD labeling guidance? No  
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Cozaar® Tablets.

**FOR THE RECORD**

1. The model labeling **was based** on the most recently approved labeling for this drug product, Cozaar® (NDA 20-386/S-049; approved June 4, 2009).
2. Storage/Dispensing Conditions:  
NDA: Store at 25°C (77°F), excursions permitted to 15 – 30°C (59 – 86°F)[See USP Controlled Room temperature].  
ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]. (b) (4)  
USP: NOT USP and NOT PF.  
NDA: Dispense in a well-closed container as defined in the USP.  
ANDA: Dispense in a tight, light resistant container.
3. **In July of 2007, this decision (below) was reversed by Peter Rickman and John Grace. (Previous submission) This applies to this application even though different patent certifications filed, they are the same pertaining to this Indication**  
After further review on 1/23/2006, Peter Rickman and John Grace decided that the exclusivity “Treatment of Type II Diabetic Neuropathy” (Use code I-383), should be included in the labeling. It was to loosely associated with patent #5210079\*PED “(U-496- Method for Treating Chronic Renal Failure).
4. Product Line:  
The innovator markets their product in three strengths (25 mg, 50 mg and 100 mg). They are packaged in bottles of 30, 90, 100 and 1000 tablets and unit-dose cartons of 100 tablets  
The applicant proposes to market their product in bottles of 30s, 90s and 1000s as well as unit-dose cartons of 100 tablets for all strengths.

**5. Patent/ Exclusivities:**

**NDA: 20-386**

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5138069*PED	<i>Feb. 11, 2010</i>			Paragraph III	None
5153197*PED	<i>April 6, 2010</i>	U-3	Treatment of Hypertension	Paragraph III	None
5210079*PED	<i>November 11, 2010</i>	U-496	Method for Treating Chronic Renal Failure	MOU	None
5608075*PED	<i>Sept 4, 2014</i>			Paragraph IV	

**Exclusivity Data– NDA 20-386**



The drug substance Losartan Potassium consist of 27.33% of the weight of the tablets.

The composition of Film coating material (b) (4) is in the table below.

Ingredients	mg/tablet			
	(b) (4)	25 mg*	50 mg**	100mg***
(b) (4)				(b) (4)
(b) (4)				(b) (4)
(b) (4)				(b) (4)
(b) (4)				(b) (4)
(b) (4)				(b) (4)

(b) (4)

c) Description of Accompanying Reconstitution Diluent(s): N/A

d) Type of Container and Enclosure used for Dosage Form:

As indicated by stability studies the proposed Losartan Potassium Tablets 25 mg, 50 mg and 100 mg are packed into HDPE bottles and closures.

These container/closure systems meet all current established acceptance criteria including USP General Chapter <661> and USP General Chapter <671> and have been approved for use with the firm's other products.

8. All manufacturing will be done by:  
 Apotex Research Pvt Ltd.  
 Plot No 1, Bommasandra Industrial Area, 4th Phase  
 Bommasandra Industrial Estate  
 Bangalore, India- 560 099

9. Container/Closure – Satisfactory per chemistry

The Losartan Potassium Tablets 25 mg, 50 mg and 100 mg are packaged in the container and closure systems as described in the below table.

Count	Strength	Container Closure System
30 's	25 mg 50 mg 100 mg	75 cc round, white, opaque, HDPE bottle with 38mm polypropylene blue CRC cap with (b) (4) liner and Lift and Peel induction seal.
90 's	25 mg 50 mg 100 mg	75 cc round, white, opaque, HDPE bottle with 38mm polypropylene blue CRC cap with (b) (4) liner and Lift and Peel induction seal.
(b) (4)		

1000's	25 mg	250 cc round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	400 cc round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
	100 mg	(b) (4) (625 cc for commercial batches) round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) (b) (4) liner and Lift and Peel induction seal. (b) (4) (625 cc for commercial batches) round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
100 U/D Blisters	25 mg 50 mg 100 mg	Blister packs comprising of white opaque (b) (4) film and aluminium foil. The blister packs will be packed in cartons containing 10 strips of 10 tablets.

Blister packaging of the exhibit and stability batch presented in this ANDA is 10 strips of 10 tablets.

(b) (4). The opaque container should be adequate enough to protect the drug product from light damage.

Date of Review: 1/6/10

Date of Submission: September 8, 2009

Primary Reviewer: Jim Barlow

Date:

Team Leader: Koung Lee

Date:

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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/s/

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JAMES T BARLOW  
01/06/2010

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

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ANDA Number: 090790  
Date of Submission: January 15, 2010  
Applicant's Name: Apotex Inc.  
Established Name: Losartan Potassium Tablets USP, 25 mg, 50 mg and 100 mg tablets

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**Labeling Deficiencies:**

1. **CONTAINER** – Bottles of 30s, 90s and 1000s (all strengths)  
Satisfactory in **final print** as of the January 15, 2010 e-submission
2. **CARTON** – 100 (10X10 unit-dose blisters) (all strengths)  
Satisfactory in **final print** as of the January 15, 2010 e-submission
3. **Unit-Dose Blisters** – 10s  
Satisfactory in **final print** as of the January 15, 2010 e-submission
4. **PACKAGE INSERT**  
Satisfactory in **final print** as of the January 15, 2010 e-submission

5. **PATIENT INFORMATION LEAFLET**

a. Please delete the following information from the text since it is protected information.

i. [REDACTED] (b) (4)

ii. [REDACTED] (b) (4)

iii. [REDACTED] (b) (4)

b. How many Patient Information Leaflets will be distributed for each count bottle you intend to market? (i.e. [REDACTED] (b) (4) PILs for the bottles of 90)

Submit your revised labels and labeling electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

[http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_17](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

**7. Revisions needed post-approval: None**

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No  
 What is the RLD on the 356(h) form: Cozaar® Tablets  
 NDA Number: 20-386/S-049  
 NDA Drug Name: Cozaar® Tablets  
 NDA Firm: Merck & Co. Inc.  
 Date of Approval of NDA Insert and supplement: NDA 20-386/S-049; June 4, 2009  
 Has this been verified by the MIS system for the NDA? Yes  
 Was this approval based upon an OGD labeling guidance? No  
 Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Cozaar® Tablets.

**FOR THE RECORD**

- The model labeling **was based** on the most recently approved labeling for this drug product, Cozaar® (NDA 20-386/S-049; approved June 4, 2009).
- Storage/Dispensing Conditions:  
 NDA: Store at 25°C (77°F), excursions permitted to 15 – 30°C (59 – 86°F)[See USP Controlled Room temperature].  
 ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]. (b) (4)  
 USP: NOT USP and NOT PF.  
 NDA: Dispense in a well-closed container as defined in the USP.  
 ANDA: Dispense in a tight, light resistant container.
- In July of 2007, this decision (below) was reversed by Peter Rickman and John Grace. (Previous submission) This applies to this application even though different patent certifications filed, they are the same pertaining to this Indication**  
 After further review on 1/23/2006, Peter Rickman and John Grace decided that the exclusivity "Treatment of Type II Diabetic Neuropathy" (Use code I-383), should be included in the labeling. It was to loosely associated with patent #5210079\*PED "(U-496- Method for Treating Chronic Renal Failure).
- Product Line:  
 The innovator markets their product in three strengths (25 mg, 50 mg and 100 mg). They are packaged in bottles of 30, 90, 100 and 1000 tablets and unit-dose cartons of 100 tablets  
 The applicant proposes to market their product in bottles of 30s, 90s and 1000s as well as unit-dose cartons of 100 tablets for all strengths.

**5. Patent/ Exclusivities:  
 NDA: 20-386**

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5138069*PED	<i>Feb. 11, 2010</i>			Paragraph III	None
5153197*PED	<i>April 6, 2010</i>	U-3	Treatment of Hypertension	Paragraph III	None
5210079*PED	<i>November 11, 2010</i>	U-496	Method for Treating Chronic Renal Failure	MOU	None
5608075*PED	<i>Sept 4, 2014</i>			Paragraph IV	

**Exclusivity Data– NDA 20-386**

Code	Reference	Expiration	Labeling Impact
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I-383	Treatment of Type II Diabetic Nephropathy	Sept. 17, 2005	Needs to be carved out of the labeling U-496 listed in FTR as per Peter Rickman
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6. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, (no tablets are scored as is the RLD not scored)

Dosage Strength	Tablet Description
25 mg	White, round, biconvex tablets with 'APO' debossed on one side and 'LS' over '25' on the other side.
50 mg	White, round, biconvex tablets with 'APO' debossed on one side and 'LS' over '50' on the other side.
100 mg	White, oval shaped, biconvex tablets with 'APO' debossed on one side and 'LS 100' on the other side.

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and The components and quantitative composition of Losartan Potassium Tablets 25 mg, 50 mg and 100 mg is summarized below:

**Composition and compositions: Satisfactory per chemistry**

**What are the components and composition of the final product? What is the function of each excipient?**

The quantitative composition of each component in the Losartan Potassium Tablets is listed below:

Components	Function	%w/w	mg/25 mg Tablet	mg/50 mg Tablet	mg/100 mg Tablet
Losartan Potassium USP (b) (4)	Active Ingredient	27.23	25.00	50.00	100.00
(b) (4)					
Coated Tablet weight		100%	91.80	183.60	367.20

(b) (4)

**The drug substance Losartan Potassium consist of 27.33% of the weight of the tablets.**

The composition of Film coating material (b) (4) is in the table below.

Ingredients	(b) (4)	mg/tablet		
		25 mg*	50 mg**	100mg***
(b) (4)				

(b) (4)

**c) Description of Accompanying Reconstitution Diluent(s): N/A**

**d) Type of Container and Enclosure used for Dosage Form:**

As indicated by stability studies the proposed Losartan Potassium Tablets 25 mg, 50 mg and 100 mg are packed into HDPE bottles and closures.

These container/closure systems meet all current established acceptance criteria including USP General Chapter <661> and USP General Chapter <671> and have been approved for use with the firm's other products.

8. All manufacturing will be done by:  
 Apotex Research Pvt Ltd.  
 Plot No 1, Bommasandra Industrial Area, 4th Phase  
 Bommasandra Industrial Estate  
 Bangalore, India- 560 099

9. Container/Closure – Satisfactory per chemistry

The Losartan Potassium Tablets 25 mg, 50 mg and 100 mg are packaged in the container and closure systems as described in the below table.

Count	Strength	Container Closure System
30 's	25 mg	75 cc round, white, opaque, HDPE bottle with 38mm polypropylene blue CRC cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	
	100 mg	
90 's	25 mg	75 cc round, white, opaque, HDPE bottle with 38mm polypropylene blue CRC cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	
	100 mg	
(b) (4)		
1000 's	25 mg	250 cc round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	400 cc round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.

	100 mg	(b) (4) (625 cc for commercial batches) round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) (b) (4) liner and Lift and Peel induction seal. (b) (4) (625 cc for commercial batches) round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
100 U/D Blisters	25 mg 50 mg 100 mg	Blister packs comprising of white opaque (b) (4) film and aluminium foil. The blister packs will be packed in cartons containing 10 strips of 10 tablets.

Blister packaging of the exhibit and stability batch presented in this ANDA is 10 strips of 10 tablets.

(b) (4)  
The opaque container should be adequate enough to protect the drug product from light damage.

10. Pertaining to information related to suspension storage: Firms response

**Did your firm submit stability data supporting this suspension storage in your Chemistry data? Please comment. (Also, please note that this information (suspension) cannot be carved out of your labeling since it is not protected.)**

**Response:**

We acknowledge your comments. Apotex has initiated a four week suspension stability study on the exhibit batch samples for 50mg strength to verify the shelf-life of the suspension. The stability data will be submitted to FDA in a gratuitous quality amendment.

Date of Review: 1/20/10

Date of Submission: January 15, 2010

Primary Reviewer: Jim Barlow

Date:

Team Leader: Koung Lee

Date:

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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

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/s/

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JAMES T BARLOW  
01/20/2010

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

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ANDA Number: 090790  
Date of Submission: January 25, 2010  
Applicant's Name: Apotex Inc.  
Established Name: Losartan Potassium Tablets USP, 25 mg, 50 mg and 100 mg tablets

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**Labeling Deficiencies:**

1. **CONTAINER** – Bottles of 30s, 90s and 1000s (all strengths)  
Satisfactory in **final print** as of the January 15, 2010 e-submission
2. **CARTON** – 100 ( (b) (4) unit-dose blisters) (all strengths)
  - a. Please add "Not for institutional use" on your carton labels since the unit dose blisters are not barcoded.
  - b. Please change the quantity to read " (b) (4) unit dose)", since the blisters are packaged as such.
3. **Unit-Dose Blisters** – (b) (4)  
Revise the established name on the strip should read "...Tablet, USP" - delete the s and add comma.
4. **PACKAGE INSERT**  
Satisfactory in **final print** as of the January 25, 2010 e-submission
5. **PATIENT INFORMATION LEAFLET**  
Satisfactory in **final print** as of the January 25, 2010 e-submission

Submit your revised labels and labeling electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - [http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_17](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

**6. Revisions needed post-approval: None**

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No  
 What is the RLD on the 356(h) form: Cozaar® Tablets  
 NDA Number: 20-386/S-049  
 NDA Drug Name: Cozaar® Tablets  
 NDA Firm: Merck & Co. Inc.  
 Date of Approval of NDA Insert and supplement: NDA 20-386/S-049; June 4, 2009  
 Has this been verified by the MIS system for the NDA? Yes  
 Was this approval based upon an OGD labeling guidance? No  
 Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Cozaar® Tablets.

**FOR THE RECORD**

- The model labeling **was based** on the most recently approved labeling for this drug product, Cozaar® (NDA 20-386/S-049; approved June 4, 2009).
- Storage/Dispensing Conditions:  
 NDA: Store at 25°C (77°F), excursions permitted to 15 – 30°C (59 – 86°F)[See USP Controlled Room temperature].  
 ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]. (b) (4)  
 USP: Store in tightly-closed containers, protected from light, at controlled room temperature  
 NDA: Dispense in a well-closed container as defined in the USP.  
 ANDA: Dispense in a tight, light resistant container.
- In July of 2007, this decision (below) was reversed by Peter Rickman and John Grace. (Previous submission) This applies to this application even though different patent certifications filed, they are the same pertaining to this Indication**  
 After further review on 1/23/2006, Peter Rickman and John Grace decided that the exclusivity “Treatment of Type II Diabetic Neuropathy” (Use code I-383), should be included in the labeling. It was to loosely associated with patent #5210079\*PED “(U-496- Method for Treating Chronic Renal Failure).
- Product Line:  
 The innovator markets their product in three strengths (25 mg, 50 mg and 100 mg). They are packaged in bottles of 30, 90, 100 and 1000 tablets and unit-dose cartons of 100 tablets  
 The applicant proposes to market their product in bottles of 30s, 90s and 1000s as well as unit-dose cartons of 100 tablets for all strengths.

**5. Patent/ Exclusivities:  
 NDA: 20-386**

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5138069*PED	<i>Feb. 11, 2010</i>			Paragraph III	None
5153197*PED	<i>April 6, 2010</i>	U-3	Treatment of Hypertension	Paragraph III	None
5210079*PED	<i>November 11, 2010</i>	U-496	Method for Treating Chronic Renal Failure	MOU	None
5608075*PED	<i>Sept 4, 2014</i>			Paragraph IV	

**Exclusivity Data– NDA 20-386**

Code	Reference	Expiration	Labeling Impact
------	-----------	------------	-----------------

I-383	Treatment of Type II Diabetic Nephropathy	Sept. 17, 2005	Needs to be carved out of the labeling U-496 listed in FTR as per Peter Rickman
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6. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, (no tablets are scored as is the RLD not scored)

Dosage Strength	Tablet Description
25 mg	White, round, biconvex tablets with 'APO' debossed on one side and 'LS' over '25' on the other side.
50 mg	White, round, biconvex tablets with 'APO' debossed on one side and 'LS' over '50' on the other side.
100 mg	White, oval shaped, biconvex tablets with 'APO' debossed on one side and 'LS 100' on the other side.

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and The components and quantitative composition of Losartan Potassium Tablets 25 mg, 50 mg and 100 mg is summarized below:

**Composition and compositions: Satisfactory per chemistry**

**What are the components and composition of the final product? What is the function of each excipient?**

The quantitative composition of each component in the Losartan Potassium Tablets is listed below:

Components	Function	%w/w	mg/25 mg Tablet	mg/50 mg Tablet	mg/100 mg Tablet
Losartan Potassium USP (b) (4)	Active Ingredient	27.23	25.00	50.00	100.00
(b) (4)					
Coated Tablet weight		100%	91.80	183.60	367.20

(b) (4)

**The drug substance Losartan Potassium consist of 27.33% of the weight of the tablets.**

The composition of Film coating material (b) (4) is in the table below.

Ingredients	mg/tablet			
	(b) (4)	25 mg*	50 mg**	100mg***
				(b) (4)

(b) (4)

**c) Description of Accompanying Reconstitution Diluent(s): N/A**

**d) Type of Container and Enclosure used for Dosage Form:**

As indicated by stability studies the proposed Losartan Potassium Tablets 25 mg, 50 mg and 100 mg are packed into HDPE bottles and closures.

These container/closure systems meet all current established acceptance criteria including USP General Chapter <661> and USP General Chapter <671> and have been approved for use with the firm's other products.

8. All manufacturing will be done by:  
 Apotex Research Pvt Ltd.  
 Plot No 1, Bommasandra Industrial Area, 4th Phase  
 Bommasandra Industrial Estate  
 Bangalore, India- 560 099

**9. Container/Closure – Satisfactory per chemistry**

The Losartan Potassium Tablets 25 mg, 50 mg and 100 mg are packaged in the container and closure systems as described in the below table.

Count	Strength	Container Closure System
30's	25 mg	75 cc round, white, opaque, HDPE bottle with 38mm polypropylene blue CRC cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	
	100 mg	
90's	25 mg	75 cc round, white, opaque, HDPE bottle with 38mm polypropylene blue CRC cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	
	100 mg	
(b) (4)		
1000's	25 mg	250 cc round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	400 cc round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.

	100 mg	(b) (4) (625 cc for commercial batches) round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) (b) (4) liner and Lift and Peel induction seal. (b) (4) (625 cc for commercial batches) round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
100 U/D Blisters	25 mg 50 mg 100 mg	Blister packs comprising of white opaque (b) (4) film and aluminium foil. The blister packs will be packed in cartons 5 x 20 strips

Blister packaging of the exhibit and stability batch presented in this ANDA is 10 strips of 10 tablets.

(b) (4)  
The opaque container should be adequate enough to protect the drug product from light damage.

10. Pertaining to information related to suspension storage: Firms response

**Did your firm submit stability data supporting this suspension storage in your Chemistry data? Please comment. (Also, please note that this information (suspension) cannot be carved out of your labeling since it is not protected.)**

**Response:**

We acknowledge your comments. Apotex has initiated a four week suspension stability study on the exhibit batch samples for 50mg strength to verify the shelf-life of the suspension. The stability data will be submitted to FDA in a gratuitous quality amendment.

11. A patient information leaflet will be dispensed with each prescription. The PILs are distributed as follows:

Bottles of 30 – one pull-out PIL attached to the package insert and a sufficient quantity provided as tear-off pads of 35 leaflets each (7 pads/ shipper).  
Bottles of 90 – one pull-out PIL attached to the package insert and a sufficient quantity provided as tear-off pads of 35 leaflets each (7 pads/ shipper of 72 bottles).  
Bottles of 1000 – one pull-out PIL attached to the package insert and a sufficient quantity provided as tear-off pads of 35 leaflets each (e.g. 25 mg – 64 pads/ shipper, 50 mg – 48 pads/shipper, 100 mg – 36 pads/shipper).

Date of Review: 2/19/10

Date of Submission: January 25, 2010

Primary Reviewer: Jim Barlow

Date:

Team Leader: Koug Lee

Date:

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAMES T BARLOW  
02/19/2010

**APPROVAL SUMMARY**  
**pending the approval of a stability study pertaining to the suspension**  
**REVIEW OF PROFESSIONAL LABELING**  
**DIVISION OF LABELING AND PROGRAM SUPPORT**  
**LABELING REVIEW BRANCH**

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ANDA Number: 090790  
Date of Submission: February 19, 2010  
Applicant's Name: Apotex Inc.  
Established Name: Losartan Potassium Tablets USP, 25 mg, 50 mg and 100 mg tablets

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**Approval Summary:**

1. **Do you have copies of final printed labels and labeling?** Yes
2. **CONTAINER** – Bottles of 30s, 90s and 1000s (all strengths)  
Satisfactory in **final print** as of the January 15, 2010 e-submission
3. **CARTON** – 100 (10 X 10 unit-dose blisters) (all strengths)  
Satisfactory in **final print** as of the January 15, 2010 e-submission
4. **Unit-Dose Blisters** – 10s  
Satisfactory in **final print** as of the February 19, 2010 e-submission
5. **PACKAGE INSERT**  
Satisfactory in **final print** as of the January 25, 2010 e-submission
6. **PATIENT INFORMATION LEAFLET**  
Satisfactory in **final print** as of the January 25, 2010 e-submission
7. **Revisions needed post-approval:** None

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cozaar® Tablets

NDA Number: 020386/S-049

NDA Drug Name: Cozaar® Tablets

NDA Firm: Merck & Co. Inc.

Date of Approval of NDA Insert and supplement: NDA 020386/S-049; June 4, 2009

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Cozaar® Tablets.

**FOR THE RECORD**

1. The model labeling **was based** on the most recently approved labeling for this drug product, Cozaar® (NDA 020386/S-049; approved June 4, 2009).
2. Storage/Dispensing Conditions:  
NDA: Store at 25°C (77°F), excursions permitted to 15 – 30°C (59 – 86°F)[See USP Controlled Room temperature].  
ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]. (b) (4)  
USP: Store in tightly-closed containers, protected from light, at controlled room temperature

NDA: Dispense in a well-closed container as defined in the USP.  
 ANDA: Dispense in a tight, light resistant container.

3. In July of 2007, It was decided by John Grace and Peter Rickman that exclusivity [I-383 – Treatment of Type II Diabetic Nephropathy], should be carved out of the package insert labeling because of its' loose association with patent #5210079\*PED [U-496 - Method of Treating Chronic Renal Failure], even though it expired on September 17, 2005 (See Patent/Exclusivity Data below)

4. Product Line:

The innovator markets their product in three strengths (25 mg, 50 mg and 100 mg). They are packaged in bottles of 30, 90, 100 and 1000 tablets and unit-dose cartons of 100 tablets  
 The applicant proposes to market their product in bottles of 30s, 90s and 1000s as well as unit-dose cartons of 100 tablets for all strengths.

5. Patent/ Exclusivities:

NDA: 020386

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5138069*PED	<i>Feb. 11, 2010</i>			Paragraph III	None
5153197*PED	<i>April 6, 2010</i>	U-3	Treatment of Hypertension	Paragraph III	None
5210079*PED	<i>November 11, 2010</i>	U-496	Method for Treating Chronic Renal Failure	MOU	None
5608075*PED	<i>Sept 4, 2014</i>			Paragraph IV	

**Exclusivity Data– NDA 020386**

Code	Reference	Expiration	Labeling Impact
I-383	Treatment of Type II Diabetic Nephropathy	<i>Sept. 17, 2005</i>	Needs to be carved out of the labeling U-496 listed in FTR as per Peter Rickman

6. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, (no tablets are scored as is the RLD not scored)

Dosage Strength	Tablet Description
25 mg	White, round, biconvex tablets with 'APO' debossed on one side and 'LS' over '25' on the other side.
50 mg	White, round, biconvex tablets with 'APO' debossed on one side and 'LS' over '50' on the other side.
100 mg	White, oval shaped, biconvex tablets with 'APO' debossed on one side and 'LS 100' on the other side.

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and The components and quantitative composition of Losartan Potassium Tablets 25 mg, 50 mg and

100 mg is summarized below:

**Composition and compositions: Satisfactory per chemistry**

**What are the components and composition of the final product? What is the function of each excipient?**

The quantitative composition of each component in the Losartan Potassium Tablets is listed below:

Components	Function	%w/w	mg/25 mg Tablet	mg/50 mg Tablet	mg/100 mg Tablet
Losartan Potassium USP (b) (4)	Active Ingredient	27.23	25.00	50.00	100.00
(b) (4)					
Coated Tablet weight		100%	91.80	183.60	367.20

(b) (4)

**The drug substance Losartan Potassium consist of 27.33% of the weight of the tablets.**

The composition of Film coating material ( (b) (4) ) is in the table below

Ingredients	(b) (4)	mg/tablet		
		25 mg*	50 mg**	100mg***
(b) (4)				

(b) (4)

**c) Description of Accompanying Reconstitution Diluent(s): N/A**

**d) Type of Container and Enclosure used for Dosage Form:**

As indicated by stability studies the proposed Losartan Potassium Tablets 25 mg, 50 mg and 100 mg are packed into HDPE bottles and closures.

These container/closure systems meet all current established acceptance criteria including USP General Chapter <661> and USP General Chapter <671> and have been approved for use with the firm's other products.

8. All manufacturing will be done by:

Apotex Research Pvt Ltd.  
Plot No 1, Bommasandra Industrial Area, 4th Phase  
Bommasandra Industrial Estate  
Bangalore, India- 560 099

9. Container/Closure – Satisfactory per chemistry

The Losartan Potassium Tablets 25 mg, 50 mg and 100 mg are packaged in the container and closure systems as described in the below table.

Count	Strength	Container Closure System
30's	25 mg	75 cc round, white, opaque, HDPE bottle with 38mm polypropylene blue CRC cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	
	100 mg	
90's	25 mg	75 cc round, white, opaque, HDPE bottle with 38mm polypropylene blue CRC cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	
	100 mg	
(b) (4)		
1000's	25 mg	250 cc round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
	50 mg	400 cc round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
	100 mg	(b) (4) (625 cc for commercial batches) round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal (b) (4) (625 cc for commercial batches) round, white, opaque, HDPE bottle with 53mm polypropylene blue screw cap with (b) (4) liner and Lift and Peel induction seal.
100 U/D Blisters	25 mg 50 mg 100 mg	Blister packs comprising of white opaque (b) (4) film and aluminium foil. The blister packs will be packed in cartons 10 x 10 strips

Blister packaging of the exhibit and stability batch presented in this ANDA is 10 strips of 10 tablets.

(b) (4)  
The opaque container should be adequate enough to protect the drug product from light damage.

10. Pertaining to information related to suspension storage: Firms response

**Did your firm submit stability data supporting this suspension storage in your Chemistry data? Please comment. (Also, please note that this information (suspension) cannot be carved out of your labeling since it is not protected.)**

**Response:**

We acknowledge your comments. Apotex has initiated a four week suspension stability study on the exhibit batch samples for 50mg strength to verify the shelf-life of the suspension. The stability data will be submitted to FDA in a gratuitous quality amendment.

11. A patient information leaflet will be dispensed with each prescription. The PILs are distributed as follows:

Bottles of 30 – one pull-out PIL attached to the package insert and a sufficient quantity provided as tear-off pads of 35 leaflets each (7 pads/ shipper).

Bottles of 90 – one pull-out PIL attached to the package insert and a sufficient quantity provided as tear-off pads of 35 leaflets each (7 pads/ shipper of 72 bottles).

Bottles of 1000 – one pull-out PIL attached to the package insert and a sufficient quantity provided as tear-off pads of 35 leaflets each (e.g. 25 mg – 64 pads/ shipper, 50 mg – 48 pads/shipper, 100 mg – 36 pads/shipper).

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Date of Review: 2/22/10

Date of Submission: February 19, 2010

Primary Reviewer: Jim Barlow

Date:

Team Leader: Koung Lee

Date:

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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

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/s/

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JAMES T BARLOW  
02/22/2010

KOUNG U LEE  
02/25/2010  
For Wm Peter Rickman

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 90-790**

**CHEMISTRY REVIEWS**

**ANDA 90-790**

**LOSARTAN POTASSIUM  
Tablets**

**25 mg, 50 mg and 100 mg**

**Apotex Inc.**

**Xueli Zhu  
Chemistry Division I**

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# Chemistry Review Data Sheet

1. ANDA 90790
2. REVIEW #1
3. REVIEW DATE: 11/29/2008
4. REVIEWER: Xueli Zhu
5. PREVIOUS DOCUMENTS: None

<u>Previous Documents</u>	<u>Document Date</u>
None	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Application	8/27/2008

7. NAME & ADDRESS OF APPLICANT:

<b>Name:</b>	Apotex Inc.
<b>Address:</b>	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston FL 33326
<b>Representative:</b>	Kiran Krishnan Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston FL 33326
<b>Telephone:</b>	(954)384-3986
<b>Fax:</b>	(954)349-4233

8. DRUG PRODUCT NAME/CODE/TYPE: Losartan Potassium Tablets

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Losartan Potassium Tablets

9. LEGAL BASIS FOR SUBMISSION:

The basis of the firm's ANDA for Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg is the approved, listed drug, COZAAR® Tablets 25 mg, 50 mg and 100 mg, the subject of NDA #020386, held by MERCK.

Per Orange Book Database: Patent Data:

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020386	001	5138069	AUG 11, 2009			
020386	001	5138069*PED	FEB 11, 2010			
020386	001	5153197	OCT 06, 2009			<u>U-3</u>
020386	001	5153197*PED	APR 06, 2010			<u>U-3</u>
020386	001	5210079	May 11, 2010			<u>U-496</u>
020386	001	5210079*PED	Nov 11, 2010			<u>U-496</u>
020386	001	5608075	MAR 04, 2014			
020386	001	5608075*PED	SEP 04, 2014			

Patent Use Code	Definition
U-496	Method For Treating Chronic Renal Failure
<u>U-3</u>	Treatment of Hypertension

There is no unexpired exclusivity for this product.

In accordance with Section 505(j)(2)(A)(vii) the firm provided paragraph IV certification for the patent 5,608,075 and paragraph III certification for the patents 5,138,069 & 5,153,197. The firm is seeking to market Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg after the expiration of patents 5,138,069 & 5,153,197.

The firm also provided a patent certificate regarding the Method of Use patent 5,210,079. The firm's label will not have this indication.

10. PHARMACOL. CATEGORY:

Losartan Potassium Tablets, is indicated for the treatment of hypertension

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 25 mg, 50 mg and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:   X   Rx        OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

       SPOTS product – Form Completed

  X   Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN	Losartan Potassium
------	--------------------

<b>USP listed chemical name</b>	1 <i>H</i> -Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt.
<b>CAS #</b>	124750-99-8
<b>Molecular Structure</b>	
<b>Molecular Formula</b>	C <sub>22</sub> H <sub>22</sub> ClKN <sub>6</sub> O
<b>Molecular Weight</b>	461.00

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	adequate	May 20, 2008	Xueli Zhu
	3			4			
	3			4			
	3			4			
	3			4			

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: None**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

**18. STATUS:**

**OGD:**

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES (b) (4) Apotex Pharmachem India Pvt Ltd Apotex Inc (Etobicoke site) Apotex Inc. (Signet Campus)	3004378446: Pending 3006091732: Pending 3002808376: Pending 3002291199: Pending 3002595397: Pending 3002806385: Pending		
Methods Validation			
Labeling	Pending		James Barlow
Bioequivalence	Pending		
EA	Exclusion ACCEPTABLE	11/29/2008	XZhu
Radiopharmaceutical	N/A		

**19. ORDER OF REVIEW (OGD Only)**

The application submission(s) covered by this review was taken in the date order of receipt.   X   Yes      No If no, explain reason(s) below:

# The Chemistry Review for A/NDA 90-790

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The chemistry section is deficient in areas of manufacturing and controls and is therefore recommended for “not-approvable”.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is Losartan Potassium. Losartan Potassium is white to off-white powder with pH dependent solubility characteristics (DMF# (b) (4)). The drug substance and the related impurities are characterized by using the standard analytical techniques of IR, UV, HPLC, etc. The active ingredient is formulated with inactive ingredients to produce the finished drug product.

The drug product Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg is based on the listed drug, COZAAR® Tablets 25 mg, 50 mg and 100 mg, the subject of NDA #020386, held by MERCK. The Losartan Potassium Tablets, is indicated for the treatment of hypertension.

The tablets contain Losartan and several excipients. The firm used (b) (4)

Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg.

#### B. Description of How the Drug Product is Intended to be Used

The maximum recommended daily dose is

Losartan Potassium: 100 mg

#### C. Basis for Approvability or Not-Approval Recommendation

- There are minor issues in the controls of the drug product.
- Labeling and Bioequivalence (clinical data review) are pending.

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

Chemist Name/Date: XZhu, Ph.D./11/29/2008  
Chemistry Team Leader Name/Date: AMueller, Ph.D./11/29/2008  
Project Manager Name/Date: D. Doan, PM, /11/29/2008  
V:\FIRMSAM\APOTEX INC. \LTRS&REV\90790.r1.def.doc  
F/T:

#### C. CC Block

ANDA  
ANDA DUP  
DIV FILE  
Field Copy

Following this page, 27 pages withheld in full - (b)(4)

- [REDACTED] (b) (4)

**Section 6: Commitment**

A commitment is provided that the [REDACTED] (b) (4)

**R3                    Methods Validation Package: Satisfactory**

The firm provided the validation packages for relevant analytical methods for Losartan Potassium drug substance and for the Tablets, 25 mg, 50 mg and 100 mg.

**II.    Review Of Common Technical Document-Quality (Ctd-Q) Module 1****A. Labeling & Package Insert**

[This information is reviewed independently in the Division of Labeling and Program Support.](#)

**B. Environmental Assessment Or Claim Of Categorical Exclusion: Satisfactory**

The firm requests for exclusion from requirement for environment impact analysis statement, Section 1.12.14.

**III.   List Of Deficiencies To Be Communicated:**

38. Chemistry Comments to be Provided to the Applicant

ANDA: 90-790 APPLICANT: APOTEX INC.

DRUG PRODUCT: Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg

The deficiencies presented below represent MINOR deficiencies:

A. Deficiencies by Applicable Section:

**P.4 Control of Excipients**

For each excipient please provide the following:

-  (b) (4)
- 

**P.5 Control of Drug Product**

As of July 1, 2008 the new USP requirements for assessing the residual solvent content in drug products in <467> went into effect. You have to comply with USP <467> for the drug product. Please refer the FDA website <http://www.fda.gov/cder/ogd/residualsolvents.pdf> for detail requirement.

**P.7 Container Closure System**

 (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The labeling information in the application will be reviewed by the division of Labeling and Program Support. The Division will communicate any questions regarding labeling of the drug product to you directly.
2. The Division of Bioequivalence will review the bio-equivalency of the drug product and communicate questions regarding to you directly.
3. The firms referenced in your ANDA relative to the manufacturing and testing of the drug substance and the product must be in compliance with the cGMP's at the time of approval.

Sincerely yours,

Rashmikant M. Patel, Ph.D. Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

cc: ANDA 90-790  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements:

HFD-623/X.Zhu  
HFD-623/A.Mueller

Project Manager:

HFD-617/D. Doan  
F/t by:

File: \\Cdsnas\ogds11\FIRMSAM\APOTEX INC. \LTRS&REV\90790.r1.def.doc  
[Date November 29, 2008](#)

CHEMISTRY REVIEW - [NOT APPROVABLE – MINOR](#)

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

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Xueli Zhu  
1/23/2009 10:45:05 AM  
CHEMIST

Albert Mueller  
1/23/2009 02:19:00 PM  
CHEMIST

Dat Doan  
1/26/2009 10:33:57 AM  
CSO

**ANDA 90-790**

**LOSARTAN POTASSIUM  
Tablets**

**25 mg, 50 mg and 100 mg**

**Apotex Inc.**

**Xueli Zhu  
Chemistry Division I**

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# Chemistry Review Data Sheet

1. ANDA: 90790
2. REVIEW #: 2
3. REVIEW DATE: 09/18/2009
4. REVIEWER: Xueli Zhu
5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
<a href="#">Original Application</a>	8/27/2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
<a href="#">Quality/Quality Information</a>	03/05/2009
<a href="#">Quality/Quality Information</a>	07/07/2009
<a href="#">Quality/Quality Information</a>	09/14/2009

7. NAME & ADDRESS OF APPLICANT:

<b>Name:</b>	Apotex Inc.
<b>Address:</b>	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston FL 33326
<b>Representative:</b>	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston FL 33326
<b>Telephone:</b>	(954)384-3986
<b>Fax:</b>	(954)349-4233

8. DRUG PRODUCT NAME/CODE/TYPE: Losartan Potassium Tablets

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Losartan Potassium Tablets

9. LEGAL BASIS FOR SUBMISSION:

The basis of the firm's ANDA for Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg is the approved, listed drug, COZAAR® Tablets 25 mg, 50 mg and 100 mg, the subject of NDA #020386, held by MERCK.

Per Orange Book Database: Patent Data:

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020386	001	5138069	AUG 11, 2009			
020386	001	5138069*PED	FEB 11, 2010			
020386	001	5153197	OCT 06, 2009			<u>U-3</u>
020386	001	5153197*PED	APR 06, 2010			<u>U-3</u>
020386	001	5210079	May 11, 2010			<u>U-496</u>
020386	001	5210079*PED	Nov 11, 2010			<u>U-496</u>
020386	001	5608075	MAR 04, 2014			
020386	001	5608075*PED	SEP 04, 2014			

Patent Use Code	Definition
U-496	Method For Treating Chronic Renal Failure
<u>U-3</u>	Treatment of Hypertension

There is no unexpired exclusivity for this product.

In accordance with Section 505(j)(2)(A)(vii) the firm provided paragraph IV certification for the patent 5,608,075 and paragraph III certification for the patents 5,138,069 & 5,153,197. The firm is seeking to market Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg after the expiration of patents 5,138,069 & 5,153,197.

The firm also provided a patent certificate regarding the Method of Use patent 5,210,079. The firm's label will not have this indication.

10. PHARMACOL. CATEGORY:

Losartan Potassium Tablets, is indicated for the treatment of hypertension

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 25 mg, 50 mg and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:   X   Rx        OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

       SPOTS product – Form Completed

  X   Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN	Losartan Potassium
------	--------------------

<b>USP listed chemical name</b>	1 <i>H</i> -Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt.
<b>CAS #</b>	124750-99-8
<b>Molecular Structure</b>	
<b>Molecular Formula</b>	C <sub>22</sub> H <sub>22</sub> ClKN <sub>6</sub> O
<b>Molecular Weight</b>	461.00

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	adequate	May 20, 2008	Xueli Zhu
	3			4			
	3			4			
	3			4			
	3			4			

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: None**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

**18. STATUS:**

**OGD:**

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES (b) (4) Apotex Pharmachem India Pvt Ltd Apotex Inc (Etobicoke site) Apotex Inc. (Signet Campus)	3004378446: Pending 3006091732: Pending 3002808376: Pending 3002291199: Pending 3002595397: Pending 3002806385: Pending		
Methods Validation			
Labeling	Pending		James Barlow
Bioequivalence	Pending		
EA	Exclusion ACCEPTABLE	09/18/2009	XZhu
Radiopharmaceutical	N/A		

**19. ORDER OF REVIEW (OGD Only)**

The application submission(s) covered by this review was taken in the date order of receipt.   X   Yes      No    If no, explain reason(s) below:

# The Chemistry Review for A/NDA 90-790

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The chemistry section is **satisfactory** in areas of manufacturing and controls and is therefore recommended for “**approvable**”.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is Losartan Potassium. Losartan Potassium is white to off-white powder with pH dependent solubility characteristics (DMF# (b) (4)). The drug substance and the related impurities are characterized by using the standard analytical techniques of IR, UV, HPLC, etc. The active ingredient is formulated with inactive ingredients to produce the finished drug product.

The drug product Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg is based on the listed drug, COZAAR® Tablets 25 mg, 50 mg and 100 mg, the subject of NDA #020386, held by MERCK. The Losartan Potassium Tablets, is indicated for the treatment of hypertension.

The tablets contain Losartan and several excipients. The firm used (b) (4)

Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg.

#### B. Description of How the Drug Product is Intended to be Used

The maximum recommended daily dose is

Losartan Potassium: 100 mg

#### C. Basis for Approvability or Not-Approval Recommendation

- The CMC including USP<467 requirement is acceptable.
- Labeling, EES and Bioequivalence are pending.

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

Chemist Name/Date: XZhu, Ph.D./09/18/2009  
Chemistry Team Leader Name/Date: AMueller, Ph.D./09/18/2009  
Project Manager Name/Date: D. Doan, PM, /09/18/2009  
V:\FIRMSAM\APOTEX INC. \LTRS&REV\90790.r1.def.doc  
F/T:

#### C. CC Block

ANDA  
ANDA DUP  
DIV FILE  
Field Copy

Following this page, 27 pages withheld in full - (b)(4)

- [REDACTED] (b) (4)

### Section 6: Commitment

A commitment is provided that the [REDACTED] (b) (4)

#### **R3 Methods Validation Package: Satisfactory**

The firm provided the validation packages for relevant analytical methods for Losartan Potassium drug substance and for the Tablets, 25 mg, 50 mg and 100 mg.

## **II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**

### **A. Labeling & Package Insert**

[This information is reviewed independently in the Division of Labeling and Program Support.](#)

### **B. Environmental Assessment Or Claim Of Categorical Exclusion: Satisfactory**

The firm requests for exclusion from requirement for environment impact analysis statement, Section 1.12.14.

## **III. List Of Deficiencies To Be Communicated:**

38. Chemistry Comments to be Provided to the Applicant

ANDA: 90-790            APPLICANT: APOTEX INC.

DRUG PRODUCT: Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg

The deficiencies presented below represent MINOR deficiencies:

- A. Deficiencies by Applicable Section:
  
- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
  - 1. The labeling information in the application will be reviewed by the division of Labeling and Program Support. The Division will communicate any questions regarding labeling of the drug product to you directly.
  - 2. The Division of Bioequivalence will review the bio-equivalency of the drug product and communicate questions regarding to you directly.
  - 3. The firms referenced in your ANDA relative to the manufacturing and testing of the drug substance and the product must be in compliance with the cGMP's at the time of approval.

Sincerely yours,

Rashmikant M. Patel, Ph.D. Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

cc: ANDA 90-790  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements:

Chemist Name/Date: XZhu, Ph.D./09/18/2009

Chemistry Team Leader Name/Date: AMueller, Ph.D./09/18/2009

Project Manager Name/Date: D. Doan, PM, /09/18/2009

V:\FIRMSAM\APOTEX INC. \LTRS&REV\90790.r1.def.doc

F/t by:

CHEMISTRY REVIEW - APPROVABLE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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

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/s/

-----  
XUELI ZHU  
10/07/2009

ALBERT J MUELLER  
10/07/2009

DAT T DOAN  
10/08/2009

**ANDA 90-790**

**LOSARTAN POTASSIUM  
Tablets**

**25 mg, 50 mg and 100 mg**

**Apotex Inc.**

**Xueli Zhu  
Chemistry Division I**

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B. Environmental Assessment Or Claim Of Categorical Exclusion .....	39
III. List Of Deficiencies To Be Communicated.....	40

# Chemistry Review Data Sheet

1. ANDA: 90790
2. REVIEW 3
3. REVIEW DATE: 03/08/2010
4. REVIEWER: Xueli Zhu
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application	8/27/2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Quality/Quality Information	03/05/2009
Quality/Quality Information	07/07/2009
Quality/Quality Information	09/14/2009
Quality/Controls Information	01/20/2010
Quality/Response To Information Request	02/18/2010
Quality/Stability Information	02/23/2010
Quality/Response To Information Request	03/05/2010

7. NAME & ADDRESS OF APPLICANT:

<b>Name:</b>	Apotex Inc.
<b>Address:</b>	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston FL 33326
<b>Representative:</b>	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston FL 33326
<b>Telephone:</b>	(954)384-3986
<b>Fax:</b>	(954)349-4233

8. DRUG PRODUCT NAME/CODE/TYPE: Losartan Potassium Tablets

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Losartan Potassium Tablets

9. LEGAL BASIS FOR SUBMISSION:

The basis of the firm's ANDA for Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg is the approved, listed drug, COZAAR® Tablets 25 mg, 50 mg and 100 mg, the subject of NDA #020386, held by MERCK.

Per Orange Book Database: Patent Data:

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020386	001	5138069	AUG 11, 2009			
020386	001	5138069*PED	FEB 11, 2010			
020386	001	5153197	OCT 06, 2009			<u>U-3</u>
020386	001	5153197*PED	APR 06, 2010			<u>U-3</u>
020386	001	5210079	May 11, 2010			<u>U-496</u>
020386	001	5210079*PED	Nov 11, 2010			<u>U-496</u>
020386	001	5608075	MAR 04, 2014			
020386	001	5608075*PED	SEP 04, 2014			

Patent Use Code	Definition
U-496	Method For Treating Chronic Renal Failure
<u>U-3</u>	Treatment of Hypertension

There is no unexpired exclusivity for this product.

In accordance with Section 505(j)(2)(A)(vii) the firm provided paragraph IV certification for the patent 5,608,075 and paragraph III certification for the patents 5,138,069 & 5,153,197. The firm is seeking to market Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg after the expiration of patents 5,138,069 & 5,153,197.

The firm also provided a patent certificate regarding the Method of Use patent 5,210,079. The firm's label will not have this indication.

10. PHARMACOL. CATEGORY:

Losartan Potassium Tablets, is indicated for the treatment of hypertension

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 25 mg, 50 mg and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

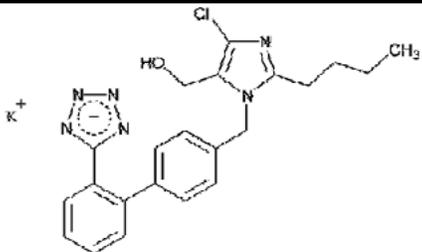
14. Rx/OTC DISPENSED:  X  Rx      OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

    SPOTS product – Form Completed

X  Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN	Losartan Potassium
USP listed chemical name	1 <i>H</i> -Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt.
CAS #	124750-99-8
Molecular Structure	
Molecular Formula	C <sub>22</sub> H <sub>22</sub> ClKN <sub>6</sub> O
Molecular Weight	461.00

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	adequate	02/01/2010	DHANESAR, SUBHASH C
	3			4			
	3			4			
	3			4			
	3			4			

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

- 6 – DMF not available  
7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: None**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

**OGD:**

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES (b) (4) Apotex Pharmachem India Pvt Ltd	3004378446: <b>Acceptable</b> 3006091732: <b>Pending</b>	21-OCT-2008	
Methods Validation			
Labeling	<b>Acceptable</b>	02/22/2010	James Barlow
Bioequivalence	<b>Acceptable</b>	02/16/2010	POPAT, ALPITA
EA	<b>Exclusion ACCEPTABLE</b>	03/08/2010	XZhu
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

# The Chemistry Review for A/NDA 90-790

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The chemistry section is **satisfactory** in areas of manufacturing and controls and is therefore recommended for “**approvable**”.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is Losartan Potassium. Losartan Potassium is white to off-white powder with pH dependent solubility characteristics (DMF# (b) (4)). The drug substance and the related impurities are characterized by using the standard analytical techniques of IR, UV, HPLC, etc. The active ingredient is formulated with inactive ingredients to produce the finished drug product.

The drug product Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg is based on the listed drug, COZAAR® Tablets 25 mg, 50 mg and 100 mg, the subject of NDA #020386, held by MERCK. The Losartan Potassium Tablets, is indicated for the treatment of hypertension.

The tablets contain Losartan and several excipients. The firm used (b) (4)

Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg.

#### B. Description of How the Drug Product is Intended to be Used

The maximum recommended daily dose is

Losartan Potassium: 100 mg

#### C. Basis for Approvability or Not-Approval Recommendation

- The CMC including USP<467 requirement is acceptable.
- Bioequivalence is acceptable.

- Labeling is acceptable.
- EES is pending

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

Chemist Name/Date: XZhu, Ph.D./03/08/2010

Chemistry Team Leader Name/Date: AMueller, Ph.D./03/08/2010

Project Manager Name/Date: D. Doan, PM, /03/08/2010

\\cdsnas\ogds11\Chemistry Division I\Team 1\TL Folder\90790.r3.doc

F/T:

#### C. CC Block

ANDA

ANDA DUP

DIV FILE

Field Copy

Following this page, 27 pages withheld in full - (b)(4)

**Section 6: Commitment**

(b) (4)

**R3 Methods Validation Package: Satisfactory**

The firm provided the validation packages for relevant analytical methods for Losartan Potassium drug substance and for the Tablets, 25 mg, 50 mg and 100 mg.

**II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1****A. Labeling & Package Insert: Satisfactory**

This information is reviewed independently in the Division of Labeling and Program Support.

**B. Environmental Assessment Or Claim Of Categorical Exclusion: Satisfactory**

The firm requests for exclusion from requirement for environment impact analysis statement, Section 1.12.14.

**III. List Of Deficiencies To Be Communicated:**

38. Chemistry Comments to be Provided to the Applicant

cc: ANDA 90-790  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements:

Chemist Name/Date: XZhu, Ph.D./03/08/2010

Chemistry Team Leader Name/Date: AMueller, Ph.D./03/08/2010

Project Manager Name/Date: D. Doan, PM, /03/08/2010

\\Cdsnas\ogds11\Chemistry Division I\Team 1\Final Version For DARRTS Folder\90790.r3.doc

F/t by:

CHEMISTRY REVIEW - APPROVABLE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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

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/s/

-----  
XUELI ZHU  
03/15/2010

ALBERT J MUELLER  
03/16/2010

DAT T DOAN  
03/16/2010

**Final Approval Following a Tentative Approval  
Abbreviated New Drug Application Regulatory Assessment**

---

1. ANDA # 090790, review #4
2. NAME AND ADDRESS OF APPLICANT  
Apotex Corp.  
U.S. Agent for: Apotex, Inc.  
Attention: Kiran Krishnan  
Associate Director, Regulatory Affairs  
2400 N. Commerce Parkway, Suite 400  
Weston, FL 33326
3. LEGAL BASIS FOR SUBMISSION  
Cozaar Tablets of Merck
4. PROPRIETARY NAME  
N/A
5. NONPROPRIETARY NAME  
Losartan Potassium Tablets, USP
6. CURRENT SUBMISSIONS AND OTHER DATES:
  - 8/12/10: final AP request
  - 9/21/10: original commitment
  - 9/28/10: final commitment
  1. Apotex commits to update ANDA No. 090790 in accordance with MAPP 5223.2 (Scoring Configuration of Generic Drug Products), within 3 months of receipt of approval. The change in scoring configuration will be submitted as a "Supplement – Expedited Review Requested".
  2. Apotex commits to demonstrate acceptable uniformity of the scored tablet segments (divided by hand) for the 50 mg tablet batch manufactured with the scored configuration. Testing and criteria will follow the recommendations as found in USP<905> for Uniformity of Dosage.
  3. Apotex will distribute the unscored 50 mg tablets manufactured in anticipation of ANDA approval, however, no new unscored 50 mg tablet batches will be manufactured without a change in the scoring configuration to match the RLD and subsequent approval of the related supplement.
7. PHARMACOLOGICAL CATEGORY  
Anti-hypertensive
8. Rx or OTC  
Rx
9. SAMPLES AND RESULTS  
N/A
10. LABELING STATUS  
Acceptable, 2/25/10
11. BIOEQUIVALENCY STATUS  
Acceptable, 2/16/10
12. MICROBIOLOGY STATUS  
N/A

13. ESTABLISHMENT INSPECTION  
Acceptable, 8/10/10

14. CONCLUSIONS AND RECOMMENDATIONS  
Acceptable

PROJECT MANAGER:      DATE COMPLETED:  
Dat Doan                      9/28/10

cc: ANDA  
Division File  
Field Copy

Endorsements:

HFD-617/DDoan, Project Manager  
HFD-623/AMueller, Team Leader

f/t by: DDoan

Approval

C:\TA to FA template2.doc

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

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/s/

---

DAT T DOAN  
09/29/2010

ALBERT J MUELLER  
09/29/2010

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 90-790**

**BIOEQUIVALENCE REVIEWS**

## DIVISION OF BIOEQUIVALENCE REVIEW

<b>ANDA No.</b>	090790		
<b>Drug Product Name</b>	Losartan Potassium Tablets		
<b>Strength(s)</b>	25 mg, 50 mg, 100 mg		
<b>Applicant Name</b>	Apotex Corp		
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<b>Original Submission Date(s)</b>	August 27, 2008		
<b>Submission Date(s) of Amendment(s) Under Review</b>	N/A		
<b>Reviewer</b>	Glendolynn S. Johnson, Pharm.D.		
<b>Study Number (s)</b>	LOSA-IMTB-05EB04-2FA (LN4840)	LOSA-IMTB-05EB05-2FE (LN4841)	
<b>Study Type (s)</b>	Fasting	Fed	
<b>Strength (s)</b>	100 mg	100 mg	
<b>Clinical Site</b>	Apotex Research Pvt. Limited		
<b>Clinical Site Address</b>	Bioequivalence Centre Site No: 2, Bommasandra Industrial area, Bommasandra Industrial Estate (P.O.), Bangalore-560 099, Karnataka, India		
<b>Analytical Site</b>	Apotex Research Pvt. Limited		
<b>Analytical Site Address</b>	Bioequivalence Centre Bioanalytical Department Site No: 2, Bommasandra Industrial area, Bommasandra Industrial Estate (P.O.), Bangalore-560 099, Karnataka, India		
<b>OVERALL REVIEW RESULT</b>	<b>INADEQUATE</b>		
<b>WAIVER REQUEST RESULT</b>	<b>ADEQUATE</b>		
<b>BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #</b>	<b>STUDY/TEST TYPE</b>	<b>STRENGTH</b>	<b>REVIEW RESULT</b>
1	FASTING STUDY	100 mg	ADEQUATE
1	FED STUDY	100 mg	ADEQUATE
1	DISSOLUTION	100 mg	INADEQUATE
1	DISSOLUTION	50 mg	INADEQUATE
1	DISSOLUTION	25 mg	INADEQUATE

## 1 EXECUTIVE SUMMARY

This application contains the results of the fasting and fed bioequivalence (BE) studies comparing a test product, Losartan Potassium Tablets, 100 mg to the corresponding reference product, Cozaar® (losartan potassium) Tablets, 100 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The firm's fasting and fed BE studies are acceptable. The results are summarized in the tables below.

<b>Losartan Potassium Tablets</b> <b>1 x 100 mg</b> <b>Fasting Bioequivalence Study No. (LN4840), N=62 (Male=62 and Female=0)</b> <b>Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals</b>					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (ng·hr/mL)	1066.12	1058.74	1.01	97.07	104.46
AUC <sub>∞</sub> (ng·hr/mL)	1089.64	1080.52	1.01	97.32	104.49
C <sub>max</sub> (ng/mL)	565.88	581.94	0.97	88.79	106.49

<b>Losartan Potassium Tablets</b> <b>1 x 100 mg</b> <b>Fed Bioequivalence Study No. (LN4841), N=68 (Male=68 and Female=0)</b> <b>Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals</b>					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (ng·hr/mL)	1111.30	1075.36	1.03	100.56	106.21
AUC <sub>∞</sub> (ng·hr/mL)	1132.08	1109.39	1.02	99.41	104.75
C <sub>max</sub> (ng/mL)	431.41	402.57	1.07	95.95	119.70

In addition, in both fasting and fed BE studies, the pharmacokinetic (PK) parameters of the test and reference products for the active metabolite, losartan acid, are comparable. Therefore, the metabolite data are supportive and are acceptable. For the fasting study, the losartan acid results (point estimate, 90% CI) are: LAUC<sub>T</sub> of 1.01, 97.8 – 103.8%, LAUC<sub>∞</sub> of 1.01, 97.9 - 103.7%, and LC<sub>max</sub> of 1.01, 96.8 - 106.1%. For the fed study, the losartan acid results (point estimate, 90% CI) are: LAUC<sub>T</sub> of 1.01, 98.6 - 103.5%, LAUC<sub>∞</sub> of 1.01, 98.2 - 103.2%, and LC<sub>max</sub> of 1.04, 98.2 - 110.0%.

The dissolution review was conducted within this ANDA review. There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). However the firm's proposed specification of NLT <sup>(b) (4)</sup> % (Q) in 45 minutes is not the FDA-recommended specification of NLT 75% (Q) in 30 minutes. The firm should acknowledge the FDA-recommended method and specification.

The formulations for the 25 mg and 50 mg strengths of the test product are proportionally similar to the formulation of the 100 mg strength which underwent bioequivalence testing. However, the waiver requests are granted. However, the application is incomplete pending the firm's acknowledgement of the dissolution method and specification.

No Division of Scientific Investigations (DSI) inspection is pending or necessary. The clinical and analytical sites were last inspected on November 13, 2008 for ANDA 65-508 and the outcome was NAI.

The application is incomplete.

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### 3 SUBMISSION SUMMARY

#### 3.1 Drug Product Information<sup>1</sup>

<b>Test Product</b>	Losartan Potassium Tablets, 100 mg, 50 mg and 25 mg
<b>Reference Product</b>	Cozaar® (Losartan Potassium) Tablets, 100 mg, 50 mg and 25 mg
<b>RLD Manufacturer</b>	Merck
<b>NDA No.</b>	20-386
<b>RLD Approval Date</b>	April 14, 1995 (25 mg and 50 mg) and October 13, 1998 (100 mg)
<b>Indication</b>	COZAAR® is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents, including diuretics. COZAAR® is also indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients. Additionally, COZAAR® is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio $\geq$ 300 mg/g) in patients with type 2 diabetes and a history of hypertension. In this population, COZAAR® reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end stage renal disease.

#### 3.2 PK/PD Information<sup>2</sup>

<b>Bioavailability</b>	Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan). The systemic bioavailability of losartan is approximately 35%. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan.
<b>Food Effect</b>	A meal slows absorption of losartan and decreases its C <sub>max</sub> but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).
<b>T<sub>max</sub></b>	Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively.
<b>Metabolism</b>	Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. Neither losartan nor its metabolite accumulates in plasma upon repeated once-daily dosing. About 14% of an orally-administered

<sup>1</sup> Online-Orange Book (2009). <http://www.fda.gov/cder/ob/default.htm>. Losartan. Last updated: 01/15/2010. Last accessed: 01/19/2010.

<sup>2</sup> Online-Clinical Pharmacology (2010). <http://www.clinicalpharmacology-ip.com/> World-Class Drug Information: Monographs: Losartan. Last updated: 6/21/06. Last accessed: 01/19/2010.

	dose of losartan is converted to the active metabolite. Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of 14 C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. In vitro studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites.
<b>Excretion</b>	When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral <sup>14</sup> C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces.
<b>Half-life</b>	The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours.
<b>Drug Specific Issues (if any)</b>	<b>Black Box Warning:</b> When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

### 3.3 OGD Recommendations for Drug Product

<b>Number of studies recommended:</b>	2, fasting and fed
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1.	<b>Type of study:</b>	Fasting
	<b>Design:</b>	Single-dose, two-treatment, two-period crossover in-vivo
	<b>Strength:</b>	100 mg
	<b>Subjects:</b>	Normal healthy males and females, general population
	<b>Additional Comments:</b>	Female subjects enrolled in the BE studies should not be pregnant, and if applicable, should practice abstinence or contraception during the study

2.	<b>Type of study:</b>	Fed
	<b>Design:</b>	Single-dose, two-treatment, two-period crossover in-vivo
	<b>Strength:</b>	100 mg
	<b>Subjects:</b>	Normal healthy males and females, general population
	<b>Additional Comments:</b>	Female subjects enrolled in the BE studies should not be pregnant, and if applicable, should practice abstinence or contraception during the study

<b>Analytes to measure (in plasma/serum/blood):</b>	Losartan (parent compound) and Losartan Acid (active metabolite)
<b>Bioequivalence based on:</b>	Losartan (90% CI)

<b>Waiver request of in-vivo testing:</b>	25 mg and 50 mg
<b>Source of most recent recommendations:</b>	<a href="http://www.fda.gov/cder/guidance/bioequivalence/recommendations/Losartan_Potassium_tab_20386_RC5-04.pdf">http://www.fda.gov/cder/guidance/bioequivalence/recommendations/Losartan_Potassium_tab_20386_RC5-04.pdf</a>
<b>Summary of OGD or DBE History (for details, see Appendix 4.4):</b>	<p>The DBE has received the following ANDAs regarding this drug product: #90-790 (Apotex -This application), #90-382 (Actavis), #90-544 (Upsher ), #90-467 (Torrent), #90-428 (Alembic), #90-083 (Aurobindo), #78-243 (Zydus), #78-232 (Lupin), #77-459 (Roxane), #77-424 (Lek Pharmaceuticals), (b) (4) and #76-958 (Teva).</p> <p>The DBE has received the following control documents regarding this drug product: C050965 ( (b) (4) ), C04476 ( (b) (4) ), C04472 ( (b) (4) ), C04742 ( (b) (4) ), C04689 ( (b) (4) ), C03052 ( (b) (4) ), C02548 ( (b) (4) ), C03220 (Teva), C041140 ( (b) (4) ), C04316 (Sandoz), C050395 (Zydus), C04572 (Lupin), C03572 ( (b) (4) ), C03829 (Mylan), C04146 ( (b) (4) ), C041133 ( (b) (4) ), and C041015 ( (b) (4) ).</p> <p>Currently, the DBE requests the following for this drug product:</p> <ol style="list-style-type: none"> <li>1. A single-dose, two-way crossover fasting in-vivo bioequivalence study comparing Losartan Tablets, 100 mg, to the reference listed drug (RLD), Cozaar ® (Losartan) Tablets, 100 mg</li> <li>2. A single-dose, two-way crossover fed in-vivo bioequivalence study comparing Losartan Tablets, 100 mg, to the RLD.</li> <li>3. Losartan and the metabolite losartan acid in plasma should be measured.</li> </ol> <p>Comparative dissolution testing on 12 individual dosage units of all strengths of the test and reference products should be conducted using the following FDA method (DBE-Method as per External Database as of 2/06/2004):</p> <p>Apparatus: USP Apparatus II (Paddle)  Speed: 50rpm  Medium: Water(deaerated)  Volume: 900 mL  Sampling Times: 10, 20, 30 and 45 minutes  Specification: NLT 75% (Q) in 30 min</p>

### 3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	---
In vitro dissolution	Yes	3
Waiver requests	Yes	2 (25 mg and 50 mg)
BCS Waivers	No	---

<b>Clinical Endpoints</b>	No	---
<b>Failed Studies</b>	No	---
<b>Amendments</b>	No	--

### 3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
<b>Bioanalytical method validation report location</b>	Section 16.6
<b>Analyte</b>	Losartan
<b>Internal standard (IS)</b>	(b) (4)
<b>Method description</b>	(b) (4) with LC-MS/MS detection
<b>Limit of quantitation</b>	5.10 ng/mL
<b>Average recovery of drug (%)</b>	96.96 %
<b>Average recovery of IS (%)</b>	102.28%
<b>Standard curve concentrations (units/mL)</b>	5.10, 10.20, 51.01, 102.02, 204.05, 408.09, 612.14, 816.19 and 1020.24 ng/mL
<b>QC concentrations (units/mL)</b>	QC A: 15.30 ng/mL QC B: 359.07 ng/mL QC C: 718.14 ng/mL
<b>QC Intraday precision range (%)</b>	QC A: 0.8 to 8.2 % QC B: 0.7 to 2.0 % QC C: 1.4 to 2.1 %
<b>QC Intraday accuracy range (%Bias)</b>	QC A: -2.9 to 3.1 % QC B: -6.9 to -2.4 % QC C: -4.7 to -1.7 %
<b>QC Interday precision range (%)</b>	2.1 to 4.8 %
<b>QC Interday accuracy range (%Bias)</b>	-1.0 to 4.2 %
<b>Bench-top stability (hrs)</b>	17 hours @ room temperature
<b>Stock stability (days)</b>	56 days @ Refrigerated Conditions
<b>Processed stability (hrs)</b>	51 hours @ Refrigerated Conditions
<b>Freeze-thaw stability (cycles)</b>	3 cycles
<b>Long-term storage stability (days)</b>	185 days at -30°C set point freezer (17-Nov-06 to 24- May-07) 97 days at -80°C set point freezer (17-Nov-06 to 30-Aug-07)
<b>Dilution integrity</b>	1530.36 ng/mL diluted 2 fold 1.6% (CV) and 4 fold 1.6% (CV)
<b>Selectivity</b>	No endogenous plasma components or common drug interfere with the analytical assay
<b>SOPs submitted</b>	Yes
<b>Bioanalytical method is acceptable</b>	Yes

**Comments on the Pre-Study Method Validation:**

1. The frozen, long-term stability data of 185 days at -30°C and 97 days at -80°C exceed the storage period for both the fasted (37 days) and fed (41 days) BE studies.
2. The firm used K<sub>2</sub>-EDTA as an anticoagulant for the method validation and clinical studies.
3. The pre-study method validation is acceptable.

### 3.6 In Vivo Studies

**Table 1. Summary of all in vivo Bioequivalence Studies**

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age†: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C <sub>max</sub> (ng/ml)	T <sub>max</sub> ‡ (h)	AUC <sub>t</sub> (ng* <sup>2</sup> h/ml)	AUC <sub>inf</sub> (ng* <sup>2</sup> h/ml)	T <sub>half</sub> (h)	Kel (1/h)	
LOSA-IMTB-05EB04-2FA (LN4840)	Comparative, randomized, 2-way crossover bioavailability study of Losartan Potassium Tablets (Apotex Inc.) and Cozaar® Tablets (Merck & Co., Inc.), (USA) under fasting conditions	Randomized, single-dose, 2-way crossover	Losartan Potassium Tablets, (1 x 100 mg Oral dose) [Lot# LMTA/08054]  Cozaar® Tablets, (1 x 100 mg Oral dose) [Lot # U2364]	62 (62/0) completing healthy subjects Age: 24.0 (18 - 44)	610.07 ±253.05	1.50 (0.33 – 4.00)	1112.99 ±342.03	1137.96 ±356.13	1.93 ±0.63	0.38912 ±0.09890	5.3.1.2
					663.95 ±406.15	1.63 (0.50 – 5.00)	1113.28 ±379.56	1136.14 ±391.97	1.85 ±0.54	0.40260 ±0.10783	
LOSA-IMTB-05EB05-2FE (LN4841)	Comparative, randomized, 2-way crossover bioavailability study of Losartan Potassium Tablets (Apotex Inc.) and Cozaar® Tablets (Merck & Co., Inc.), (USA) under fed conditions	Randomized, single-dose, 2-way crossover	Losartan Potassium Tablets, (1 x 100 mg Oral dose) [Lot# LMTA/08054]  Cozaar® Tablets, (1 x 100 mg Oral dose) [Lot # U2364]	68 (68/0) completing healthy subjects Age: 25.2 (19 – 44)	481.22 ±226.85	2.50 (1.00 – 7.00)	1144.95 ±291.76	1170.99 ±299.69	1.88 ±0.57	0.39802 ±0.10857	5.3.1.2
					443.60 ±193.07	4.17 (1.00 – 14.00)	1103.95 ±261.76	1136.42 ±262.40	1.97 ±0.78	0.38776 ±0.10557	

† Based on number of subjects dosed in period 1

‡ T<sub>max</sub> is presented as median (range)

**Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer**

<b>Losartan Potassium Tablet 1 x 100 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals</b>					
<b>Fasting Bioequivalence Study (LN4840)</b>					
<b>Parameter</b>	<b>Test</b>	<b>Reference</b>	<b>Ratio</b>	<b>90% C.I.</b>	
<b>AUC<sub>0-t</sub> (ng·hr/mL)</b>	1066.12	1058.74	1.01	97.07	104.46
<b>AUC<sub>∞</sub> (ng·hr/mL)</b>	1089.64	1080.52	1.01	97.32	104.49
<b>C<sub>max</sub> (ng/mL)</b>	565.88	581.94	0.97	88.79	106.49

<b>Losartan Potassium Tablet 1 x 100 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals</b>					
<b>Fed Bioequivalence Study (LN4841)</b>					
<b>Parameter</b>	<b>Test</b>	<b>Reference</b>	<b>Ratio</b>	<b>90% C.I.</b>	
<b>AUC<sub>0-t</sub> (ng·hr/mL)</b>	1111.30	1075.36	1.03	100.56	106.21
<b>AUC<sub>∞</sub> (ng·hr/mL)</b>	1132.08	1109.39	1.02	99.41	104.75
<b>C<sub>max</sub> (ng/mL)</b>	431.41	402.57	1.07	95.95	119.70

**Table 3. Reanalysis of Study Samples**

Study No. LN4840 Additional information in Table 16.5.1.8.6								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic <sup>1</sup>	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Code B-Incomplete analysis	2.0	1.0	0.13	0.07	0.0	0.0	0.0	0.0
Code C-Poor assay	2.0	2.0	0.13	0.13	0.0	0.0	0.0	0.0
Code F-Outside range	8.0	16.0	0.54	1.08	0.0	0.0	0.0	0.0
Total	12.0	19.0	0.80	1.28	0.0	0.0	0.0	0.0

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Study No. LN4841 Additional information in Table 16.5.1.8.6								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic <sup>1</sup>	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Code B-Incomplete analysis	1.0	1.0	0.07	0.0	0.0	0.0	0.0	0.0
Code F-Outside range	1.0	0.0	0.07	0.00	0.0	0.0	0.0	0.0
Total	2.0	1.0	0.14	0.07	0.0	0.0	0.0	0.0

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

**Did use of recalculated plasma concentration data change study outcome? No**

**Comments from the Reviewer:**

1. There were no pharmacokinetic repeats for Losartan in the fasting study (LN4840). Code F-(Outside range), % deviation did not exceed 5%. The reassays were conducted objectively based on the SOPs submitted by the firm.
2. There were no pharmacokinetic repeats for Losartan in the fed study (LN4841). Code F-(Outside range), % deviation did not exceed 6%. The reassays were conducted objectively based on the SOPs submitted by the firm.

**3.7 Formulation**

Location in appendix	Section 4.2, Page 40
If a tablet, is the RLD scored?	No

<b>If a tablet, is the test product biobatch scored</b>	No
<b>Is the formulation acceptable?</b>	<b>FORMULATION ACCEPTABLE</b>
<b>If not acceptable, why?</b>	N/A

### 3.8 In Vitro Dissolution

<b>Location of DBE Dissolution Review</b>	Dissolution review completed within this review
<b>Source of Method (USP, FDA or Firm)</b>	FDA
<b>Medium</b>	Water (deaerated)
<b>Volume (mL)</b>	900
<b>USP Apparatus type</b>	II (Paddle)
<b>Rotation (rpm)</b>	50
<b>DBE-recommended specifications</b>	NLT 75% (Q), 30 min
<b>If a modified-release tablet, was testing done on ½ tablets?</b>	N/A
<b>F2 metric calculated?</b>	No
<b>If no, reason why F2 not calculated</b>	Rapidly dissolving
<b>Is method acceptable?</b>	<b>METHOD ACCEPTABLE</b>
<b>If not then why?</b>	N/A

**Note:** The firm's dissolution testing data with the FDA method are acceptable. The firm's proposed specification of NLT  $\frac{(b)}{(4)}$ % (Q) in 45 minutes is not acceptable for this drug product. The firm should accept and acknowledge the FDA-recommended specification of NLT 75% (Q) in 30 minutes.

### 3.9 Waiver Request(s)

<b>Strengths for which waivers are requested</b>	25 mg and 50 mg
<b>Proportional to strength tested in vivo?</b>	Yes
<b>Is dissolution acceptable?</b>	Incomplete (pending acknowledgement of the specification)
<b>Waivers granted?</b>	<b>WAIVERS GRANTED</b>
<b>If not then why?</b>	

### 3.10 Deficiency Comments

1. The firm's proposed specification of NLT  $\frac{(b)}{(4)}\%$  (Q) in 45 minutes is not acceptable. The firm should be advised to acknowledge the FDA-recommended specification of NLT 75% (Q) in 30 minutes.

### 3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (LN4840) is acceptable. Apotex conducted the fasting BE study on its Losartan Potassium Tablets, 100 mg, (lot # LMTA/08054) comparing it to Merck & Co. Inc.'s Cozaar<sup>®</sup> Tablets, 100 mg (lot # U2364).
2. The Division of Bioequivalence finds the fed BE study (LN4841) is acceptable. Apotex conducted the fed BE study on its Losartan Potassium Tablets, 100 mg, (lot # LMTA/08054) comparing it to Merck & Co. Inc.'s Cozaar<sup>®</sup> Tablets, 100 mg (lot # U2364).
3. The firm's *in vitro* dissolution testing is incomplete. The dissolution testing should be conducted in 900 mL of water (deaerated) at 37°C ± 0.5°C using USP apparatus II (Paddles) at 50 rpm. The test product should meet the following specification: Not less than 75% (Q) in 30 minutes.

The firm is requested to acknowledge the FDA-recommended method and specification above.

4. The dissolution testing comparing the 25 mg and 50 mg strength of the test and RLD product is acceptable. The formulations for Apotex's Losartan Potassium Tablets, 25 mg (lot # LMTC/08052) and 50 mg (lot # LMTB/08053) are proportionally similar to the 100 mg strength of Losartan Potassium Tablets that underwent bioequivalence testing. However, the waiver requests for the 25 mg and 50 mg strength of the test product are granted.
5. This application is **incomplete**.

The firm should be informed of the above deficiency comments and recommendations.

### 3.12 Comments for Other OGD Disciplines

Discipline	Comment
None	None

## 4 APPENDIX

### 4.1 Individual Study Reviews

#### 4.1.1 Single-dose Fasting Bioequivalence Study

##### 4.1.1.1 Study Design

**Table 4 Study Information**

<b>Study Number</b>	LOSA-IMTB-05EB04-2FA (LN4840)
<b>Study Title</b>	COMPARATIVE, RANDOMIZED, 2-WAY CROSSOVER BIOAVAILABILITY STUDY OF LOSARTAN POTASSIUM TABLETS (APOTEX) AND COZAAR TABLETS (MERCK) (USA) UNDER FASTING CONDITIONS
<b>Clinical Site (Name &amp; Address)</b>	Apotex Research Pvt. Limited Bioequivalence Centre Site No: 2, Bommasandra Industrial area, Bommasandra Industrial Estate (P.O.), Bangalore-560 099, Karnataka, India Tel: +91-80-2289 1300 Fax: +91-80-2289 1364
<b>Principal Investigator</b>	Dr. Vimla D'souza
<b>Dosing Dates</b>	Period 1: 15-Apr-08 Period 2: 22-Apr-08
<b>Analytical Site (Name &amp; Address)</b>	Apotex Research Pvt. Limited Bioequivalence Centre Bioanalytical Department Site No: 2, Bommasandra Industrial area, Bommasandra Industrial Estate (P.O.), Bangalore-560 099, Karnataka, India Phone: + 91-80-22891308
<b>Analysis Dates</b>	06-MAY-08 to 22-MAY-08
<b>Analytical Director</b>	(b) (6), M.Sc
<b>Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)</b>	37 days (15-APR-08 to 22-MAY-08)

**Table 5. Product information**

Product	Test	Reference
Treatment ID	T	R
Product Name	Losartan Potassium Tablets	Cozaar® Tablets
Manufacturer	Apotex Inc.	Merck & Co., Inc., USA
Batch/Lot No.	LMTA/08054	U2364
Manufacture Date	03/2008	Not applicable
Expiration Date	03/2010	10/2010
Strength	100 mg	100 mg
Dosage Form	Tablet	Tablet
Bio-Batch Size	(b) (4) Tablets	Not applicable
Production Batch Size	(b) (4) Tablets	Not applicable
Potency (Assay)	100.5 %	97.0%
Content Uniformity (mean, %CV)	Mean: 100.0% Range: 99.4 – 100.9% RSD: 0.5%	Not applicable
Dose Administered	100 mg	100 mg
Route of Administration	Oral	Oral

**Table 6. Study Design, Single-Dose Fasting Bioequivalence Study**

Number of Subjects	66 subjects were enrolled and 65 subjects were dosed in the study 62 subjects completed the study (dropout #63, #65 and #66*) 62 subjects included in the statistical analysis
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1 group
Washout Period	7 days
Randomization Scheme	<b>AB:</b> 3, 4, 6, 7, 9, 12, 15, 16, 17, 19, 23, 24, 26, 27, 30, 31, 33, 36, 39, 40, 41, 42, 47, 48, 49, 52, 54, 55, 57, 60, 62 and 65 <b>BA:</b> 1, 2, 5, 8, 10, 11, 13, 14, 18, 20, 21, 22, 25, 28, 29, 32, 34, 35, 37, 38, 43, 44, 45, 46, 50, 51, 53, 56, 58, 59, 61, 63, 64, 66, 67 and 68
Blood Sampling Times	Blood samples were collected at pre-dose, 0.25, 0.33, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.33, 2.66, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 18 and 24 hours post dosing.
Blood Volume Collected/Sample	Twenty six (26) 6 mL blood samples were drawn from each subject during each clinical period by individual venipuncture or indwelling catheter at pre-set times.

<b>Blood Sample Processing/Storage</b>	Blood samples were collected using 6 mL lavender cap vacuum tubes containing K2 EDTA at the following time-points: Two 6 mL blood samples were taken 5–45 minutes prior to dosing time (0) followed by single 6 mL samples at each sampling time after dosing at the sample times listed above. Blood samples were collected after discarding 0.5 mL of heparinised blood for all the sample time points. Blood samples were centrifuged and the plasma obtained were divided into two portions and transferred into pre-chilled-prelabelled polypropylene storage tubes and stored in a – 30°C set point freezer pending assay.
<b>IRB Approval</b>	Yes, 04/09/08
<b>Informed Consent</b>	Yes, 04/09/08
<b>Length of Fasting</b>	All subjects fasted overnight for at least 10 hours (overnight) prior to scheduled time for dosing. Fasting was maintained for at least 4 hours after dosing.
<b>Length of Confinement</b>	At least 10.5 hours prior to dosing until 24 hours post-dose
<b>Safety Monitoring</b>	Vital signs (including scheduled blood pressure and pulse rate measurements), diagnostic tests were performed at the times specified in the protocol.

\*Subject No. 63, 65 and 66 did not report for period 2 check in due to personal reasons.

**Comments on Study Design:**

The study design is acceptable.

**4.1.1.2 Clinical Results**

**Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study**

Study No.LN4840		Treatment Groups	
		Test Product N =62	Reference Product N =62
Age (years)	Mean ± SD	24.2 ± 5.39	24.2 ± 5.39
	Range	18 - 44	18 - 44
Age Groups	< 18	-	-
	18 – 40	61 (98.38 %)	61 (98.38 %)
	40 – 64	1 (1.61 %)	1 (1.61 %)
	65 – 75	-	-
	> 75	-	-
Sex	Male	62 (100 %)	62 (100 %)
	Female	-	-
Race	Asian	62 (100 %)	62 (100 %)
	Black	-	-
	Caucasian	-	-
	Hispanic	-	-
	Other	-	-
BMI	Mean ± SD	21.6 ± 2.07	21.6 ± 2.07

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	Range	19.0 – 26.0	19.0 – 26.0
Other Factors		-	-

**Table 8. Dropout Information, Fasting Bioequivalence Study**

Subject No.	Reason	Period	Replaced?
63	did not report for period 2 check in due to personal reasons	2	N/A
65	did not report for period 2 check in due to personal reasons	2	N/A
66	did not report for period 2 check in due to personal reasons	2	N/A

**Table 9. Study Adverse Events, Fasting Bioequivalence Study**

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No.LN4840	
	Test N <sup>1</sup> (% <sup>2</sup> )	Reference N <sup>1</sup> (% <sup>2</sup> )
<b>Gastrointestinal</b>		
Loose stools	2 (3.17 %)	1 (1.56 %)
<b>Others</b>		
Pain at catheter insertion site	1 (1.58 %)	2 (3.12 %)
Decreased hemoglobin and PCV	-	1 (1.56 %)
Giddiness	1(1.58 %)	-
Headache	1(1.58%)	1(1.56%)
Increased SGOT	1(1.58%)	-
Total	6 (9.52 %)	4 (6.25 %)
Number of subject dosed	63	64

<sup>1</sup> The number of subjects that reported adverse event (AE).

<sup>2</sup> % (rate of occurrence) = N divided by number of subjects dosed with respective study drug x100

**Table 10. Protocol Deviations, Fasting Bioequivalence Study**

Type	Subject #s (Test)	Subject #s (Ref.)
N/A	N/A	N/A

**Comments on Dropouts/Adverse Events/Protocol Deviations:**

1. No serious adverse events (SAEs) were reported during the fasting BE study.
2. Several blood sampling deviations were recorded and there was no impact as the PK and statistical analysis used the actual times. The blood sampling time deviations were insignificant.
3. No subject experienced emesis during the fasting BE study.

4. Two (2) subjects (#31 and #56) experienced adverse events (AEs) that required therapy. All AEs were mild in severity and resolved without an impact on the outcome of the study.

### 4.1.1.3 Bioanalytical Results

**Table 11. Assay Validation – Within the Fasting Bioequivalence Study**

Analyte 1									
Parameter	Standard Curve Samples								
Concentration (ng/mL)	5.10	10.19	50.97	101.95	203.90	407.80	611.69	815.59	1019.49
Inter day Precision (%CV)	1.8	3.8	2.6	2.2	1.6	1.3	1.6	1.5	1.7
Inter day Accuracy (%Bias)	-0.6	0.6	2.7	1.6	0.5	0.7	-0.7	-1.8	-3.0
Linearity	0.9960 to 0.9999								
Linearity Range (ng/mL)	5.10 to 1019.49								
Sensitivity/LOQ (ng/mL)	5.10								

Parameter	Quality Control Samples		
Concentration (ng/mL)	15.28	360.79	721.58
Inter day Precision (%CV)	4.4	2.9	3.1
Inter day Accuracy (%Bias)	-4.2	-0.5	-3.9

**Comments on Study Assay Validation:**

Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially (Subjects #10 - #25)

**Comments on Chromatograms:**

Acceptable

**Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples**

SOP No.	Effective Date of SOP	SOP Title
BEC-BL-010-00	18-Apr-06	ANALYTICAL RUN ANALYSIS AND DOCUMENTATION PROCEDURES
BEC-BL-006-00	11-Apr-06	ROUTINE BATCH SAMPLE ANALYSIS
BEC-BL-006-01	28-May-08	ROUTINE BATCH SAMPLE ANALYSIS
BEC-BL-008-01	03-Sep-07	CHROMATOGRAPHY ACCEPTANCE

BEC-BL-013-00	04-May-06	EVENT RESOLUTION
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**Table 13. Additional Comments on Repeat Assays**

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	--

**Summary/Conclusions, Study Assays:**

Acceptable

**4.1.1.4 Pharmacokinetic Results**

**Table 14. Arithmetic Mean Pharmacokinetic Parameters**

Mean plasma concentrations are presented in [Table 18](#) and [Figure 1](#)

Fasting Bioequivalence Study, Study No. LN4840									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
AUC <sub>0-t</sub> (hr *ng/ml)	1112.87	30.72	564.27	2245.81	1113.36	34.09	617.62	2693.01	1.00
AUC <sub>∞</sub> (hr *ng/ml)	1137.84	31.29	582.35	2474.17	1136.23	34.49	630.17	2865.21	1.00
C <sub>max</sub> (ng/ml)	610.07	41.48	220.46	1746.10	663.95	61.17	217.11	2543.82	0.92
T <sub>max</sub> * (hr)	1.50	.	0.33	4.00	1.63	.	0.50	5.00	0.92
K <sub>el</sub> (hr <sup>-1</sup> )	0.39	25.42	0.14	0.60	0.40	26.78	0.15	0.75	0.97
T <sub>1/2</sub> (hr)	1.93	32.66	1.16	4.85	1.85	29.31	0.92	4.49	1.04

\* T<sub>max</sub> values are presented as median, range

**Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated**

Losartan Potassium Tablet 1 x 100 mg Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No. LOSA-IMTB-05EB04-2FA (LN4840)				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC <sub>0-t</sub> (hr *ng/ml)	1066.21	1058.66	1.01	97.1 - 104.5
AUC <sub>∞</sub> (hr *ng/ml)	1089.73	1080.44	1.01	97.3 - 104.5
C <sub>max</sub> (ng/ml)	565.88	581.94	0.97	88.8 - 106.5

**Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated**

Losartan Potassium Tablet 1 x 100 mg Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No LOSA-IMTB-05EB04-2FA (LN4840).					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (hr *ng/ml)	1066.12	1058.74	1.01	97.07	104.46
AUC <sub>∞</sub> (hr *ng/ml)	1089.64	1080.52	1.01	97.32	104.49
C <sub>max</sub> (ng/ml)	565.88	581.94	0.97	88.79	106.49

**Table 17. Additional Study Information, Fasting Study No.**

Root mean square error, AUC <sub>0-t</sub>	0.1224			
Root mean square error, AUC <sub>∞</sub>	0.1184			
Root mean square error, C <sub>max</sub>	0.3029			
	Test	Reference		
Kel and AUC <sub>∞</sub> determined for how many subjects?	62	62		
Do you agree or disagree with firm's decision?	Agree	Agree		
Indicate the number of subjects with the following:				
measurable drug concentrations at 0 hr	0	0		
first measurable drug concentration as C <sub>max</sub>	0	0		
Were the subjects dosed as more than one group?	No	No		
Ratio of AUC <sub>0-t</sub> /AUC <sub>∞</sub>				
Treatment	n	Mean	Minimum	Maximum
Test	62	0.98	0.91	0.99

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Reference	62	0.98	0.94	0.99
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**Comments on Pharmacokinetic and Statistical Analysis:**

The mean  $AUC_t/AUC_\infty$  ratio  $>0.9$  for both test and reference indicates that the firm's sampling schedule was carried out for a sufficient period of time. All subjects illustrated an  $AUC_t/AUC_\infty$  ratio  $>0.9$  for the parent compound, losartan. The reviewer agrees with the firm's determination for Kel and therefore used the SAS Code, "CONTINU2".

Bioequivalence is based on the statistical analysis of the data for the parent drug, losartan, and the active metabolite, losartan acid, is used only as supportive data.

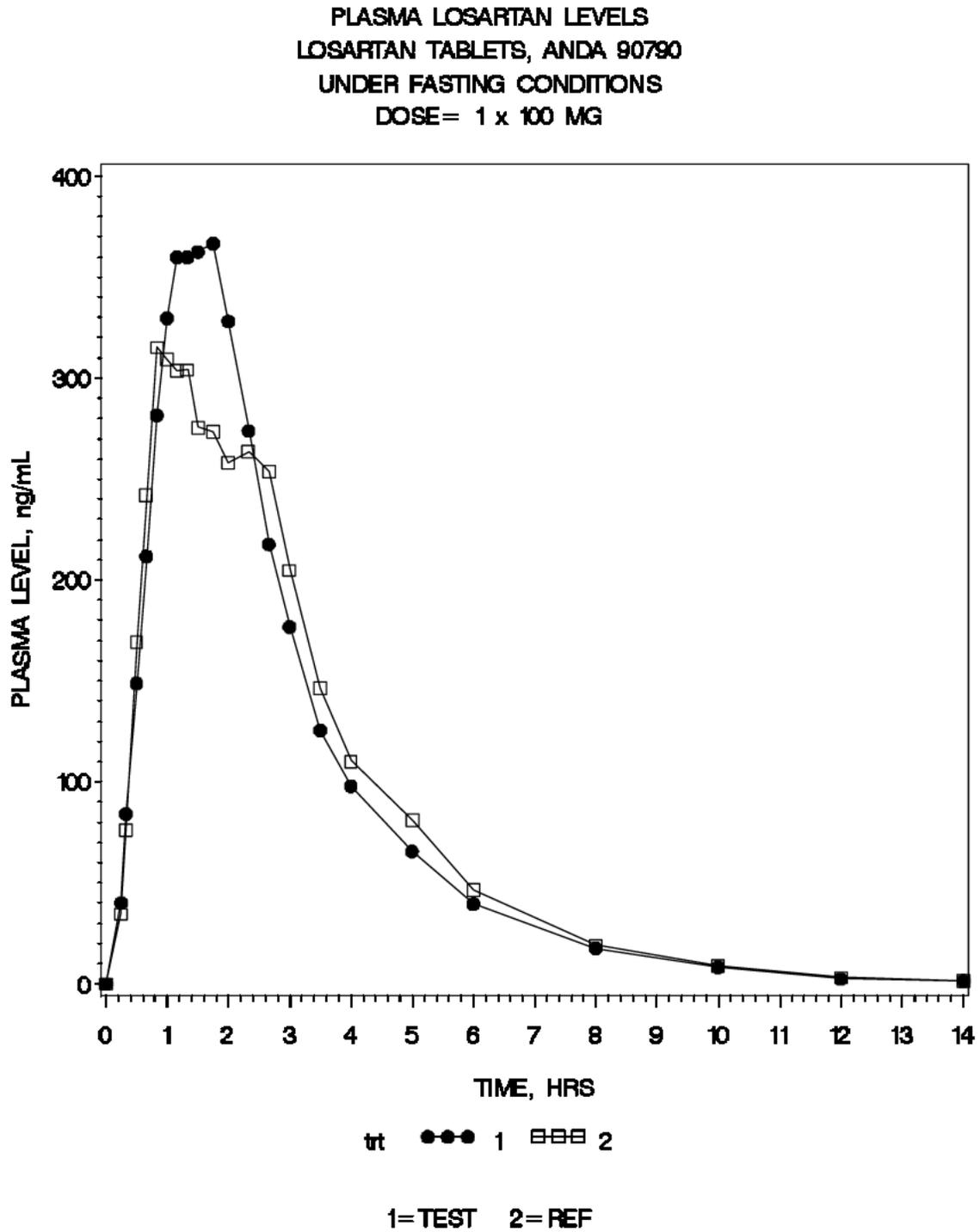
**Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:**

The single-dose fasting bioequivalence study on 1 x 100 mg tablet is acceptable.

**Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**

Analyte 1					
Time (hr)	Test (n= 62)		Reference (n= 62)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.25	40.15	312.58	34.56	338.04	1.16
0.33	84.19	255.57	76.21	315.81	1.10
0.50	148.83	169.47	169.61	232.91	0.88
0.66	211.76	121.23	242.21	153.94	0.87
0.83	281.63	101.07	315.19	126.65	0.89
1.00	329.79	81.55	309.41	108.49	1.07
1.16	359.94	72.17	303.81	98.43	1.18
1.33	359.93	66.69	304.08	93.25	1.18
1.50	362.59	59.75	275.67	75.88	1.32
1.75	366.74	49.72	273.59	56.02	1.34
2.00	328.21	52.00	258.04	60.91	1.27
2.33	273.90	54.21	263.45	63.79	1.04
2.66	217.68	55.13	253.87	66.84	0.86
3.00	176.85	66.89	204.80	67.38	0.86
3.50	125.61	63.28	146.47	72.23	0.86
4.00	97.92	72.73	110.30	79.83	0.89
5.00	65.62	64.04	81.12	81.75	0.81
6.00	39.65	63.47	46.74	76.11	0.85
8.00	17.52	74.26	19.12	78.91	0.92
10.00	8.40	116.37	9.05	111.24	0.93
12.00	2.53	247.01	3.13	210.39	0.81
14.00	1.44	335.10	1.49	289.76	0.97

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



## 4.1.2 Single-dose Fed Bioequivalence Study

### 4.1.2.1 Study Design

**Table 19. Study Information**

<b>Study Number</b>	LOSA-IMTB-05EB05-2FE (LN4841)
<b>Study Title</b>	COMPARATIVE, RANDOMIZED, 2-WAY CROSSOVER BIOAVAILABILITY STUDY OF LOSARTAN POTASSIUM TABLETS (APOTEX) AND COZAAR TABLETS (MERCK) (USA) UNDER FED CONDITIONS
<b>Clinical Site (Name &amp; Address)</b>	Apotex Research Pvt. Limited Bioequivalence Centre Site No: 2, Bommasandra Industrial area, Bommasandra Industrial Estate (P.O.), Bangalore-560 099, Karnataka, India Tel: +91-80-2289-1300 Fax: +91-80-2289-1364
<b>Principal Investigator</b>	Dr. Vimla D'Souza, M.B.B.S
<b>Dosing Dates</b>	Period 1: 30-Apr-08 Period 2: 07-May-08
<b>Analytical Site (Name &amp; Address)</b>	Apotex Research Pvt. Limited Bioequivalence Centre Bioanalytical Department Site No: 2, Bommasandra Industrial area, Bommasandra Industrial Estate (P.O.), Bangalore-560 099, Karnataka, India Phone: + 91-80-22891308
<b>Analysis Dates</b>	26-MAY-08 to 10-JUN-08
<b>Analytical Director</b>	(b) (6), M.Sc
<b>Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)</b>	41 days (30-APR-08 to 10-JUN-08)

**Table 20. Product Information**

Product	Test	Reference
<b>Treatment ID</b>	T	R
<b>Product Name</b>	Losartan Potassium Tablets	Cozaar <sup>®</sup> Tablets
<b>Manufacturer</b>	Apotex Inc.	Merck & Co., Inc., USA
<b>Batch/Lot No.</b>	LMTA/08054	U2364
<b>Manufacture Date</b>	03/2008	Not applicable
<b>Expiration Date</b>	03/2010	10/2010
<b>Strength</b>	100 mg	100 mg
<b>Dosage Form</b>	Tablet	Tablet

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<b>Bio-Batch Size</b>	(b) (4) Tablets	Not applicable
<b>Production Batch Size</b>	(b) (4) Tablets	Not applicable
<b>Potency (Assay)</b>	100.5 %	97.0%
<b>Content Uniformity (mean, %CV)</b>	Mean: 100.0% Range: 99.4 – 100.9% RSD: 0.5%	Not applicable
<b>Dose Administered</b>	100 mg	100 mg
<b>Route of Administration</b>	Oral	Oral

**Table 21. Study Design, Single-Dose Fed Bioequivalence Study**

<b>No. of Subjects</b>	77 subjects were enrolled and dosed in the study 68 subjects completed the study (dropout #2, #9, #11, #35, #51, #52, #54, #61 and #68) 68 subjects included in the statistical analysis
<b>No. of Sequences</b>	2
<b>No. of Periods</b>	2
<b>No. of Treatments</b>	2
<b>No. of Groups</b>	1 group
<b>Washout Period</b>	7 days
<b>Randomization Scheme</b>	<b>AB:</b> 1, 2, 6, 7, 10, 12, 15, 16, 18, 19, 21, 23, 26, 28, 29, 31, 33, 35, 39, 40, 42, 44, 45, 47, 50, 52, 54, 56, 57, 59, 61, 63, 66, 67, 71, 72, 73, 75 and 78 <b>BA:</b> 3, 4, 5, 8, 9, 11, 13, 14, 17, 20, 22, 24, 25, 27, 30, 32, 34, 36, 37, 38, 41, 43, 46, 48, 49, 51, 53, 55, 58, 60, 62, 64, 65, 68, 69, 70, 74, 76 and 77
<b>Blood Sampling Times</b>	Blood samples were collected at pre-dose, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.33, 4.66, 5, 5.5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24 and 30 hours post dosing.
<b>Blood Volume Collected/Sample</b>	Twenty four (24) 6 mL blood samples were drawn from each subject during each clinical period by individual venipuncture or indwelling catheter at pre-set times..
<b>Blood Sample Processing/Storage</b>	Blood samples were collected using 6 mL lavender cap vacuum tubes containing K2EDTA at the following time-points: Two 6 mL samples of blood were taken prior to dosing and single 6 mL samples at each sampling time after dosing at blood sampling times listed above. Blood samples were collected after discarding 0.5 mL of heparinised blood for all the sampling times except for 30 hours. Blood samples were centrifuged and the plasma obtained were divided into two portions and transferred into prelabelled polypropylene storage tubes and stored in a -30°C set point freezer pending assay.
<b>IRB Approval</b>	Yes, 04/09/08
<b>Informed Consent</b>	Yes, 04/09/08
<b>Length of Fasting Before Meal</b>	All subjects fasted overnight for at least 10 hours (overnight) prior to scheduled time for dosing. Fasting was maintained for at least 4 hours after dosing.

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<b>Length of Confinement</b>	At least 10 hours prior to dosing until 30 hours post-dose
<b>Safety Monitoring</b>	Vital signs (including scheduled blood pressure and pulse rate measurements) diagnostic tests were performed at the times specified in the protocol.

<b>Standard FDA Meal Used?</b>	No	
<b>If No, then meal components and composition is listed in the tables below</b>		
<b>Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study</b>		
<b>Composition</b>	<b>Percent</b>	<b>Kcal</b>
<b>Fat</b>	53.64 %	520.38
<b>Carbohydrate</b>	27.86 %	270.28
<b>Protein</b>	18.49 %	179.36
<b>Total</b>	99.99 %	970.02

<b>Components of Non-standard FDA Meal Used in Fed Bioequivalence Study</b>	
<b>Component</b>	
Two slices of toast bread	
Omelette (2 eggs)	
Chicken Tikka (60 gm)	
Hash brown potato (4 Nos.),	
240 mL of whole milk	
Sugar (5 gm),	
Butter (10 gm)	

**Comments on Study Design:**

The study design is acceptable.

**4.1.2.2 Clinical Results**

**Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study**

Study No. LN4841			
		Treatment Groups	
		Test Product N =68	Reference Product N =68
Age (years)	Mean ± SD	25.4 ± 5.86	25.4 ± 5.86
	Range	19 - 44	19 - 44
Age Groups	< 18	-	-
	18 – 40	65 (95.58 %)	65 (95.58 %)
	40 – 64	3 (4.41 %)	3 (4.41 %)
	65 – 75	-	-
	> 75	-	-
Sex	Male	68 (100 %)	68 (100 %)
	Female	-	-
Race	Asian	68 (100 %)	68 (100 %)
	Black	-	-
	Caucasian	-	-
	Hispanic	-	-
	Other	-	-
BMI	Mean ± SD	21.7 ± 1.99	21.7 ± 1.99
	Range	19.0 – 25.6	19.0 – 25.6
Other Factors		-	-

**Table 23. Dropout Information, Fed Bioequivalence Study**

Subject No.	Reason	Period	Replaced?
LN02	LN02 was withdrawn (on 30-Apr-08 at around 15:05 hrs) as he had vomited in period 1 (post dose) of the study. This was possibly related to test preparation	Period 1	No
LN09	LN09 was withdrawn (on 07-May-08 at around 09:57 hrs) as he had vomited in period 2 (post dose). This was possibly related to test preparation.	Period 2	No
LN11	LN11 was withdrawn (on 30-Apr-08 at around 10:22 hrs) as he vomited in period 1 (post dose). This was possibly related to reference preparation	Period 1	No
LN51	LN51 was withdrawn (on 30-Apr-08 at around 19:38 hrs) as per PK recommendations as he did not consume the standardized breakfast 30 minutes prior to dosing in period 1.	Period 1	No

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LN52	LN52 was withdrawn (on 30-Apr-08 at around 19:40 hrs) as per PK recommendations as he did not consume the standardized breakfast 30 minutes prior to dosing in period 1.	Period 1	No
LN54	LN54 was withdrawn (on 30-Apr-08 at around 19:42 hrs) as per PK recommendations as he did not consume the standardized breakfast 30 minutes prior to dosing in period 1.	Period 1	No
LN61	LN61 was withdrawn (on 06-May-08 at around 20:13 hrs) at period 2 check in as he tested positive for Benzodiazepine in urine drug screen. This was not related to test preparation.	Period 2 check in	No

Note: LN35 was withdrawn as he did not check in for period 2 due to personal reasons on 06-May-08. LN68 was withdrawn as he did not check in for period 2 due to personal reasons on 06-May-08

**Table 24. Study Adverse Events, Fed Bioequivalence Study**

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. LN4841	
	Test N <sup>1</sup> (% <sup>2</sup> )	Reference N <sup>1</sup> (% <sup>2</sup> )
<b>Body as a whole</b>		
Flu like syndrome	1 (1.35 %)	1 (1.38 %)
<b>Gastrointestinal</b>		
Nausea and vomiting	1 (1.35 %)	1 (1.38 %)
Vomiting	1 (1.35 %)	-
<b>Respiratory system</b>		
Upper respiratory tract infection	1 (1.35 %)	-
<b>Others</b>		
Headache	1 (1.35 %)	-
Increased SGPT	-	1 (1.38 %)
Total	5 (6.75 %)	2 (2.77 %)
Number of subject dosed	74	72

<sup>1</sup> The number of subjects that reported adverse event (AE).

<sup>2</sup> % (rate of occurrence) = N divided by number of subjects dosed with respective study drug x 100

**Table 25. Protocol Deviations, Fed Bioequivalence Study**

Type	Subject #s (Test)	Subject #s (Ref.)
Unplanned: According to the section 4.4 of the study protocol under Administration of Food and Fluid, "The standard breakfast to be served a maximum of 30 minutes prior to dosing will consist of Two slices of toast bread, Omelette (2 eggs), Chicken Tikka (60 gm), Hash brown potato (4 Nos.), 240	--	LN01

ANDA 90-790  
Single-Dose Fed Bioequivalence Study Review

<p>mL of whole milk, Sugar (5 gm), Butter (10 gm) The meal must be completely eaten by each of the study subjects prior to dosing”. In period 2 of the study, subject ID LN01 did not consume 35 gms of Chicken tikka which amounted to 69.65 calories. The subject consumed all the contents of the standardized breakfast except for chicken tikka amounting to 35 gms within 30 minutes prior to dosing and hence was non compliant to the protocol requirements. No implications are expected as the total calorie consumed by subject is 900.37 calories instead of 970.02 calories contributed by Carbohydrates, Fats and Proteins. Also as per FDA regulatory guidance on Food effect Bioavailability and Fed Bioequivalence studies guidelines approximately 800-1000 calories meal is required, hence no implications are expected. However subject consumed approximately 50 percent of the total caloric content of the meal derived from fat. The violation to this restriction was documented and also it was decided by Principal Investigator that the subject can be dosed for the study and hence the subject was continued in the study.</p>		
<p>Unplanned: According to the section 4.1 of the study protocol under standardization, “The subjects will be housed until 30 hours post-dose in each period”. In period 1 of the study, Subject No. LN72 left the clinical facility at 09:43 hrs on 01-May-08, accounting to around 24.0 hours of housing instead of 30 hours post dose. LN72 had to leave the clinical site due to personal reasons which he mentioned as urgent. 30.0 hr sample was not collected as he did not report back after release from the site and directly reported for period 2 check in. No implications are expected as the subject had no clinical complaints and the checkout procedures including vitals and physician assessment were completed. The subject’s safety was not compromised and also the study integrity is not affected. The subject was counseled about completing the study and the importance of obtaining the samples as per the protocol was explained to him. The subject reported for period 2 and completed the study.</p>	LN72	--
<p>Unplanned: According to the section 4.4 of the study protocol under administration of food and fluid, “The standard breakfast to be served a maximum of 30 minutes prior to dosing” and according to the section 4.7 of the study protocol under sampling times, “Blood samples will be taken at 5–45 minutes prior to dosing time (0), followed by further samples at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.33, 4.66, 5, 5.5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24 and 30 hours after dosing”. In period 1 of the study, subject nos. LN51, LN52 &amp; LN54 consumed the given breakfast by exceeding the 30 minutes of their given time and hence the dosing time was rescheduled for the same subjects. Also the pre dose sample timings exceeded 45 minutes prior to dosing for the same subjects. For subject number LN51 breakfast</p>	LN52 and LN54	LN51

<p>start and end timings were 0854 hrs and 0933 hrs, respectively, whereas scheduled and actual dosing timings were 0924 hrs and 0938 hrs, respectively. Similarly, for subject number LN52 breakfast start and end timings were 0854 hrs and 0930 hrs, respectively, whereas scheduled and actual dosing timings were 0924 hrs and 0940 hrs, respectively. Also for subject number LN54 breakfast start and end timings were 0856 hrs and 0940 hrs whereas scheduled and actual dosing timings were 0926 hrs and 0942 hrs, respectively. All the activities including blood sample collection, vitals and meal etc for these three subjects were rescheduled accordingly.</p> <p>The subjects were unable to consume the given quantity of the breakfast within 30 minutes prior to dosing and they were non compliant to the protocol requirements. Due to delay in consumption of breakfast and dosing time, pre dose sample timings were beyond 45 minutes of their dosing time. No implications are expected as the subjects were withdrawn from the study. The violations to these restrictions were documented on a case to case basis and also the subjects were withdrawn from the study as recommended by Pharmacokinetic department and also due to noncompliance with FDA regulatory guidance on Food effect Bioavailability and Fed Bioequivalence studies guidelines.</p>		
---	--	--

**Comments on Adverse Events/Protocol Deviations:**

1. No serious adverse events (SAEs) were reported during the fed BE study.
2. Several blood sampling deviations were recorded at various time points. The blood sampling time deviations were not significant ( $\pm 5\%$ ).
3. Three (3) subjects (#2, #9 and #11) experienced emesis during the fed study. All subjects reported vomiting on one (1) occasion. The episodes were mild in severity and occurred approximately 4 hours, 48 minutes and 45 minutes, respectively after the subjects had received a single-oral dose of the test product (#2 and #9) or reference product (#11). The data for all three (3) subjects were excluded in BE statistical evaluations for losartan and losartan acid, since; the episode (s) of emesis were reported within 2x the median Tmax for losartan and losartan acid, 1 hour and 3-4 hours, respectively.
4. Three (3) subjects (#1, #62 and #67) experienced an adverse event (AEs) that required therapy. All AEs were mild in severity, not related to drug treatment and resolved without an impact on the outcome of the study.

**4.1.2.3 Bioanalytical Results**

**Table 26. Assay Validation – Within the Fed Bioequivalence Study**

Analyte 1									
Parameter	Standard Curve Samples								
Concentration (ng/mL)	5.10	10.19	50.97	101.95	203.90	407.80	611.69	815.59	1019.49
Inter day Precision (%CV)	1.6	3.2	1.5	1.8	1.7	1.6	2.1	1.5	2.2
Inter day Accuracy (%Bias)	-0.4	0.0	2.8	1.2	0.1	0.8	-0.8	-1.2	-2.6
Linearity	0.9972 to 0.9997								
Linearity Range (ng/mL)	5.10 to 1019.49								
Sensitivity/LOQ (ng/mL)	5.10								

Parameter	Quality Control Samples		
Concentration (ng/mL)	15.28	360.79	721.58
Inter day Precision (%CV)	3.9	2.4	2.9
Inter day Accuracy (%Bias)	-5.8	-0.7	-3.9

**Comments on Study Assay Validation:**

Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially (Subjects #12 - #27)

**Comments on Chromatograms:**

Acceptable

**Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples**

SOP No.	Effective Date of SOP	SOP Title
BEC-BL-010-00	18-Apr-06	ANALYTICAL RUN ANALYSIS AND DOCUMENTATION PROCEDURES
BEC-BL-006-00	11-Apr-06	ROUTINE BATCH SAMPLE ANALYSIS
BEC-BL-006-01	28-May-08	ROUTINE BATCH SAMPLE ANALYSIS

BEC-BL-008-01	03-Sep-07	CHROMATOGRAPHY ACCEPTANCE
BEC-BL-013-00	04-May-06	EVENT RESOLUTION

**Table 28. Additional Comments on Repeat Assays**

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	--

**Summary/Conclusions, Study Assays:**

Acceptable

**4.1.2.4 Pharmacokinetic Results**

**Table 29. Arithmetic Mean Pharmacokinetic Parameters**

Mean plasma concentrations are presented in [Table 33](#) and [Figure 2](#)

Fed Bioequivalence Study, Study No. LN4841									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
AUC <sub>0-t</sub> (hr *ng/ml)	1145.15	25.51	609.70	2302.00	1103.83	23.70	637.92	1946.87	1.04
AUC <sub>∞</sub> (hr *ng/ml)	1171.19	25.62	624.35	2426.69	1136.30	23.08	650.01	2011.93	1.03
C <sub>max</sub> (ng/ml)	481.22	47.14	151.38	1228.26	443.60	43.52	116.97	952.27	1.08
T <sub>max</sub> * (hr)	2.50	.	1.00	7.00	4.17	.	1.00	14.00	0.60
K <sub>el</sub> (hr <sup>-1</sup> )	0.40	27.28	0.19	0.74	0.39	27.23	0.11	0.72	1.03
T <sub>1/2</sub> (hr)	1.88	30.11	0.93	3.67	1.97	39.55	0.96	6.37	0.96

\* T<sub>max</sub> values are presented as median, range

**Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated**

Losartan Potassium Tablet 1 x 100 mg Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study, Study No. LOSA-IMTB-05EB05-2FE (LN4841)				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC <sub>0-t</sub> (hr *ng/ml)	1111.17	1075.47	1.03	100.5 - 106.2
AUC <sub>∞</sub> (hr *ng/ml)	1131.94	1109.52	1.02	99.4 - 104.7
C <sub>max</sub> (ng/ml)	431.41	402.57	1.07	95.9 - 119.7

**Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated**

Losartan Potassium Tablet 1 x 100 mg Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study, Study No. LOSA-IMTB-05EB05-2FE (LN4841)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (hr *ng/ml)	1111.30	1075.36	1.03	100.56	106.21
AUC <sub>∞</sub> (hr *ng/ml)	1132.08	1109.39	1.02	99.41	104.75
C <sub>max</sub> (ng/ml)	431.41	402.57	1.07	95.95	119.70

**Table 32. Additional Study Information**

Root mean square error, AUC <sub>0-t</sub>	0.0955	
Root mean square error, AUC <sub>∞</sub>	0.0900	
Root mean square error, C <sub>max</sub>	0.3863	
	<b>Test</b>	<b>Reference</b>
Kel and AUC <sub>∞</sub> determined for how many subjects?	67	67
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C <sub>max</sub>	5 subjects (#3, #14, #17, #32 and #66)	4 subjects (#17, #26, #60 and #62)
Were the subjects dosed as more than one group?	No	No

Ratio of AUC <sub>0-t</sub> /AUC <sub>∞</sub>				
Treatment	n	Mean	Minimum	Maximum
Test	67	0.98	0.95	0.99
Reference	67	0.98	0.68	0.99

**Comments on Pharmacokinetic and Statistical Analysis:**

The firm's analysis of losartan PK parameters included the data for subjects #3, #14, #17, #32 and #66 for the test product and data for subjects #17, #26, #60 and #62 who had the first measurable drug concentration as the subject's C<sub>max</sub>. According to the General BA/BE Guidance, collection of an early time point between 5 and 15 minutes after dosing followed by additional sample collections in the first hour after dosing may be sufficient to assess early peak concentrations. The firms scheduled time points are **not** within the recommended collection time (pre-dose, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.33, 4.66, 5, 5.5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24 and 30 hours post dosing). The reviewer does not agree with the firm's decision to include the subjects listed above for the statistical analysis. The reviewer reanalyzed the PK parameters excluding the following subjects: #3, #14, #17, #26, #32, #60, #62 and #66 and the losartan results (90% CI) remained within the acceptable range of 80 to 125 %

The mean AUC<sub>t</sub>/AUC<sub>∞</sub> ratio >0.9 for both test and reference indicates that the firm's sampling schedule was carried out for a sufficient period of time. The reviewer agrees with the firm's determination for Kel and therefore used the SAS Code, "CONTINU2.

Based on the literature data on T<sub>max</sub> (1 hour and 3-4 hours) and T<sub>1/2</sub> (2 hour and 6-9 hours) for losartan and losartan acid, respectively, the firm's study design with a sampling time of 30 hours is appropriate. However, there is one subject with an observed T<sub>1/2</sub>

much longer than the reported values of 2 hour and 6-9 hours, that's illustrated by an AUCt/AUC $\infty$  ratio below 0.8. See table below:

<b>Subject</b>	<b>AUCt/AUC<math>\infty</math> ratio</b>	<b>Treatment</b>
22	0.68	Test

Bioequivalence is based on the statistical analysis of the data for the parent drug, losartan, and the active metabolite, losartan acid, is used only as supportive data.

**Comment on Tmax Difference:**

Although the median Tmax for the test and RLD products was comparable in the fasting study, the median Tmax for the test and RLD products in the fed study was dissimilar: 2.50 hours and 4.17 hours, respectively. Per the RLD labeling, the food delayed Tmax of the RLD product. The delay was observed for the test product in the current ANDA. Additionally, based on the Tmax data from a fed study of ANDA 90083 (Aurobindo) reviewed previously (DARRTS), the median Tmax for the test and RLD products from this study was both 2.5 hours. Also, based on the Tmax data from a fed study of ANDA 78243 (Zydus) reviewed previously (DARRTS), the median Tmax for the test and RLD products from this study was 2.35 hours and 2.52 hours, respectively. The median Tmax for the current test product under nonfasting conditions, although different from that of the RLD in the current fed study, appeared to be within the median Tmax values obtained in other fed studies. Therefore, the Tmax difference could be contributed to the variability in the RLD product, and is considered acceptable.

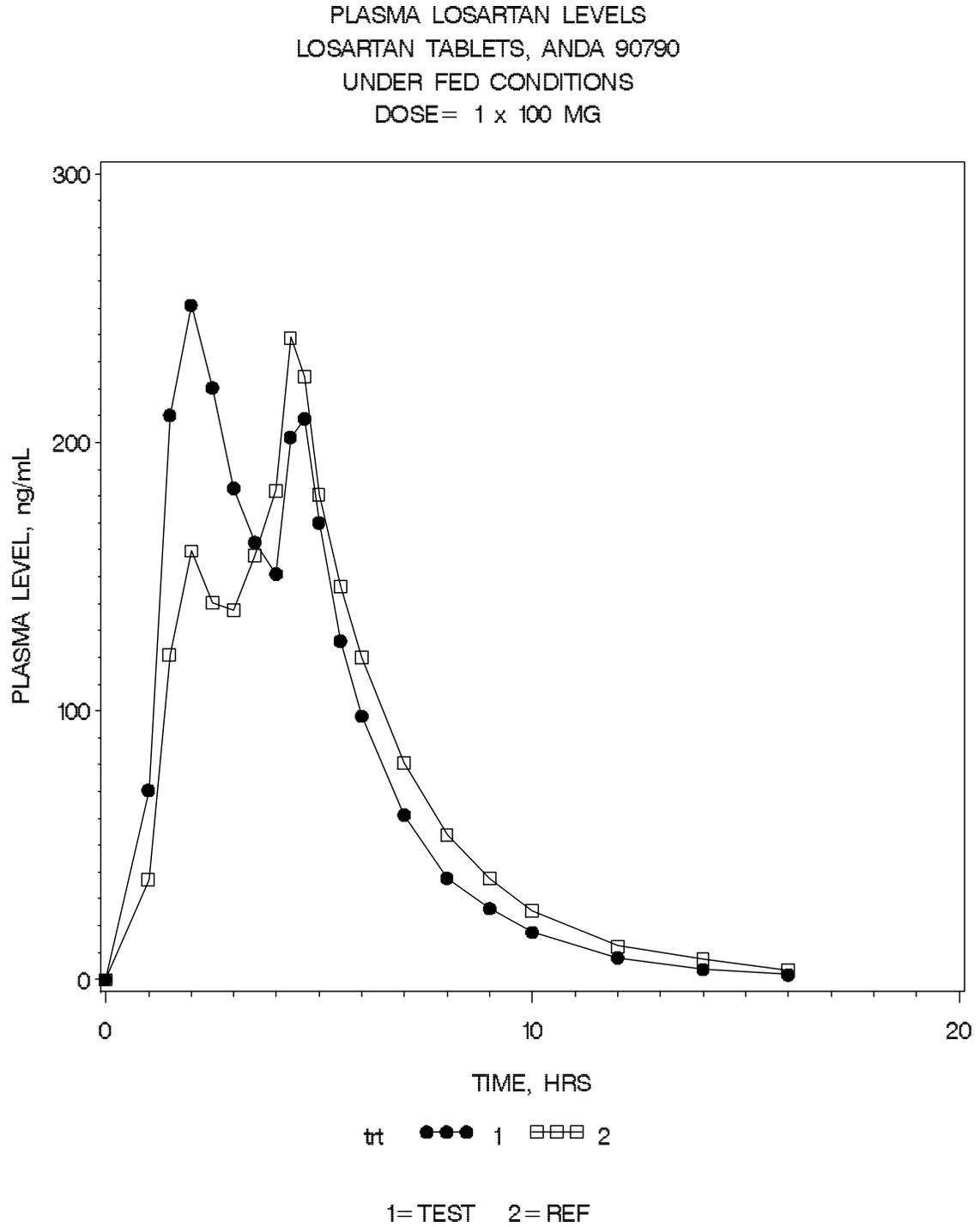
**Summary/Conclusions, Single-Dose Fed Bioequivalence Study:**

The single-dose fed bioequivalence study on 1 x 100 mg tablet is acceptable.

**Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study**

Analyte 1					
Time (hr)	Test (n= 68)		Reference (n= 68)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
1.00	70.48	261.35	37.33	322.46	1.89
1.50	210.15	122.39	120.94	160.63	1.74
2.00	251.15	80.96	159.63	116.99	1.57
2.50	220.37	68.67	140.35	104.17	1.57
3.00	183.01	70.79	137.72	95.99	1.33
3.50	162.89	63.63	158.02	101.68	1.03
4.00	151.08	64.96	182.21	93.85	0.83
4.33	201.97	80.54	239.13	83.29	0.84
4.66	208.90	83.01	224.46	68.91	0.93
5.00	170.14	77.08	180.57	71.31	0.94
5.50	126.12	75.11	146.29	72.72	0.86
6.00	98.08	69.13	119.91	67.02	0.82
7.00	61.29	72.85	80.78	73.05	0.76
8.00	37.74	67.25	53.78	75.77	0.70
9.00	26.43	70.57	37.78	81.97	0.70
10.00	17.59	81.14	25.72	93.04	0.68
12.00	8.07	142.89	12.46	125.48	0.65
14.00	3.75	186.44	7.48	239.27	0.50
16.00	1.76	303.53	3.54	266.80	0.50
20.00	.	.	.	.	.

**Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study**



## 4.2 Formulation Data

Component	Reference to Quality Standard	Function	% w/w of coated tablet	mg / tablet		
				25 mg	50 mg	100 mg
(b) (4)						
Losartan Potassium	(b) (4) USP	Active Pharmaceutical Ingredient	27.23	25.00	50.00	100.00
(b) (4)						
<b>Coated Tablet Weight</b>			<b>100.00</b>	<b>91.80</b>	<b>183.60</b>	<b>367.20</b>

USP = United States of Pharmacopoeia  
 NF = National Formulary  
 IH = Apotex specification

Ingredients	(b) (4)		
	(b) (4)	mg/tablet	
		25mg*	50mg**

(b) (4)

**Note:** Formulation data above is taken from the ANDA checklist review and the IIG limits have been verified by the reviewer. Also, the IIG limits are within limits based on the Maximum Daily Dose (MDD) of losartan, which is 100 mg (1 x 100 mg) daily for hypertension.

<b>Is there an overage of the active pharmaceutical ingredient (API)?</b>	NO
<b>If the answer is yes, has the appropriate chemistry division been notified?</b>	N/A
<b>If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?</b>	N/A
<b>Comments on the drug product formulation:</b>	Acceptable. The quantities of the inactive ingredients in the test products, based on the maximum daily dose (MDD) of 100 mg losartan are within the limits recommended in FDA's inactive ingredients database. Also, all colors are within the IIG limits limits.

### 4.3 Dissolution Data

<b>Dissolution Review Path</b>	Dissolution review completed within this review
--------------------------------	---

**Table 34. Dissolution Data**

<b>Dissolution Conditions</b>		<b>Apparatus:</b>		USP-II, Paddle						
		<b>Speed of Rotation:</b>		50 RPM						
		<b>Medium:</b>		Water						
		<b>Volume:</b>		900 mL						
		<b>Temperature:</b>		37 ± 0.5°C						
<b>Firm's Proposed Specifications</b>		Not less than 75% (Q= (b) (4)) of the labeled amount (100mg) Losartan Potassium is dissolved in 45 minutes (NOTE: The FDA-recommended specification is NLT 75% (Q) in 30 minutes)								
<b>Dissolution Testing Site (Name, Address)</b>		Apotex Research Private Limited Plot No 1, Bommasandra Industrial Area, 4th Phase Jigani Link Road, Jigani Bangalore India- 560 099								
<b>Study Ref No.</b>	<b>Testing Date</b>	<b>Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)</b>	<b>Dosage Strength &amp; Form</b>	<b>No. of Dosage Units</b>	<b>Collection Times (minutes)</b>				<b>Study Report Location</b>	
					<b>10</b>	<b>20</b>	<b>30</b>	<b>45</b>		
Comparative Dissolution study	26-Mar-2008	Losartan Potassium Tablets 100 mg, Batch No.: LMTA/08054 (ARPL, India) Manufacture: March - 2008 Exp. Date : March - 2010	100 mg & Tablets	12	Mean	46.32	76.98	89.82	97.78	Section 5.3.1.3
					Range	(b) (4)				
					%CV	12.3	5.7	4	2.5	
	04-Feb-2008	Cozaar Tablets, 100 mg (Merck & Co., Inc., USA), Batch No.: U2364, Exp Date: 10 - 2010	12	Mean	48.59	86.75	98.12	101.43		
Range				(b) (4)						

					%CV	6.7	2.9	3.7	0.7	
--	--	--	--	--	-----	-----	-----	-----	-----	--

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location
						10	20	30	45	
Comparative Dissolution study	02-Apr-2008	Losartan Potassium Tablets 50 mg, Batch No.: LMTB/08053 (ARPL, India) Manufacture: March - 2008 Exp. Date : March - 2010	50 mg & Tablets	12	Mean	46.72	83.59	96.67	99.49	Section 5.3.1.3
					Range	(b) (4)				
					%CV	17.3	5.9	2.6	1.9	
	17-May-2007	Cozaar Tablets, 50 mg (Merck & Co., Inc., USA), Batch No.: R2290 Exp Date: 02 - 2008			Mean	59.77	92.64	96.78	98.56	
					Range	(b) (4)				
					%CV	15.48	8.60	5.08	2.65	
Comparative Dissolution study	02-Apr-2008	Losartan Potassium Tablets 25 mg, Batch No.: LMTC/08052 (ARPL, India) Manufacture: March - 2008 Exp. Date : March - 2010	25 mg & Tablets	12	Mean	61.55	93.42	98.06	99.31	Section 5.3.1.3
					Range	(b) (4)				
					%CV	8.3	3.4	2.1	1.8	
	21-May-2007	Cozaar Tablets, 25 mg (Merck & Co., Inc., USA), Batch No.: R2173 Exp Date: 11 - 2007			Mean	65.48	98.43	99.88	99.49	
					Range	(b) (4)				
					%CV	8.94	2.33	1.65	1.78	

**4.4 Detailed Regulatory History (If Applicable)**

None

**4.5 Consult Reviews**

None

Following this page, 142 pages withheld in full - (b)(4) SAS Output

**4.7 Additional Attachments**

None

BIOEQUIVALENCE DEFICIENCIES

ANDA: 090790  
APPLICANT: Apotex Corp  
DRUG PRODUCT: Losartan Potassium Tablets, 100 mg, 50 mg  
and 25 mg

The Division of Bioequivalence (DBE) has completed its review of your submissions acknowledged on the cover sheet. The following deficiency has been identified:

Your dissolution testing data using the FDA-recommended method are acceptable. However, your proposed specification (NLT <sup>(b)</sup><sub>(4)</sub>% (Q), 45 min) is not acceptable. Based on the data submitted, the DBE recommends a more appropriate specification for the test product. Please acknowledge your acceptance of the following FDA-recommended dissolution method and specification:

:  
The dissolution testing should be conducted in 900 mL of water (deaerated) at 37°C, using USP Apparatus II (paddles) @ 50 rpm. The test products should meet the following specification: Not less than 75% (Q) in 30 minutes.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

#### 4.8 Outcome Page

ANDA: 090790

#### Enter Review Productivity and Generate Report

<http://cdsogd1/bioproduct>

**5 COMPLETED ASSIGNMENT FOR 90790 ID: 10197**

**Reviewer:** Johnson, Glendolynn      **Date Completed:**

**Verifier:** ,      **Date Verified:**

**Division:** Division of Bioequivalence

**Description:** Losartan Tablets (Apotex)

---

*Productivity:*

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
10197	8/27/2008	Bioequivalence Study	Fasting Study	1	1
10197	8/27/2008	Bioequivalence Study	Fed Study	1	1
10197	8/27/2008	Other	Dissolution Waiver	2	2
				<b>Bean Total:</b>	<b>4</b>

---

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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

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/s/

-----  
GLENDOLYNN S JOHNSON  
01/28/2010

YIH CHAIN HUANG  
01/28/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER  
01/28/2010

**DIVISION OF BIOEQUIVALENCE  
DISSOLUTION ACKNOWLEDGEMENT REVIEW**

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<b>ANDA No.</b>	90-790
<b>Drug Product Name</b>	Losartan Tablets
<b>Strength</b>	25 mg, 50 mg, and 100 mg
<b>Applicant Name</b>	Apotex Corp.
<b>Original Submission Date</b>	August 27, 2008
<b>Submission Date(s) of Amendment(s) Under Review</b>	February 1, 2010
<b>Reviewer</b>	Alpita Popat, PharmD

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**EXECUTIVE SUMMARY**

This is a review of the dissolution specification acknowledgement from the firm.

The firm has accepted the FDA-recommended dissolution method and specification.

The bioequivalence section of the application is complete.

**COMMENTS:**

None

**DEFICIENCY COMMENTS:**

None

**RECOMMENDATIONS:**

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing. The bioequivalence section of the application is acceptable.

**Enter Review Productivity and Generate Report**

<http://cdsogd1/bioprod>

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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/s/

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ALPITA POPAT  
02/03/2010

AIDA L SANCHEZ  
02/04/2010

DALE P CONNER  
02/16/2010

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 90-790**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

# APOTEX

ADVANCING GENERICS

August 27, 2008

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

To Whom It May Concern,

**Re: Original Abbreviated New Drug Application Pre-Assigned ANDA # 090790  
Losartan Potassium Tablets, 25mg, 50mg and 100mg.**

Apotex Corp. is hereby submitting an Abbreviated New Drug Application seeking approval to market Losartan Potassium Tablets, 25mg, 50mg and 100mg on the basis of demonstrating comparable bioavailability to the Reference Listed Drug Cozaar<sup>®</sup> Tablets manufactured by Merck & Co., Inc., to NDA No. 020386.

Losartan Potassium Tablets 25mg, 50mg and 100mg was developed and manufactured at Apotex Research Private Limited, Bangalore, India. Apotex Research Private Limited is a wholly owned subsidiary of Apotex Inc.

Comparative, randomized, 2-way crossover bioavailability studies of Apotex's Losartan Potassium Tablets and Merck's Cozaar<sup>®</sup> Tablets under fasting and fed conditions are included in this application.

The ANDA is submitted in the eCTD format provided on the enclosed CD. Please note the following:

- In Module 2, the Quality Overall Summary (QOS) is provided in accordance with the Question-based Review (QbR) format. The QOS is provided in both pdf and MS-Word format.
- In Module 2, the Clinical Summary section includes the tables for the bioavailability study (Table 1 through 8). The remaining tables for the bioavailability study (Tables 9 through 16) are located in Module 5.
- In Module 3, there is information on drug substance Losartan Potassium. The source of the drug substance, Losartan Potassium is (b) (4) DMF (b) (4). This application includes all the test methods and the specifications for the drug substance. Reference is made to Apotex's ANDA No. 090150 Losartan Potassium and Hydrochlorothiazide Tablets 50/12.5 mg, 100/12.5 mg and 100/25 mg submitted on November 30, 2007 for information on the drug substance Losartan Potassium. The drug substance manufacturer and information relating to the drug substance Losartan Potassium provided in this application are the same as provided in Apotex's ANDA No. 090150.
- In Module 3, Section 3.2.R.2.P, a comparability protocol has been submitted.



- In Module 5, comparative dissolution testing between the test and reference products has been provided using the USP Apparatus # 2 (paddle), 50 rpm, 900mL water with sampling times of 10, 20, 30 and 45 minutes. The proposed specification is Q: <sup>(b) (4)</sup>% in 45 minutes for Losartan Potassium Tablets.

Furthermore, Apotex Corp. commits to resolve any issues identified in the methods validation process after approval.

A signed Form 356h is provided.

Please note Apotex has submitted a letter for Non-Repudiation Agreement.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., at telephone (954) 384-3986 or fax: (954) 349-4233, or alternatively, please do not hesitate to contact myself at tel: (416) 401-7889 or fax: (416) 401-3809.

Sincerely,

*h*   
\_\_\_\_\_  
Bernice Tao  
Director, Regulatory Affairs – US

*08/27/08*  
\_\_\_\_\_  
Date

# **APOTEX**

**ADVANCING GENERICS**

October 17, 2008

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

To Whom It May Concern,

**Re: Response to FDA Screening Deficiency received on October 16, 2008**  
**Losartan Potassium Tablets 25 mg, 50 mg and 100 mg**  
**ANDA No. 090-790**

Apotex Corp. is hereby submitting a response to the screening deficiency comments for Losartan Potassium Tablets 25 mg, 50 mg and 100mg ANDA No. 090790 dated October 16, 2008. The response is submitted in a Question and Answer format and follows on a separate page.

Please note that a fax copy was also provided to Ian Margand, Project Manager, Regulatory Support Branch, FDA on October 17, 2008.

This amendment is being submitted in eCTD format and is provided on the enclosed CD. Please note that Apotex has submitted a Letter of Non-Repudiation Agreement (dated December 17, 2007) and therefore only a copy of the cover letter is provided along with the CD. An electronic copy of the 356h form is included in section 1.1.2. The enclosed CD has been confirmed to be virus free using McAfee VirusScan Enterprise 7.1.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at (954) 984-3986 by fax at (954) 349-4233, or alternatively please do not hesitate to contact me at (416) 401-7889, by fax at (416) 401-3809 or via email at [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,





**MODULE 1**  
**ADMINISTRATIVE**

ACCEPTABLE

<b>1.1</b>	<b>1.1.2 Signed and Completed Application Form (356h) (original signature)</b> (Check Rx/OTC Status) RX YES	<input checked="" type="checkbox"/>
<b>1.2</b>	<b>Cover Letter</b> Dated: AUGUST 27, 2008	<input checked="" type="checkbox"/>
<b>1.2.1</b>	<b>Form FDA 3674</b> <a href="#">(PDF)</a> YES Box "B"	<input checked="" type="checkbox"/>
*	<b>Table of Contents (paper submission only)</b> YES	<input checked="" type="checkbox"/>
<b>1.3.2</b>	<b>Field Copy Certification (original signature)</b> NA (N/A for E-Submissions)	<input type="checkbox"/>
<b>1.3.3</b>	<b>Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:</b> 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	<input checked="" type="checkbox"/>
<b>1.3.4</b>	<b>Financial Certifications</b> Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	<input checked="" type="checkbox"/>
<b>1.3.5</b>	<b>1.3.5.1 Patent Information</b> Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations <b>1.3.5.2 Patent Certification</b> 1. Patent number(s) PIV '075 exp. 9/4/2014 PIII '197 exp. 4/6/2010 2. Paragraph: (Check all certifications that apply) '069 exp. 2/11/2010 MOU <input checked="" type="checkbox"/> PI <input type="checkbox"/> PII <input type="checkbox"/> PIII <input type="checkbox"/> PIV <input checked="" type="checkbox"/> (Statement of Notification) <input type="checkbox"/> MOU '079 exp. 11/11/2010 3. Expiration of Patent(s): 9/4/2014 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES PED exp. 9/11/07	<input checked="" type="checkbox"/>
<b>1.4.1</b>	<b>References</b> Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Y b. Type III DMF authorization letter(s) for container closure Y 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) Y	<input checked="" type="checkbox"/>
<b>1.12.11</b>	<b>Basis for Submission</b> NDA#: 20-386 Ref Listed Drug: COZAAR Firm: MERCK & CO., INC. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	<input checked="" type="checkbox"/>

**MODULE 1 (Continued)**  
**ADMINISTRATIVE**

ACCEPTABLE

<b>1.12.12</b>	<b>Comparison between Generic Drug and RLD-505(j)(2)(A)</b> 1. Conditions of use Same except for MOU 2. Active ingredients Losartan Potassium 3. Inactive ingredients 4. Route of administration Oral 5. Dosage Form Tablet 6. Strength 25 mg, 50 mg, 100 mg	<input checked="" type="checkbox"/>
<b>1.12.14</b>	<b>Environmental Impact Analysis Statement YES</b>	<input checked="" type="checkbox"/>
<b>1.12.15</b>	<b>Request for Waiver 21 CFR 320.22(d)(2)</b> Request for Waiver of In-Vivo BA/BE Study(ies): YES ON 25 MG AND 50 MG	<input checked="" type="checkbox"/>
<b>1.14.1</b>	<b>Draft Labeling (Mult Copies N/A for E-Submissions)</b> <b>1.14.1.1</b> 4 copies of draft (each strength and container) Y <b>1.14.1.2</b> 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y <b>1.14.1.3</b> 1 package insert (content of labeling) submitted electronically Y ***Was a proprietary name request submitted? No (If yes, send email to Labeling Reviewer indicating such.)	<input checked="" type="checkbox"/>
<b>1.14.3</b>	<b>Listed Drug Labeling</b> <b>1.14.3.1</b> 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained Y <b>1.14.3.3</b> 1 RLD label and 1 RLD container label Y	<input checked="" type="checkbox"/>

<p>2.3</p>	<p><b>Quality Overall Summary (QOS)</b>  E-Submission: PDF Y  Word Processed e.g., MS Word Y</p> <p>A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage <a href="http://www.fda.gov/cder/ogd/">http://www.fda.gov/cder/ogd/</a></p> <p>Question based Review (QbR) Y</p> <p><b>2.3.S</b>  <b>Drug Substance (Active Pharmaceutical Ingredient)</b>  2.3.S.1 General Information  2.3.S.2 Manufacture  2.3.S.3 Characterization  2.3.S.4 Control of Drug Substance  2.3.S.5 Reference Standards or Materials  2.3.S.6 Container Closure System  2.3.S.7 Stability</p> <p><b>2.3.P</b>  <b>Drug Product</b>  2.3.P.1 Description and Composition of the Drug Product  2.3.P.2 Pharmaceutical Development  2.3.P.2.1 Components of the Drug Product  2.3.P.2.1.1 Drug Substance  2.3.P.2.1.2 Excipients  2.3.P.2.2 Drug Product  2.3.P.2.3 Manufacturing Process Development  2.3.P.2.4 Container Closure System  2.3.P.3 Manufacture  2.3.P.4 Control of Excipients  2.3.P.5 Control of Drug Product  2.3.P.6 Reference Standards or Materials  2.3.P.7 Container Closure System  2.3.P.8 Stability</p>	<p>☒</p>
<p>2.7</p>	<p><b>Clinical Summary (Bioequivalence)</b>  <b>Model Bioequivalence Data Summary Tables</b>  E-Submission: PDF Y  Word Processed e.g., MS Word Y</p> <p><b>2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods</b>  <b>2.7.1.1 Background and Overview</b>  Table 1. Submission Summary  Table 4. Bioanalytical Method Validation  Table 6. Formulation Data  <b>2.7.1.2 Summary of Results of Individual Studies</b>  Table 5. Summary of In Vitro Dissolution  <b>2.7.1.3 Comparison and Analyses of Results Across Studies</b>  Table 2. Summary of Bioavailability (BA) Studies  Table 3. Statistical Summary of the Comparative BA Data  <b>2.7.1.4 Appendix</b>  <b>2.7.4.1.3 Demographic and Other Characteristics of Study Population</b>  Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study  <b>2.7.4.2.1.1 Common Adverse Events</b>  Table 8. Incidence of Adverse Events in Individual Studies</p>	<p>☒</p>

**MODULE 3**

**3.2.S DRUG SUBSTANCE**

ACCEPTABLE

3.2.S.1	<p><b>General Information</b>  <b>3.2.S.1.1 Nomenclature</b>  <b>3.2.S.1.2 Structure</b>  <b>3.2.S.1.3 General Properties</b></p>	☒
3.2.S.2	<p><b>Manufacturer</b>  <b>3.2.S.2.1</b>  <b>Manufacturer(s) (This section includes contract manufacturers and testing labs)</b>  <b>Drug Substance (Active Pharmaceutical Ingredient)</b>            1. Name and Full Address(es) of the Facility(ies)      Y            2. Function or Responsibility      Y            3. Type II DMF number for API      DMF# (b) (4)            4. CFN or FEI numbers</p>	☒
3.2.S.3	<p><b>Characterization</b></p>	☒
3.2.S.4	<p><b>Control of Drug Substance (Active Pharmaceutical Ingredient)</b>  <b>3.2.S.4.1 Specification</b>            Testing specifications and data from drug substance manufacturer(s)      Y  <b>3.2.S.4.2 Analytical Procedures</b>      Y  <b>3.2.S.4.3 Validation of Analytical Procedures</b>            1. Spectra and chromatograms for reference standards and test samples see 3.2.S.4.4            2. Samples-Statement of Availability and Identification of:                a. Drug Substance      Y                b. Same lot number(s)      Y  <b>3.2.S.4.4 Batch Analysis</b>            1. COA(s) specifications and test results from drug substance mfgr(s)      Y            2. Applicant certificate of analysis      Y  <b>3.2.S.4.5 Justification of Specification</b> Y</p>	☒
3.2.S.5	<p><b>Reference Standards or Materials</b></p>	☒
3.2.S.6	<p><b>Container Closure Systems</b>      Refer to DMF # (b) (4)</p>	☐
3.2.S.7	<p><b>Stability</b>      Refer to DMF # (b) (4)</p>	☐

**MODULE 3**

**3.2.P DRUG PRODUCT**

ACCEPTABLE

<p><b>3.2.P.1</b></p>	<p><b>Description and Composition of the Drug Product</b></p> <p>1. Unit composition Y</p> <p>2. Inactive ingredients and amounts are appropriate per IIG Y – see attached</p>	<p>☒</p>
<p><b>3.2.P.2</b></p>	<p><b>Pharmaceutical Development</b> Pharmaceutical Development Report</p>	<p>☒</p>
<p><b>3.2.P.3</b></p>	<p><b>Manufacture</b></p> <p><b>3.2.P.3.1 Manufacture(s)</b> (Finished Dosage Manufacturer and Outside Contract Testing Laboratories)</p> <p>1. Name and Full Address(es) of the Facility(ies) YES</p> <p>2. CGMP Certification: YES</p> <p>3. Function or Responsibility YES</p> <p>4. CFN or FEI numbers</p> <p><b>3.2.P.3.2 Batch Formula</b> Y</p> <p><b>3.2.P.3.3 Description of Manufacturing Process and Process Controls</b></p> <p>1. Description of the Manufacturing Process Y</p> <p>2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 25mg – (b)(4) tabs 50mg – (b)(4) tabs 100mg – (b)(4) tabs</p> <p>3. If sterile product: Aseptic fill / Terminal sterilization N/A</p> <p>4. Reprocessing Statement Y</p> <p><b>3.2.P.3.4 Controls of Critical Steps and Intermediates</b> Y</p> <p><b>3.2.P.3.5 Process Validation and/or Evaluation</b> N/A</p> <p>1. Microbiological sterilization validation</p> <p>2. Filter validation (if aseptic fill) N/A</p>	<p>☒</p>
<p><b>3.2.P.4</b></p>	<p><b>Controls of Excipients (Inactive Ingredients)</b></p> <p>Source of inactive ingredients identified see 3.2.R.1.P.2</p> <p><b>3.2.P.4.1 Specifications</b></p> <p>1. Testing specifications (including identification and characterization) Y</p> <p>2. Suppliers' COA (specifications and test results) see 3.2.P.4.4</p> <p><b>3.2.P.4.2 Analytical Procedures</b> Y</p> <p><b>3.2.P.4.3 Validation of Analytical Procedures</b> N/A</p> <p><b>3.2.P.4.4 Justification of Specifications</b></p> <p>Applicant COA Y</p>	<p>☒</p>

**MODULE 3**  
**3.2.P DRUG PRODUCT**

ACCEPTABLE

<p><b>3.2.P.5</b></p>	<p><b>Controls of Drug Product</b></p> <p><b>3.2.P.5.1 Specification(s)</b> Y</p> <p><b>3.2.P.5.2 Analytical Procedures</b> Y</p> <p><b>3.2.P.5.3 Validation of Analytical Procedures</b> Y</p> <p>Samples - Statement of Availability and Identification of:</p> <p>1. Finished Dosage Form Y</p> <p>2. Same lot numbers Y</p> <p><b>3.2.P.5.4 Batch Analysis</b> 25mg – LMTC/08052</p> <p>Certificate of Analysis for Finished Dosage Form 50mg – LMTB/08053</p> <p><b>3.2.P.5.5 Characterization of Impurities</b> Y 100mg – LMTA/08054</p> <p><b>3.2.P.5.6 Justification of Specifications</b> Y</p>	<p>☒</p>
<p><b>3.2.P.7</b></p>	<p><b>Container Closure System</b></p> <p>1. Summary of Container/Closure System (if new resin, provide data) Y</p> <p>2. Components Specification and Test Data Y</p> <p>3. Packaging Configuration and Sizes 75cc, 250cc, 400cc, 625cc, (b) (4) plastic bottles, blister pack</p> <p>4. Container/Closure Testing Y</p> <p>5. Source of supply and suppliers address Y</p>	<p>☒</p>
<p><b>3.2.P.8</b></p>	<p><b>3.2.P.8.1 Stability (Finished Dosage Form)</b></p> <p>1. Stability Protocol submitted Y</p> <p>2. Expiration Dating Period 24 months</p> <p><b>3.2.P.8.2 Post-approval Stability and Conclusion</b></p> <p>Post Approval Stability Protocol and Commitments Y</p> <p><b>3.2.P.8.3 Stability Data</b> 25mg – LMTC/08052</p> <p>1. 3 month accelerated stability data Y 50mg – LMTB/08053</p> <p>2. Batch numbers on stability records the same as the test batch 100mg – LMTA/08054</p>	<p>☒</p>

**MODULE 3**

**3.2.R Regional Information**

ACCEPTABLE

<p><b>3.2.R</b> (Drug Substance)</p>	<p><b>3.2.R.1.S Executed Batch Records for drug substance (if available)</b>  <b>3.2.R.2.S Comparability Protocols</b>  <b>3.2.R.3.S Methods Validation Package YES</b>                  Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions)                  (Required for Non-USP drugs)</p>	<p><input checked="" type="checkbox"/></p>
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<p><b>3.2.R</b> (Drug Product)</p>	<p><b>3.2.R.1.P.1 Executed Batch Records</b>                  Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures)                  Batch Reconciliation and Label Reconciliation see attached                  Theoretical Yield                  Actual Yield                  Packaged Yield  <b>3.2.R.1.P.2 Information on Components Y</b>  <b>3.2.R.2.P Comparability Protocols Y</b>  <b>3.2.R.3.P Methods Validation Package YES</b>                  Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions)                  (Required for Non-USP drugs)</p>	<p><input checked="" type="checkbox"/></p>
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**MODULE 5**

**CLINICAL STUDY REPORTS**

ACCEPTABLE

<p><b>5.2</b></p>	<p><b>Tabular Listing of Clinical Studies</b></p>	<p><input type="checkbox"/></p>
<p><b>5.3.1</b> (complete study data)</p>	<p><b>Bioavailability/Bioequivalence</b>  <b>1. Formulation data same?</b>                  a. Comparison of all Strengths (check proportionality of multiple strengths)                  Strengths are proportional                  b. Parenterals, Ophthalmics, Otics and Topicals                  per 21 CFR 314.94 (a)(9)(iii)-(v) N/A  <b>2. Lot Numbers of Products used in BE Study(ies):</b> 100 mg – LMTA/08054  <b>3. Study Type: IN-VIVO PK STUDY(IES)</b> (Continue with the appropriate study type box below)</p>	<p><input checked="" type="checkbox"/></p>

	<p><b>5.3.1.2 Comparative BA/BE Study Reports</b></p> <p>1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Y</p> <p>2. Summary Bioequivalence tables:</p> <p>Table 10. Study Information</p> <p>Table 12. Dropout Information</p> <p>Table 13. Protocol Deviations</p> <p><b>5.3.1.3</b></p> <p><b>In Vitro-In-Vivo Correlation Study Reports</b></p> <p>1. Summary Bioequivalence tables:</p> <p>Table 11. Product Information</p> <p>Table 16. Composition of Meal Used in Fed Bioequivalence Study</p> <p><b>5.3.1.4</b></p> <p><b>Reports of Bioanalytical and Analytical Methods for Human Studies</b></p> <p>1. Summary Bioequivalence table:</p> <p>Table 9. Reanalysis of Study Samples</p> <p>Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses</p> <p>Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples</p> <p><b>5.3.7</b></p> <p><b>Case Report Forms and Individual Patient Listing</b></p>	<input checked="" type="checkbox"/>
<b>5.4</b>	<b>Literature References</b>	<input type="checkbox"/>
	<b>Possible Study Types:</b>	
Study Type	<p><b>IN-VIVO BE STUDY(IES) with PK ENDPOINTS</b> (i.e., fasting/fed/sprinkle) FASTING AND FED ON 100 MG</p> <p>1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Y - see attached</p> <p>2. EDR Email: Data Files Submitted: YES SENT TO EDR</p> <p>3. In-Vitro Dissolution: YES</p>	<input checked="" type="checkbox"/>
Study Type	<p><b>IN-VIVO BE STUDY with CLINICAL ENDPOINTS</b> NO</p> <p>1. Properly defined BE endpoints (eval. by Clinical Team)</p> <p>2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25).</p> <p>3. Summary results indicate superiority of active treatments (test &amp; reference) over vehicle/placebo (p&lt;0.05) (eval. by Clinical Team)</p> <p>4. EDR Email: Data Files Submitted</p>	<input type="checkbox"/>
Study Type	<p><b>IN-VITRO BE STUDY(IES)</b> (i.e., in vitro binding assays) NO</p> <p>1. Study(ies) meets BE criteria (90% CI of 80-125)</p> <p>2. EDR Email: Data Files Submitted:</p> <p>3. In-Vitro Dissolution:</p>	<input type="checkbox"/>

Study Type	<p><b>NASALLY ADMINISTERED DRUG PRODUCTS</b></p> <p>1. <u>Solutions</u> (Q1/Q2 sameness):</p> <p>a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming &amp; Repriming)</p> <p>2. <u>Suspensions</u> (Q1/Q2 sameness):</p> <p>a. In-Vivo PK Study</p> <p>1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC)</p> <p>2. EDR Email: Data Files Submitted</p> <p>b. In-Vivo BE Study with Clinical End Points</p> <p>1. Properly defined BE endpoints (eval. by Clinical Team)</p> <p>2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125)</p> <p>3. Summary results indicate superiority of active treatments (test &amp; reference) over vehicle/placebo (p&lt;0.05) (eval. by Clinical Team)</p> <p>4. EDR Email: Data Files Submitted</p> <p>c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming &amp; Repriming)</p>	<input type="checkbox"/>
Study Type	<p><b>IN-VIVO BE STUDY(IES) with PD ENDPOINTS (e.g., topical corticosteroid vasoconstrictor studies)</b></p> <p>1. Pilot Study (determination of ED50)</p> <p>2. Pivotal Study (study meets BE criteria 90%CI of 80-125)</p>	<input type="checkbox"/>
Study Type	<p><b>TRANSDERMAL DELIVERY SYSTEMS</b></p> <p>1. <u>In-Vivo PK Study</u></p> <p>1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC)</p> <p>2. In-Vitro Dissolution</p> <p>3. EDR Email: Data Files Submitted</p> <p>2. <u>Adhesion Study</u></p> <p>3. <u>Skin Irritation/Sensitization Study</u></p>	<input type="checkbox"/>

Updated 8/11/2008

Active Ingredient Search - Microsoft Internet Explorer

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Address <http://www.accessdata.fda.gov/scripts/cder/job/docs/tempai.cfm> Go Links

Active Ingredient Search Results from "OB\_Rx" table for query on "LOSARTAN."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Strength Route	Proprietary Name	Applicant Name
<a href="#">020387</a>	No		HYDROCHLOROTHIAZIDE; LOSARTAN POTASSIUM	TABLET; ORAL 12.5MG;100MG	HYZAAR	MERCK
<a href="#">020387</a>	No		HYDROCHLOROTHIAZIDE; LOSARTAN POTASSIUM	TABLET; ORAL 12.5MG;50MG	HYZAAR	MERCK
<a href="#">020387</a>	Yes		HYDROCHLOROTHIAZIDE; LOSARTAN POTASSIUM	TABLET; ORAL 25MG;100MG	HYZAAR	MERCK
<a href="#">020386</a>	Yes		LOSARTAN POTASSIUM	TABLET; ORAL 100MG	COZAAR	MERCK
<a href="#">020386</a>	No		LOSARTAN POTASSIUM	TABLET; ORAL 25MG	COZAAR	MERCK
<a href="#">020386</a>	No		LOSARTAN POTASSIUM	TABLET; ORAL 50MG	COZAAR	MERCK

[Return to Electronic Orange Book Home Page](#)

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FDA/Center for Drug Evaluation and Research  
Office of Generic Drugs  
Division of Labeling and Program Support  
Update Frequency:  
Orange Book Data - **Monthly**  
Generic Drug Product Information & Patent Information - **Daily**  
Orange Book Data Updated Through July, 2008  
Patent and Generic Drug Product Data Last Updated: September 03, 2008

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Address [http://www.accessdata.fda.gov/scripts/cder/job/docs/jobdetail.cfm?Appl\\_No=020386&TABLE1=OB\\_Rx](http://www.accessdata.fda.gov/scripts/cder/job/docs/jobdetail.cfm?Appl_No=020386&TABLE1=OB_Rx) Go Links

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Search results from the "OB\_Rx" table for query on "020386."

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Active Ingredient:	LOSARTAN POTASSIUM
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	COZAAR
Applicant:	MERCK
Strength:	25MG
Application Number:	020386
Product Number:	001
Approval Date:	Apr 14, 1995
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: [View](#)

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Active Ingredient:	LOSARTAN POTASSIUM
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	COZAAR
Applicant:	MERCK
Strength:	50MG
Application Number:	020386
Product Number:	002
Approval Date:	Apr 14, 1995
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: [View](#)

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Active Ingredient:	LOSARTAN POTASSIUM
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	COZAAR
Applicant:	MERCK
Strength:	100MG
Application Number:	020386
Product Number:	003
Approval Date:	Oct 13, 1998
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	

Done Local intranet

Patent and Exclusivity Search Results - Microsoft Internet Explorer

Address: [http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexdnew.cfm?Appl\\_No=020386&Product\\_No=001&table1=OB\\_Rx](http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexdnew.cfm?Appl_No=020386&Product_No=001&table1=OB_Rx)

Patent and Exclusivity Search Results from query on Appl No 020386 Product 001 in the OB\_Rx list.

### Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
<a href="#">020386</a>	001	5138069	Aug 11, 2009				
<a href="#">020386</a>	001	5138069*PED	Feb 11, 2010				
<a href="#">020386</a>	001	5153197	Oct 6, 2009			<a href="#">U-3</a>	
<a href="#">020386</a>	001	5153197*PED	Apr 6, 2010			<a href="#">U-3</a>	
<a href="#">020386</a>	001	5210079	May 11, 2010			<a href="#">U-496</a>	
<a href="#">020386</a>	001	5210079*PED	Nov 11, 2010			<a href="#">U-496</a>	
<a href="#">020386</a>	001	5608075	Mar 4, 2014				Y
<a href="#">020386</a>	001	5608075*PED	Sep 4, 2014				

### Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
<a href="#">020386</a>	001	<a href="#">PED</a>	Sep 11, 2007

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

[View a list of all patent use codes](#)  
[View a list of all exclusivity codes](#)

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Patent and Exclusivity Search Results - Microsoft Internet Explorer

Address: [http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexdnew.cfm?Appl\\_No=020386&Product\\_No=002&table1=OB\\_Rx](http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexdnew.cfm?Appl_No=020386&Product_No=002&table1=OB_Rx)

Patent and Exclusivity Search Results from query on Appl No 020386 Product 002 in the OB\_Rx list.

### Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
<a href="#">020386</a>	002	5138069	Aug 11, 2009				
<a href="#">020386</a>	002	5138069*PED	Feb 11, 2010				
<a href="#">020386</a>	002	5153197	Oct 6, 2009			<a href="#">U-3</a>	
<a href="#">020386</a>	002	5153197*PED	Apr 6, 2010			<a href="#">U-3</a>	
<a href="#">020386</a>	002	5210079	May 11, 2010			<a href="#">U-496</a>	
<a href="#">020386</a>	002	5210079*PED	Nov 11, 2010			<a href="#">U-496</a>	
<a href="#">020386</a>	002	5608075	Mar 4, 2014				Y
<a href="#">020386</a>	002	5608075*PED	Sep 4, 2014				

### Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
<a href="#">020386</a>	002	<a href="#">PED</a>	Sep 11, 2007

Additional information:

- Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
- Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

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[View a list of all exclusivity codes](#)  
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Done Local intranet

Patent and Exclusivity Search Results - Microsoft Internet Explorer

Address: [http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexchnew.cfm?AppNo=020386&Product\\_No=003&table1=OB\\_Rx](http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexchnew.cfm?AppNo=020386&Product_No=003&table1=OB_Rx)

Patent and Exclusivity Search Results from query on Appl No 020386 Product 003 in the OB\_Rx list.

### Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
<a href="#">020386</a>	003	5138069	Aug 11, 2009				
<a href="#">020386</a>	003	5138069*PED	Feb 11, 2010				
<a href="#">020386</a>	003	5153197	Oct 6, 2009			<a href="#">U-3</a>	
<a href="#">020386</a>	003	5153197*PED	Apr 6, 2010			<a href="#">U-3</a>	
<a href="#">020386</a>	003	5210079	May 11, 2010			<a href="#">U-496</a>	
<a href="#">020386</a>	003	5210079*PED	Nov 11, 2010			<a href="#">U-496</a>	
<a href="#">020386</a>	003	5608075	Mar 4, 2014				Y
<a href="#">020386</a>	003	5608075*PED	Sep 4, 2014				

### Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
<a href="#">020386</a>	003	<a href="#">PED</a>	Sep 11, 2007

Additional information:

- Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
- Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

[View a list of all patent use codes](#)  
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**Table 2: Target Composition Statement**

(b) (4)

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this page is the manifestation of the electronic signature.**  
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/s/

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Martin Shimer

10/23/2008 07:32:00 AM



ANDA 90-790

Apotex Corp.  
U.S. Agent for: Apotex Corp.  
Attention: Kiran Krishnan  
2400 North Commerce Parkway  
Suite 400  
Weston, FL 33326

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated October 16, 2008 and your correspondence dated October 17, 2008.

NAME OF DRUG: Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg

DATE OF APPLICATION: August 27, 2008

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 29, 2008

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

#### **CONTENTS OF THE NOTICE**

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

#### **SENDING THE NOTICE**

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:
  - 1) Each owner of the patent or the representative designated by the owner to receive the notice;

- 2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.
- 3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

#### **DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE**

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.
- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

#### **DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME**

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.
- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240)276-8419.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Dat Doan  
Project Manager  
240-276-8573

Sincerely yours,

*{See appended electronic signature page}*

Wm Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

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

-----  
Martin Shimer  
10/23/2008 07:31:38 AM  
Signing for Wm Peter Rickman



October 29, 2008

Office of Generic Drugs, HFD-600  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir/Madam:

**Re: PATENT AMENDMENT**  
**Losartan Potassium Tablets 25 mg, 50 mg, and 100 mg**  
**ANDA No. 090-790**

Further to our above-mentioned Abbreviated New Drug Application dated August 27, 2008, and in accordance with 21 CFR 314.95 (b), please find enclosed a statement indicating that the required Notice of Certification of Invalidity/Non-Infringement has been given to Merck & Co. Inc., the holder of the approved New Drug Application No. 020386 for Cozaar<sup>®</sup> Tablets, 25 mg, 50 mg, 100 mg, and the owner (according to the records of the U.S. Patent and Trademark Office) of U.S. Patent No. 5608075 ("the '075 Patent"). The statement indicates that said notice meets the requirements of 21 CFR 314.95(a) and 21 CFR 314.95(c), and is enclosed in section 1.3.5.2.

In addition, as required by 21 CFR 314.95(e), courier return receipt as evidence of receipt of the patent notice by Merck & Co. Inc. is provided in Section 1.3.5.2 of this amendment.

This patent amendment is being submitted in eCTD format and is provided on the enclosed CD. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted, and therefore only a hardcopy of the cover letter is provided along with the CD. An electronic copy of the 356h form is included in section 1.1.2. The enclosed CD has been confirmed to be virus free using McAfee VirusScan Enterprise 7.1.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone: (954) 384-3986 or fax: (954) 349-4233. Alternatively, please do not hesitate to contact me by telephone at: (416) 401-7889.

Sincerely,

A small, handwritten signature in blue ink, which appears to be a stylized 'A' or similar character.

# APOTEX

ADVANCING GENERICS

November 10, 2008

Office of Generic Drugs, HFD-600  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir/Madam:

**Re: PATENT AMENDMENT – Notice of Non-Litigation**  
**Losartan Potassium Tablets, 25 mg, 50 mg, and 100 mg,**  
**ANDA No. 090-790**

Further to our above-mentioned Abbreviated New Drug Application dated August 27, 2007 and our Patent Amendment dated October 28, 2008, we would like to inform the Agency that no litigation has been filed against Apotex Inc. by Merck & Co. Inc., the owner of U.S. Patent No. 5608075 ("the '075 Patent"); and the holder of the approved New Drug Application No. 020386 for Cozaar<sup>®</sup> Tablets 25 mg, 50 mg, and 100 mg.

An electronic copy of the 356h form is included along with the notification of non-litigation by Merck & Co., Inc. in section 1.35.2 of this amendment.

This patent amendment is being submitted in eCTD format and is provided on the enclosed CD. Please note that a Letter of Non-Repudiation Agreement dated November 3, 2007 has been submitted, and therefore only a hardcopy of the cover letter is provided along with the CD. The enclosed CD has been confirmed to be virus free using McAfee VirusScan Enterprise 7.1.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone: (954) 384-3986 or fax: (954) 349-4233. Alternatively, please do not hesitate to contact myself at telephone: (416) 401-7889.

Sincerely,



**From:** Shimer, Martin  
**Sent:** Tuesday, October 28, 2008 6:00 AM  
**To:** 'Bernice Tao'  
**Cc:** Shimer, Martin  
**Subject:** RE: Apotex Losartan Potassium Tablets ANDA 90-790 - Fedex Courier of Notice  
[Bernice,](#)

It is acceptable to use FedEx in lieu of the US Postal service for the purpose of providing notice to the NDA holder and any patent assignees associated with PIV certifications contained within ANDA 90-790.

Sincerely,

Martin Shimer

---

**From:** Bernice Tao [mailto:[btao@apotex.com](mailto:btao@apotex.com)]  
**Sent:** Tuesday, October 28, 2008 12:40 AM  
**To:** Shimer, Martin  
**Subject:** Apotex Losartan Potassium Tablets ANDA 90-790 - Fedex Courier of Notice

Hi Martin

Further to the Acceptable for Filing letter for the Losartan Potassium Tablets ANDA # 90-790 dated October 23, 2008, we would like to request authorisation to utilise Fedex courier in lieu of US Postal Service for the purpose of providing notice to the NDA holders and patent owners associated with the Paragraph IV certifications provided in the ANDA . Could you please confirm acceptability?

Regards,  
**Bernice Tao**  
Director, Regulatory Affairs US  
Apotex Inc.  
Tel: (416) 401-7889  
Fax: (416) 401-3817  
[www.apotex.com](http://www.apotex.com)

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/s/

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Martin Shimer  
12/1/2008 09:13:32 AM  
CSO

## COMPLETE RESPONSE -- MINOR

ANDA 90-790

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Apotex Corp.

TEL: (954) 384-3986

ATTN: Kiran Krishnan

FAX: (954) 349-4233

FROM: Dat Doan

FDA CONTACT PHONE: (240) 276-8573

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 27, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg.

**SPECIAL INSTRUCTIONS: please see attached**

**Please submit your response in electronic format.**

**This will improve document availability to review staff.**

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachment (1 page). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

**Chemistry Comments to be Provided to the Applicant**

ANDA: 90-790 APPLICANT: APOTEX INC.

DRUG PRODUCT: Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg

The deficiencies presented below represent MINOR deficiencies:

A. Deficiencies by Applicable Section:

**P.4 Control of Excipients**

For each excipient please provide the following:

-  (b) (4)
- 

**P.5 Control of Drug Product**

As of July 1, 2008 the new USP requirements for assessing the residual solvent content in drug products in <467> went into effect. You have to comply with USP <467> for the drug product. Please refer the FDA website

<http://www.fda.gov/cder/ogd/residualsolvents.pdf> for detail requirement.

**P.7 Container Closure System**

 (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The labeling information in the application will be reviewed by the division of Labeling and Program Support. The Division will communicate any questions regarding labeling of the drug product to you directly.
2. The Division of Bioequivalence will review the bio-equivalency of the drug product and communicate questions regarding to you directly.
3. The firms referenced in your ANDA relative to the manufacturing and testing of the drug substance and the product must be in compliance with the cGMP's at the time of approval.

Sincerely yours,

*{See appended electronic signature page}*

Rashmikant M. Patel, Ph.D.  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

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/s/

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Albert Mueller  
1/26/2009 11:24:01 AM

# APOTEX

ADVANCING GENERICS

March 05, 2009

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North I  
7520 Standish Place  
Rockville, MD 20855-2773

To Whom It May Concern,

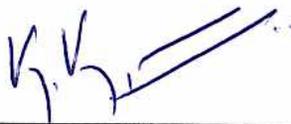
**Re: Response to FDA Minor deficiencies letter dated January 26, 2009**  
**ANDA No. 90-790: Losartan Potassium Tablets 25mg, 50mg and 100mg**

Apotex Corp. is hereby submitting a response of minor deficiencies to the ANDA No. 90-790 for Losartan Potassium Tablets 25 mg, 50 mg and 100 mg. The amendment is being filed response to FDA deficiency letter dated January 26, 2009. The response is presented in a question-and-answer format and follows on a separate page.

This amendment is filed through the Electronic Submission Gateway (ESG) and a letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted and therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form 356h has been provided in section 1.1.2.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at (954) 984-3986 by fax at (866)392-1774, or alternatively please do not hesitate to contact me at (416) 401-7889, by fax at (416) 401-3809 or via email at [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,



*W*  
\_\_\_\_\_  
Bernice Tao  
Director, U.S. Regulatory Affairs



July 07, 2009

Office of Generic Drugs  
CDER, FDA  
Document Control Room,  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir/Madam,

**Re: Gratuitous Amendment for withdrawal of the Apotex Inc., Weston road site as an alternate packaging site.  
ANDA No. 090790 : Losartan Potassium Tablets 25 mg, 50 mg and 100 mg**

Apotex Corp. is hereby submitting an amendment to ANDA for Losartan Potassium Tablets 25 mg, 50 mg and 100 mg to withdraw the following site as alternative site for packaging of the final dosage form.

Apotex Inc., (Signet Campus)  
4100 Weston road,  
Weston, Ontario, M9L 2Y6, Canada

An updated manufacturing section 3.2.P.3.1 is provided with this amendment.

This amendment is filed through the Electronic Submission Gateway (ESG) and a letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted and therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form 356h has been provided in section 1.1.2.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at (954) 984-3986 by fax at (866)392-1774, or alternatively please do not hesitate to contact me at (416) 401-7889, by fax at (416) 401-3809 or via email at [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,

# Telephone Fax

ANDA 90-790

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North I  
7520 Standish Place  
Rockville, MD 20855-2773



TO: Apotex Corp.

TEL: 954-384-3986

ATTN: Kiran Krishnan

FAX: 954-349-4233

FROM: Jim Barlow

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for losartan potassium tablets.

**Pages (including cover):** 4

## **SPECIAL INSTRUCTIONS:**

### *Labeling Comments*

[James.barlow@fda.hhs.gov](mailto:James.barlow@fda.hhs.gov)

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

ANDA Number: 90-790  
Date of Submission: August 27, 2008  
Applicant's Name: Apotex Corporation  
Established Name: Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg tablets

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**Labeling Deficiencies:**

**1. GENERAL COMMENTS**

- a. Referring to the [REDACTED] <sup>(b) (4)</sup> proposed count bottles, **the Agency does NOT approve bulk labeling.** Please delete this count bottle from your HOW SUPPLIED section.
- b. We note that you did NOT include information related to the "Preparation of the suspension" and/or the suspension in the labeling. This is not protected information. Please revise and/or comment.

**2. CONTAINER – Bottles of 30s, 90s and 1000s**

Side Panel: Revise to read

Each tablet contains:  
xx mg Losartan Potassium USP

**3. CARTON – 100 (10X10 unit-dose blisters)**

**See comment above.**

**4. Unit-Dose Blisters – 10s**

Satisfactory in **draft** as of the August 27, 2008 electronic submission

**5. PACKAGE INSERT and PATIENT INFORMATION LEAFLET**

- a. Please revise your labeling to be in accord with the most recently approved labeling for the reference listed drug, Cozaar® Tablets (NDA 20-386/S-049; June 4, 2009).
- b. See comment under CONTAINER above

Submit your revised labels and labeling electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - [http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_17](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

*{See appended electronic signature page}*

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Wm Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAMES T BARLOW  
08/20/2009

# APOTEX

ADVANCING GENERICS

September 08, 2009

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

To Whom It May Concern,

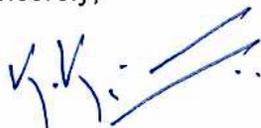
**Re: Telephone Fax, FDA Labeling Deficiencies dated August 20, 2009**  
**ANDA No. 90-790: Losartan Potassium Tablets 25 mg, 50 mg and 100 mg Tablets**

Apotex Corp. is hereby submitting an Amendment to the ANDA No. 90-790 for Losartan Potassium Tablets, 25mg, 50mg and 100mg. The amendment is being filed in response to telephone fax, FDA labeling deficiency dated August 20, 2009. The response is presented in a question-and-answer format and follows on a separate page.

This amendment is filed through the Electronic Submission Gateway (ESG) and a letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted and therefore only an electronic copy of cover letter is provided. A signed electronic copy of Form 356h has been provided in section 1.1.2.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at (954) 384-3986 or fax: (866) 392-1774, or alternatively, please do not hesitate to contact me at (416) 401-7889 or fax: (416) 401-3817 or via email at [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,



1.7

# APOTEX

ADVANCING GENERICS

September 11, 2009

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

To Whom It May Concern,

**Re: Telephone Amendment – Response to CMC Deficiencies dated Sept. 4, 2009**  
**ANDA No. 90-790: Losartan Potassium Tablets 25 mg, 50 mg and 100 mg Tablets**

Apotex Corp. is submitting a Telephone Amendment to ANDA No. 90-790 for Losartan Potassium Tablets, 25mg, 50mg and 100mg. The amendment is being filed in response to a telephone call from Shirley Zhu on September 4, 2009. The response is presented in a question-and-answer format and follows on a separate page.

This amendment is filed through the Electronic Submission Gateway (ESG) and a letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted and therefore only an electronic copy of cover letter is provided. A signed electronic copy of Form 356h has been provided in section 1.1.2.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at (954) 384-3986 or fax: (866) 392-1774, or alternatively, please do not hesitate to contact me at (416) 401-7889 or fax: (416) 401-3817 or via email at [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,



*br*  
\_\_\_\_\_  
Bernice Tao  
Director, Regulatory Affairs – US

# Telephone Fax

ANDA 90-790

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North I  
7520 Standish Place  
Rockville, MD 20855-2773



TO: Apotex Corp.

TEL: 954-384-3986

ATTN: Kiran Krishnan

FAX: 954-349-4233

FROM: Jim Barlow

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for losartan potassium tablets.

**Pages (including cover):** 4

## **SPECIAL INSTRUCTIONS:**

### *Labeling Comments*

[James.barlow@fda.hhs.gov](mailto:James.barlow@fda.hhs.gov)

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

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**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

ANDA Number: 090790  
Date of Submission: September 8, 2009  
Applicant's Name: Apotex Inc.  
Established Name: Losartan Potassium Tablets USP, 25 mg, 50 mg and 100 mg tablets

---

**Labeling Deficiencies:**

**1. GENERAL COMMENTS**

- a. Did your firm submit stability data supporting this suspension storage in your Chemistry data? Please comment. (Also, please note that this information (suspension) cannot be carved out of your labeling since it is not protected.)
- b. Please note that Losartan Potassium Tablets are now subject to a "USP" monograph. Please revise to include this designation in your labeling where appropriate.

**2. CONTAINER – Bottles of 30s, 90s and 1000s**

See comment 1.(b.) above.

**3. CARTON – 100 (10X10 unit-dose blisters)**

See comment 1.(b.) above.

**4. Unit-Dose Blisters – 10s**

Satisfactory in **draft** as of the August 27, 2008 electronic submission

**5. PACKAGE INSERT**

**PRECAUTIONS**

Revise the following subsection to read as follows –

***Electrolyte Imbalance***

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed.

***Information for Patients***

*Pregnancy:* Female patients.....

**6. PATIENT INFORMATION LEAFLET**

We note that a Patient Information Leaflet was never submitted for review. Note that a PIL was approved for the reference listed drug on April 13 and September 21, 2006. Please address this and/or comment.

Submit your revised labels and labeling electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - [http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_17](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

*{See appended electronic signature page}*

---

Wm Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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

JAMES T BARLOW  
01/06/2010

# APOTEX

ADVANCING GENERICS

January 15, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir or Madam,

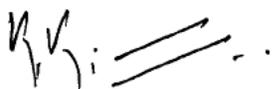
**Re: MINOR AMENDMENT – RESPONSE TO LABELING DEFICIENCY (dated 01/06/2010)**  
**Losartan Potassium Tablets USP, 25 mg, 50 mg, 100 mg; ANDA No. 090790**

Apotex Corp. is hereby submitting an amendment to the ANDA No. 90-790 for Losartan Potassium Tablets USP, 25 mg, 50 mg, 100 mg. The amendment is being filed in response to the FDA's Telephone Fax (labeling deficiency) dated January 06, 2010. The response is presented in a question-and-answer format and follows on a separate page.

Please note that this amendment is filed through the Electronic Submission Gateway (ESG) and a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted; therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form FDA 356h has been provided in section 1.1.2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889.

Sincerely,



*hr*  
\_\_\_\_\_  
Bernice Tao  
Director, Regulatory Affairs US

# APOTEX

ADVANCING GENERICS

January 20, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir or Madam,

**Re: (1) GRATUITOUS QUALITY AMENDMENT - CHANGES TO COMPLY WITH  
COMPENDIAL CHANGES (NEW USP MONOGRAPH)  
(2) REQUEST FOR FINAL APPROVAL**

**Losartan Potassium Tablets USP, 25 mg, 50 mg, 100 mg; ANDA No. 090790**

Apotex is hereby submitting a Gratuitous Quality Amendment to ANDA No. 090790 as the drug product, Losartan Potassium Tablets, is now subject to a USP monograph. A description of the changes and related documentation is appended to the cover letter.

Apotex is also requesting final approval for Losartan Potassium Tablets, USP, 25 mg, 50 mg, and 100 mg. A paragraph IV certification to U.S. Patent No. 5,608,075 (the '075 patent) was filed in our ANDA. No litigation for infringement was brought against Apotex. Paragraph III certifications to U.S. Patent Nos. 5,138,069 (the '069 patent) and 5,153,197 (the '197 patent) were also filed in our ANDA. This request for final approval is submitted in anticipation of the expiration of these patents and their associated pediatric exclusivities on April 6, 2010. (Please note that the MOU certification with regard to Patent No. 5,210,079 (U-496 for treating chronic renal failure) remains in effect until expiration of the patent and pediatric exclusivity on 11/11/2010).

The product labeling has been revised to add the USP designation and final printed labeling was submitted as a labeling amendment on 01/15/2010. This amendment includes revised finished product release and stability specifications and dissolution method in accordance with the USP monograph. There have been no other changes to the labeling or chemistry and manufacturing information.

Please note that this amendment is filed through the Electronic Submission Gateway (ESG) and a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted; therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form FDA 356h has been provided in section 1.1.2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889.

Sincerely,

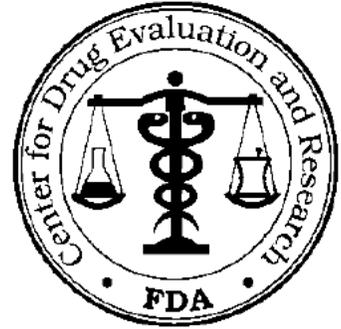


 Bernice Tao  
Director, Regulatory Affairs US

# Telephone Fax

ANDA 90-790

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North I  
7520 Standish Place  
Rockville, MD 20855-2773



TO: Apotex Corp.

TEL: 954-384-3986

ATTN: Kiran Krishnan

FAX: 954-349-4233

FROM: Jim Barlow

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for losartan potassium tablets USP.

**Pages (including cover):** 4

**SPECIAL INSTRUCTIONS:**

*Labeling Comments*

[James.barlow@fda.hhs.gov](mailto:James.barlow@fda.hhs.gov)

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**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

---

ANDA Number: 090790  
Date of Submission: January 15, 2010  
Applicant's Name: Apotex Inc.  
Established Name: Losartan Potassium Tablets USP, 25 mg, 50 mg and 100 mg tablets

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**Labeling Deficiencies:**

1. **CONTAINER** – Bottles of 30s, 90s and 1000s (all strengths)  
Satisfactory in **final print** as of the January 15, 2010 e-submission
2. **CARTON** – 100 (10X10 unit-dose blisters) (all strengths)  
Satisfactory in **final print** as of the January 15, 2010 e-submission
3. **Unit-Dose Blisters** – 10s  
Satisfactory in **final print** as of the January 15, 2010 e-submission
4. **PACKAGE INSERT**  
Satisfactory in **final print** as of the January 15, 2010 e-submission
5. **PATIENT INFORMATION LEAFLET**
  - a. Please delete the following information from the text since it is protected information.
    - i. [REDACTED] (b) (4)
    - ii. [REDACTED] (b) (4)
    - iii. [REDACTED] (b) (4)
  - b. How many Patient Information Leaflets will be distributed for each count bottle you intend to market? (i.e. [REDACTED] (b) (4) PILs for the bottles of 90)

Submit your revised labels and labeling electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - [http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_17](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

*{See appended electronic signature page}*

---

Wm Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAMES T BARLOW  
01/20/2010

# APOTEX

ADVANCING GENERICS

January 25, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir or Madam,

**Re: MINOR AMENDMENT- RESPONSE TO LABELING DEFICIENCY dated 01/20/2010  
Losartan Potassium Tablets, USP, 25 mg, 50 mg, 100 mg: ANDA No. 90-790**

Apotex Corp. is hereby submitting an amendment to the ANDA No. 90-790 for Losartan Potassium Tablets, USP, 25 mg, 50 mg, and 100 mg. The amendment is being filed in response to the FDA's Telephone Fax (Labeling Comments) dated January 20, 2010 and the January 20, 2010 email from Jim Barlow. The response is presented in a question-and-answer format and follows on a separate page.

Please note that this amendment is filed through the Electronic Submission Gateway (ESG) and a letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted; therefore only an electronic copy of cover letter is provided. A signed electronic copy of Form 356h has been provided in section 1.1.2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 984-3986, or by fax at (866) 392-1774. Alternatively, please do not hesitate to contact me at (416) 401-7889.

Sincerely,



*H*  
\_\_\_\_\_  
Bernice Tao  
Director, U.S. Regulatory Affairs

# BIOEQUIVALENCE AMENDMENT

ANDA 90-790

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Apotex Corp.

TEL: (954) 384-3986

ATTN: Kiran Krishnan

FAX: (954) 349-4233

FROM: Alpita Popat

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on August 27, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

## **Bioequivalence Dissolution Acknowledgement**

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**

**Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket.** Please direct any questions concerning this communication to the project manager identified above.

**Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.**

## **SPECIAL INSTRUCTIONS:**

*Please submit your response in electronic format. This will improve document availability to review staff.*

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ANDA: 090790  
APPLICANT: Apotex Corp  
DRUG PRODUCT: Losartan Potassium Tablets, 100 mg, 50 mg and 25 mg

The Division of Bioequivalence (DBE) has completed its review of your submissions acknowledged on the cover sheet. The following deficiency has been identified:

Your dissolution testing data using the FDA-recommended method are acceptable. However, your proposed specification (NLT <sup>(b)(4)</sup> (Q), 45 min) is not acceptable. Based on the data submitted, the DBE recommends a more appropriate specification for the test product. Please acknowledge your acceptance of the following FDA-recommended dissolution method and specification:

The dissolution testing should be conducted in 900 mL of water (deaerated) at 37°C, using USP Apparatus II (paddles) @ 50 rpm. The test products should meet the following specification: Not less than 75% (Q) in 30 minutes.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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/s/  
-----

DALE P CONNER  
02/01/2010

# APOTEX

ADVANCING GENERICS

February 1, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir or Madam,

**Re: BIOEQUIVALENCE AMENDMENT – Bioequivalence Dissolution Acknowledgement  
Losartan Potassium Tablets USP, 25 mg, 50 mg, 100 mg; ANDA No. 090790**

Apotex is hereby submitting a Bioequivalence Amendment to ANDA No. 090790 in response to the Division of Bioequivalence's deficiency letter dated February 1, 2010.

Apotex acknowledges and accepts the FDA-recommended dissolution method and specifications:

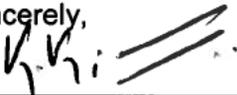
"The dissolution testing should be conducted in 900 mL of water (deaerated) at 37°C, using USP Apparatus II (paddles) @ 50 rpm. The test products should meet the following specification: Not less than 75% (Q) in 30 minutes."

Please note that we have revised our release and stability specifications to reflect the FDA-recommended specifications. The revised release and stability specifications and supportive analytical test data were submitted to the Division of Chemistry on January 20, 2010, in a gratuitous amendment in accordance with the new USP monograph for losartan potassium tablets.

This amendment is filed through the Electronic Submission Gateway (ESG) and a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted; therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form FDA 356h has been provided in section 1.1.2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889.

Sincerely,



*W*  
Bernice Tao  
Director, Regulatory Affairs US

“Suspension” Letter to all ANDA applicants of Losartan Potassium Tablets USP

The following letter was sent out to all Losartan ANDA holders on January 25, 2010.

ANDA Holder Address

Dear Madam/Sir,

Currently approved labeling from the Reference Listed Drug (RLD) for Losartan Potassium Tablets USP provides for the preparation of a suspension as an alternate dosage option.

We are requiring data that show your drug product is stable under the conditions of preparation and storage of the suspension. The RLD labeling, as well as your labeling, quotes the following:

“Add 10 mL of Purified Water USP to an 8 ounce (240 mL) amber polyethylene terephthalate (PET) bottle containing ten 50 mg losartan potassium tablets. Immediately shake for at least 2 minutes. Let the concentrate stand for 1 hour and then shake for 1 minute to disperse the tablet contents. Separately prepare a 50/50 volumetric mixture of Ora-Plus™<sup>1</sup> and Ora-Sweet SF™<sup>1</sup>. Add 190 mL of the 50/50 Ora-Plus™/Ora-Sweet SF™ mixture to the tablet and water slurry in the PET bottle and shake for 1 minute to disperse the ingredients. The suspension should be refrigerated at 2 to 8°C (36 to 46°F) and can be stored for up to 4 weeks. Shake the suspension prior to each use and return promptly to the refrigerator.” Ora-Plus™ and Ora-Sweet SF™ are trademarks of Paddock Laboratories.

As the above labeling suggests, the data should be generated on the prepared suspension upon storage in a refrigerator at 2 to 8°C (36 to 46°F) for four weeks. Evaluation should consist of testing for any significant changes in appearance, potency and impurity profile of the suspension. “Accelerated” data generated at room temperature 25°C (77°F) is not considered appropriate.

This test data need only be generated on a one-time basis and need not be repeated on subsequent production batches.

These data should be submitted as soon as possible. This information from the package insert can not be removed from the product labeling and must be retained.

If you have supplied these data previously, please indicate the manner and reference of this response.

Questions regarding these requested data should be referred to Mr. Dat Doan, Project Manager, at 240-276-8573 for this drug product.

Sincerely yours,

Etc

File: c:\documents and settings\muellera\my documents\suspension.doc

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90544	ORIG-1	UPSHER SMITH LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-76958	ORIG-1	TEVA PHARMACEUTICALS USA INC	LOSARTAN POTASSIUM
ANDA-91129	ORIG-1	COBALT LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-91590	ORIG-1	MYLAN PHARMACEUTICALS INC	LOSARTAN POTASSIUM
ANDA-91497	ORIG-1	HUAHAI US INC	LOSARTAN POTASSIUM
ANDA-90467	ORIG-1	TORRENT PHARMACEUTICALS LTD	LOSARTAN POTASSIUM
ANDA-91541	ORIG-1	MICRO LABS LIMITED	LOSARTAN POTASSIUM
ANDA-90428	ORIG-1	ALEMBIC LTD	LOSARTAN POTASSIUM
ANDA- (b) (4)	ORIG-1	(b) (4)	LOSARTAN POTASSIUM
ANDA-90083	ORIG-1	AUROBINDO PHARMA LTD	LOSARTAN POTASSIUM
ANDA-78232	ORIG-1	LUPIN LTD	LOSARTAN POTASSIUM
ANDA-77459	ORIG-1	ROXANE LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-77424	ORIG-1	LEK PHARMACEUTICALS D D	LOSARTAN POTASSIUM
ANDA-90790	ORIG-1	APOTEX CORP	LOSARTAN POTASSIUM
ANDA-78243	ORIG-1	ZYDUS PHARMACEUTICALS USA INC	LOSARTAN POTASSIUM

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

/s/

DAT T DOAN  
02/12/2010

ALBERT J MUELLER

02/12/2010

# APOTEX

ADVANCING GENERICS

February 18, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room,  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir/Madam,

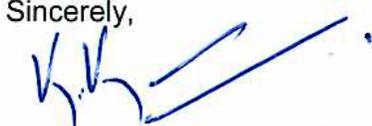
**Re: Telephone Amendment - CMC**  
**ANDA No. 090790 : Losartan Potassium Tablets 25 mg, 50 mg and 100 mg**

Apotex Corp. is hereby submitting a Telephone Amendment to ANDA No. 90790 for Losartan Potassium Tablets 25 mg, 50 mg and 100 mg to withdraw Apotex's Etobicoke Site and Signet Campus as alternative manufacturing and release testing sites for the drug substance, excipients and drug product. The amendment is being filed in response to a telephone call from Dat Doan on February 17, 2010. The response is presented in a question-and-answer format and follows on a separate page.

This amendment is filed through the Electronic Submission Gateway (ESG) and a letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted and therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form 356h has been provided in section 1.1.2.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 984-3986 or by fax at (866)392-1774, or alternatively please do not hesitate to contact me at (416) 401-7889, by fax at (416) 401-3809 or via email at [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,

  
hr  
Bernice Tao  
Director, U.S. Regulatory Affairs

# Telephone Fax

ANDA 90-790

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North I  
7520 Standish Place  
Rockville, MD 20855-2773



TO: Apotex Corp.

TEL: 954-384-3986

ATTN: Kiran Krishnan

FAX: 954-349-4233

FROM: Jim Barlow

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for losartan potassium tablets USP.

**Pages (including cover): 3**

**SPECIAL INSTRUCTIONS:**

*Labeling Comments*

[James.barlow@fda.hhs.gov](mailto:James.barlow@fda.hhs.gov)

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

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**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

ANDA Number: 090790  
Date of Submission: January 25, 2010  
Applicant's Name: Apotex Inc.  
Established Name: Losartan Potassium Tablets USP, 25 mg, 50 mg and 100 mg tablets

---

**Labeling Deficiencies:**

1. **CONTAINER** – Bottles of 30s, 90s and 1000s (all strengths)  
Satisfactory in **final print** as of the January 15, 2010 e-submission
2. **CARTON** – 100 ( (b) (4) unit-dose blisters) (all strengths)
  - a. Please add "Not for institutional use" on your carton labels since the unit dose blisters are not barcoded.
  - b. Please change the quantity to read " (b) (4) unit dose)", since the blisters are packaged as such.
3. **Unit-Dose Blisters** – (b) (4)  
Revise the established name on the strip should read "...Tablet, USP" - delete the s and add comma.
4. **PACKAGE INSERT**  
Satisfactory in **final print** as of the January 25, 2010 e-submission
5. **PATIENT INFORMATION LEAFLET**  
Satisfactory in **final print** as of the January 25, 2010 e-submission

Submit your revised labels and labeling electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - [http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_17](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

*{See appended electronic signature page}*

---

Wm Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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

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/s/

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JAMES T BARLOW  
02/19/2010

# APOTEX

ADVANCING GENERICS

February 19, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir or Madam,

**Re: MINOR AMENDMENT- RESPONSE TO LABELING DEFICIENCY dated 02/19/2010  
Losartan Potassium Tablets, USP, 25 mg, 50 mg, 100 mg: ANDA No. 90-790**

Apotex Corp. is hereby submitting an amendment to the ANDA No. 90-790 for Losartan Potassium Tablets, USP, 25 mg, 50 mg, and 100 mg. The amendment is being filed in response to the FDA's Telephone Fax (Labeling Comments) dated February 19, 2010. The response is presented in a question-and-answer format and follows on a separate page.

Please note that this amendment is filed through the Electronic Submission Gateway (ESG) and a letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted; therefore only an electronic copy of cover letter is provided. A signed electronic copy of Form 356h has been provided in section 1.1.2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 984-3986, or by fax at (866) 392-1774. Alternatively, please do not hesitate to contact me at (416) 401-7889.

Sincerely,



  
\_\_\_\_\_  
Bernice Tao  
Director, U.S. Regulatory Affairs

February 23, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir or Madam,

**Re: GRATUITOUS AMENDMENT – Stability Data to Support Suspension Storage Statement  
Losartan Potassium Tablets USP 25 mg, 50 mg, 100 mg; ANDA No. 090790**

Apotex is hereby submitting a Gratuitous Amendment to ANDA No. 090790 for Losartan Potassium Tablets USP to provide stability data to show that the drug product is stable under the conditions of preparation and storage of the suspension as described in the product labeling. This data is provided as a follow-up to labeling comment 1.a. in the Jan. 6, 2010 labeling deficiency facsimile and to respond to the information request dated January 25<sup>th</sup>, 2010 from Dat Doan, Project Manager, and office of generic drugs.

Please note that this amendment is filed through the Electronic Submission Gateway (ESG) and a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted; therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form FDA 356h has been provided in section 1.1.2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889.

Sincerely,

  
\_\_\_\_\_  
Bernice Tao  
Director, Regulatory Affairs US

March 5, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir or Madam,

**Re: TELEPHONE AMENDMENT – RESPONSE INFORMATION REQUEST**

**ANDA No. 090790: Losartan Potassium Tablets USP 25 mg, 50 mg and 100 mg.**

Apotex Corp. is hereby submitting a Telephone Amendment to the ANDA No. 090790 for Losartan Potassium Tablets USP 25 mg, 50 mg and 100 mg. The amendment is being filed in response to telephone request to Bernice Tao Director, U.S. Regulatory Affairs, Apotex, from Paul Schwartz on March 01, 2010.

Apotex has (b) (4) specification limits for 25 mg, 50 mg and 100 mg strengths (b) (4). The following revised (b) (4) (b) (4) specification is included in section 3.2.P.3.4 of this amendment:

- (b) (4)

This amendment is filed through the Electronic Submission Gateway (ESG) and a letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted and therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form 356h has been provided in section 1.1.2.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at (954) 984-3986 by fax at (866)392-1774, or alternatively please do not hesitate to contact me at (416) 401-7889, by fax at (416) 401-3809 or via email at [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,



SENT VIA TELEFAX

Docket No. FDA-2010-N-0134

Dear ANDA Applicant:

We are writing to solicit comment on legal and regulatory issues pertaining to 180-day exclusivity as described in section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act for abbreviated new drug applications (ANDAs) for losartan potassium tablets and losartan potassium-hydrochlorothiazide tablets. Merck Research Laboratories (Merck) holds the NDAs for Cozaar (losartan potassium) tablets and Hyzaar (potassium-hydrochlorothiazide) tablets, the reference listed drugs for these ANDAs. You have an ANDA pending with FDA for one or more of these drug products.

Merck submitted U.S. Patent No. 5,608,075 to FDA for listing for the Cozaar and Hyzaar NDAs 20-386 and 20-387, respectively. Merck requested in March 2005 that FDA delist the patent for these drug products. The patent has remained listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for Cozaar and Hyzaar as a placeholder for any exclusivity that may result from an ANDA applicant's paragraph IV certification to the patent. The current Orange Book listing for U.S. Patent No. 5,608,075 shows a patent expiration date of March 4, 2014.

FDA has received the attached information asserting that the expiration date for U.S. Patent No. 5,608,075 was March 30, 2009. As described in the regulation at 21 CFR 314.53(f), persons disputing the accuracy or relevance of patent information submitted to the agency are requested to notify the agency in writing stating the grounds for disagreement. The agency then will request the applicable new drug application holder to confirm the correctness of the patent information submitted. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the Orange Book.

Consistent with the regulation, FDA has forwarded the inquiry regarding the correct expiration date for U.S. Patent No. 5,608,075 to Merck. Eligibility for 180-day exclusivity based on U.S. Patent No. 5,608,075 is at issue in litigation currently pending in the U.S. Court of Appeals for the District of Columbia. See *Teva Pharmaceuticals USA, Inc. v. Sebelius*, No. 09-5281 (D.C. Cir. Mar. 2, 2010). The litigation schedule for this case and for FDA's consideration of the regulatory issues associated with related ANDAs is very time sensitive. Therefore FDA has notified Merck that it is essential FDA have accurate information about this patent as soon as possible, and requested that Merck respond by close of business on March 11, 2010.

As you may know, in the *Teva* case described above, the D.C. Circuit addressed the role of patent delisting in the forfeiture of exclusivity pursuant to section 505(j)(5)(D)(i)(I) of the Act. The court issued an opinion on March 2, 2010; the mandate has not yet issued.

FDA now has before it the assertion that U.S. Patent No. 5,608,075, the patent at issue in the litigation, expired on March 30, 2009. Because of the time sensitive nature of this issue, we are asking for comment on what effect, if any, a change in the patent expiration date for U.S. Patent No. 5,608,075 to March 30, 2009, would have on a first applicant's eligibility for 180-day exclusivity for losartan potassium tablets and losartan potassium-hydrochlorothiazide tablets.

To permit the agency to consider submissions in a timely manner, we are asking that you submit your comments to [www.regulations.gov](http://www.regulations.gov) by close of business on March 18, 2010. Please include the proper FDA docket number, FDA-2010-N-0134, in your correspondence. If you have any questions regarding this correspondence, please contact Dave Read, Regulatory Counsel, Office of Generic Drugs, at 240-276-9310.

Sincerely,

{See appended electronic signature page}

Gary J. Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Attachments

**BUG & BEARDSLEY, LLP**  
919 EIGHTEENTH STREET, N.W.  
SUITE 600  
WASHINGTON, D.C. 20006-5503

WRITER'S TELEPHONE

202-736-3620

TELEPHONE  
202-736-3600  
FACSIMILE  
202-736-3608

March 9, 2010

Gary J. Buehler, R. Ph.  
Office of Generic Drugs  
HFD-600  
7519 Standish Place  
Rockville, Maryland 20855

Dear Mr. Buehler:

We write on behalf of our client, Apotex, Inc., to bring to your attention certain patent information of relevance in connection with Teva v. Sebelius, No. 09-528 (D.C.Cir. Mar. 2, 2010) and the approval of Apotex, Inc.'s pending ANDAs referencing Hyzaar and Cozaar. Specifically, Teva Pharmaceuticals USA, Inc. has claimed an entitlement to 180-day exclusivity as a result of its certification to Merck's U.S. Patent No. 5, 608, 075 ("the '075 patent"). That patent, however, has expired. In fact, according to the United States Patent & Trademark Office ("USPTO"), the '075 patent expired at least as of March 30, 2009. The patent expired as a matter of law pursuant to 35 U.S.C. § 41(b) for failure to pay maintenance fees. Attachment A is a printout of the USPTO's Patent Application Information and Retrieval website reflecting that the '075 patent expired. Attachment B is a copy of the USPTO Official Gazette dated April 21, 2009 which, on page 5, reports that the '075 patent expired.

As Merck & Co., Inc., the patent holder, disclaimed the '075 patent in 2005 (Attachment C) and requested some time ago that this patent be delisted from the Orange Book altogether, it is not surprising that Merck did not update patent expiration information.

Gary J. Buehler, R. Ph.  
March 9, 2010  
Page 2

We have no objection to the public dissemination of this letter, or the information contained herein.

Sincerely,


Carmen M. Shepard  
Kate C. Beardsley

cc: Elizabeth H. Dickinson, Esq.  
Office of Chief Counsel  
PKLN-671  
5600 Fishers Lane  
Rockville, Maryland 20857

Office of Generic Drugs  
OGD Document Room  
Attention: Orange Book Staff  
7500 Standish Place  
Rockville, MD 20855

# ATTACHMENT

A



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08/371,937

POLYMORPHS OF LOSARTAN AND THE PROCESS FOR THE PREPARATION OF FORM II OF LOSARTAN



Select New Case	Application Date	Transaction History	Continuity Data	Fees	Published Documents	Address & Attorney/Agent
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**Bibliographic Data**

Application Number:	08/371,937	Customer Number:	-
Filing or 371 (c) Date:	01-12-1995	Status:	Patent Expired Due to NonPayment of Maintenance Fees Under 37 CFR 1.362
Application Type:	Utility	Status Date:	03-30-2009
Examiner Name:	SPRINGER, DAVID B	Location:	FILE REPOSITORY (FRANCONIA)
Group Art Unit:	1201	Location Date:	08-13-2009
Confirmation Number:	4230	Earliest Publication No:	-
Attorney Docket Number:	19157CA	Earliest Publication Date:	-
Class / Subclass:	548/252	Patent Number:	5,608,075
First Named Inventor:	GORDON C. CAMPBELL JR. , WILMINGTON, DE (US)	Issue Date of Patent:	03-04-1997

Title of Invention: POLYMORPHS OF LOSARTAN AND THE PROCESS FOR THE PREPARATION OF FORM II OF LOSARTAN

*If you need help:*

- Call the Patent Electronic Business Center at (866) 217-9197 (toll free) or e-mail [EBC@uspto.gov](mailto:EBC@uspto.gov) for specific questions about Patent Application Information Retrieval (PAIR).
- Send general questions about USPTO programs to the [USPTO Contact Center \(UCC\)](#).
- If you experience technical difficulties or problems with this application, please report them via e-mail to [Electronic Business Support](#) or call 1 800-786-9199.

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# ATTACHMENT

B

Notice of Expiration of Patents Due to Failure to Pay Maintenance Fee
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Notice of Expiration of Patents  
Due to Failure to Pay Maintenance Fee

35 U.S.C. 41 and 37 CFR 1.362(g) provide that if the required maintenance fee and any applicable surcharge are not paid in a patent requiring such payment, the patent will expire at the end of the 4th, 8th or 12th anniversary of the grant of the patent depending on the first maintenance fee which was not paid.

According to the records of the Office, the patents listed below have expired due to failure to pay the required maintenance fee and any applicable surcharge.

PATENTS WHICH EXPIRED ON March 4, 2009  
DUE TO FAILURE TO PAY MAINTENANCE FEES

Patent Number	Application Number	Issue Date
5,606,745	08/589,803	03/04/97
5,606,747	08/490,421	03/04/97
5,606,755	08/417,518	03/04/97
5,606,765	08/523,166	03/04/97
5,606,772	08/382,694	03/04/97
5,606,782	08/424,715	03/04/97
5,606,783	08/527,030	03/04/97
5,606,784	08/472,112	03/04/97
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5,606,797	08/494,368	03/04/97
5,606,811	08/432,427	03/04/97
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5,606,833	08/295,939	03/04/97
5,606,834	08/509,148	03/04/97
5,606,835	08/285,320	03/04/97
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5,606,842	08/625,676	03/04/97
5,606,846	08/304,226	03/04/97
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5,606,923	08/371,818	03/04/97
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5,606,944	08/618,316	03/04/97
5,606,953	08/392,885	03/04/97
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5,606,969	08/414,416	03/04/97
5,606,970	07/952,327	03/04/97
5,606,972	08/513,465	03/04/97
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April 21, 2009

US PATENT AND TRADEMARK  
OFFICE

1341 OG 119

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5,607,036	08/398,283	03/04/97
5,607,038	08/407,863	03/04/97
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5,607,339	08/278,333	03/04/97
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April 21, 2009

US PATENT AND TRADEMARK  
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1341 OG 120

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5,607,377	08/239,599	03/04/97
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5,607,667	08/076,349	03/04/97
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5,607,694	08/459,345	03/04/97
5,607,695	08/364,080	03/04/97
5,607,701	08/389,902	03/04/97
5,607,706	08/416,954	03/04/97
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April 21, 2009

US PATENT AND TRADEMARK  
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1341 OG 121

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5,607,714	08/384,585	03/04/97
5,607,720	08/285,547	03/04/97
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5,607,726	08/323,990	03/04/97
5,607,734	08/416,479	03/04/97
5,607,735	08/577,368	03/04/97
5,607,739	08/400,165	03/04/97
5,607,745	08/259,238	03/04/97
5,607,747	08/228,221	03/04/97
5,607,749	08/635,407	03/04/97
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5,607,757	08/552,658	03/04/97
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5,607,769	08/286,058	03/04/97
5,607,771	08/450,858	03/04/97
5,607,774	08/441,189	03/04/97
5,607,784	08/375,528	03/04/97
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5,607,798	08/442,618	03/04/97
5,607,809	08/514,084	03/04/97

5,607,816	08/531,853	03/04/97
5,607,824	08/281,398	03/04/97
5,607,827	08/531,714	03/04/97
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5,607,835	08/473,589	03/04/97
5,607,847	08/275,053	03/04/97
5,607,857	08/489,859	03/04/97
5,607,862	08/497,731	03/04/97
5,607,863	08/163,860	03/04/97
5,607,865	08/381,425	03/04/97
5,607,869	08/595,369	03/04/97
5,607,885	08/636,970	03/04/97
5,607,887	08/367,265	03/04/97
5,607,888	08/452,939	03/04/97
5,607,894	08/487,847	03/04/97
5,607,904	08/421,224	03/04/97
5,607,911	08/635,630	03/04/97
5,607,920	08/278,617	03/04/97
5,607,924	08/469,177	03/04/97
5,607,925	08/333,017	03/04/97
5,607,935	08/232,029	03/04/97
5,607,955	08/431,425	03/04/97
5,607,958	08/394,757	03/04/97
5,607,959	08/495,509	03/04/97
5,607,960	08/532,573	03/04/97
5,607,961	08/517,999	03/04/97
5,607,962	08/591,329	03/04/97
5,607,967	08/330,518	03/04/97
5,607,971	08/413,797	03/04/97
5,607,995	08/583,218	03/04/97
5,607,996	08/318,395	03/04/97
5,608,017	08/449,250	03/04/97
5,608,028	08/189,984	03/04/97
5,608,029	08/402,067	03/04/97
5,608,035	08/190,788	03/04/97
5,608,041	08/591,565	03/04/97
5,608,042	08/594,487	03/04/97
5,608,057	08/518,303	03/04/97
5,608,058	08/189,700	03/04/97
5,608,059	08/356,187	03/04/97
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5,608,063	08/412,409	03/04/97
5,608,075	08/371,937	03/04/97
5,608,079	08/473,509	03/04/97
5,608,080	08/424,504	03/04/97

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5,608,082	08/281,639	03/04/97
5,608,095	08/637,968	03/04/97
5,608,096	08/580,417	03/04/97
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5,608,119	08/463,896	03/04/97
5,608,128	08/495,662	03/04/97
5,608,154	08/397,969	03/04/97
5,608,157	08/544,591	03/04/97
5,608,160	08/627,740	03/04/97
5,608,167	08/390,980	03/04/97

5,608,176	08/479,219	03/04/97
5,608,179	08/200,785	03/04/97
5,608,194	08/476,574	03/04/97
5,608,197	08/289,151	03/04/97
5,608,198	08/494,754	03/04/97
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5,608,269	08/424,616	03/04/97
5,608,274	08/391,391	03/04/97
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5,608,284	08/504,139	03/04/97
5,608,291	08/075,092	03/04/97
5,608,293	08/542,248	03/04/97
5,608,296	08/639,042	03/04/97
5,608,302	08/312,601	03/04/97
5,608,318	08/589,618	03/04/97
5,608,334	08/425,921	03/04/97
5,608,337	08/481,744	03/04/97
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5,608,388	08/543,769	03/04/97
5,608,403	08/381,137	03/04/97
5,608,408	08/553,502	03/04/97
5,608,416	08/557,871	03/04/97
5,608,418	08/441,262	03/04/97
5,608,438	08/286,282	03/04/97
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5,608,441	08/628,140	03/04/97
5,608,453	08/551,736	03/04/97
5,608,456	08/307,080	03/04/97
5,608,474	08/600,899	03/04/97
5,608,478	08/403,437	03/04/97
5,608,479	08/585,729	03/04/97
5,608,483	08/539,582	03/04/97
5,608,488	08/358,711	03/04/97
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5,608,520	08/455,269	03/04/97
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5,608,525	08/404,817	03/04/97
5,608,535	08/258,868	03/04/97
5,608,538	08/295,318	03/04/97
5,608,566	08/513,701	03/04/97

5,608,573	08/362,230	03/04/97
5,608,579	08/407,098	03/04/97
5,608,590	08/263,605	03/04/97
5,608,611	08/538,807	03/04/97
5,608,612	08/531,457	03/04/97
5,608,614	08/280,552	03/04/97
5,608,618	08/397,471	03/04/97
5,608,622	07/944,148	03/04/97
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5,608,626	08/217,861	03/04/97
5,608,654	08/315,352	03/04/97
5,608,666	08/380,698	03/04/97
5,608,676	08/114,478	03/04/97
5,608,689	08/460,797	03/04/97
5,608,698	08/556,051	03/04/97
5,608,699	08/200,740	03/04/97
5,608,701	08/510,201	03/04/97
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5,608,706	08/295,045	03/04/97
5,608,709	08/334,071	03/04/97
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5,608,712	08/400,672	03/04/97
5,608,718	08/335,728	03/04/97
5,608,719	08/447,639	03/04/97
5,608,724	08/534,291	03/04/97
5,608,751	08/209,963	03/04/97
5,608,758	08/091,267	03/04/97
5,608,780	08/522,795	03/04/97
5,608,784	08/186,450	03/04/97
5,608,790	08/485,927	03/04/97
5,608,791	08/192,668	03/04/97
5,608,797	08/332,702	03/04/97
5,608,798	08/520,917	03/04/97
5,608,809	08/355,237	03/04/97
5,608,812	08/593,692	03/04/97
5,608,814	08/341,470	03/04/97
5,608,818	08/003,782	03/04/97
5,608,826	08/482,642	03/04/97
5,608,831	08/483,024	03/04/97
5,608,849	08/187,621	03/04/97
5,608,858	08/430,827	03/04/97
5,608,860	08/610,768	03/04/97
5,608,861	08/195,932	03/04/97
5,608,870	08/459,367	03/04/97
5,608,871	08/343,872	03/04/97
5,608,893	08/480,627	03/04/97
5,608,894	08/325,056	03/04/97
5,608,900	08/262,999	03/04/97
5,608,908	08/539,000	03/04/97

PATENTS WHICH EXPIRED ON February 27, 2009  
DUE TO FAILURE TO PAY MAINTENANCE FEES

Patent Number	Application Number	Issue Date
6,192,524	09/338,504	02/27/01
6,192,528	09/518,238	02/27/01
6,192,530	09/313,840	02/27/01

6,192,532	09/502,289	02/27/01
6,192,540	09/395,276	02/27/01
6,192,541	09/538,225	02/27/01
6,192,551	09/157,127	02/27/01
6,192,552	09/322,432	02/27/01
6,192,556	09/251,344	02/27/01
6,192,557	09/347,351	02/27/01

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6,192,558	09/322,016	02/27/01
6,192,566	09/470,239	02/27/01
6,192,571	09/194,381	02/27/01
6,192,579	09/211,797	02/27/01
6,192,583	09/308,481	02/27/01
6,192,598	09/459,275	02/27/01
6,192,599	09/159,415	02/27/01
6,192,600	09/392,966	02/27/01
6,192,602	09/620,280	02/27/01
6,192,606	09/534,687	02/27/01
6,192,607	08/834,578	02/27/01
6,192,613	09/259,383	02/27/01
6,192,616	09/422,764	02/27/01
6,192,617	09/466,079	02/27/01
6,192,625	09/353,850	02/27/01
6,192,626	09/436,451	02/27/01
6,192,627	09/442,581	02/27/01
6,192,628	09/368,691	02/27/01
6,192,630	09/409,228	02/27/01
6,192,644	09/147,124	02/27/01
6,192,648	09/398,758	02/27/01
6,192,652	09/300,308	02/27/01
6,192,655	09/386,616	02/27/01
6,192,667	09/217,713	02/27/01
6,192,691	09/399,246	02/27/01
6,192,692	09/017,738	02/27/01
6,192,701	09/378,988	02/27/01
6,192,712	09/035,076	02/27/01
6,192,716	09/148,594	02/27/01
6,192,723	09/232,519	02/27/01
6,192,728	09/580,850	02/27/01
6,192,730	09/397,352	02/27/01
6,192,731	09/383,389	02/27/01
6,192,733	09/254,753	02/27/01
6,192,738	09/244,933	02/27/01
6,192,741	09/389,627	02/27/01
6,192,744	09/295,637	02/27/01
6,192,754	09/057,811	02/27/01
6,192,759	09/241,453	02/27/01
6,192,776	08/935,019	02/27/01
6,192,783	09/354,378	02/27/01
6,192,790	09/367,401	02/27/01
6,192,801	08/935,302	02/27/01
6,192,805	09/318,869	02/27/01
6,192,808	09/315,905	02/27/01
6,192,810	09/307,469	02/27/01
6,192,815	09/475,898	02/27/01
6,192,825	09/285,231	02/27/01

6,192,837	09/426,421	02/27/01
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6,192,839	09/308,268	02/27/01
6,192,842	09/413,394	02/27/01
6,192,846	09/462,277	02/27/01
6,192,859	09/312,400	02/27/01
6,192,866	09/396,425	02/27/01
6,192,869	09/360,677	02/27/01
6,192,880	09/421,047	02/27/01
6,192,883	09/366,622	02/27/01
6,192,886	08/734,469	02/27/01
6,192,890	09/280,496	02/27/01
6,192,893	09/616,775	02/27/01
6,192,907	09/303,384	02/27/01
6,192,908	09/373,119	02/27/01
6,192,909	09/340,986	02/27/01
6,192,912	09/512,527	02/27/01
6,192,922	09/323,591	02/27/01

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6,192,925	09/414,011	02/27/01
6,192,926	09/420,378	02/27/01
6,192,944	09/558,243	02/27/01
6,192,949	09/442,265	02/27/01
6,192,950	09/088,588	02/27/01
6,192,958	09/215,291	02/27/01
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6,192,992	09/142,709	02/27/01
6,192,993	09/340,775	02/27/01
6,192,997	09/548,395	02/27/01
6,193,007	09/370,061	02/27/01
6,193,008	09/308,329	02/27/01
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6,193,013	09/385,311	02/27/01
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6,193,025	09/192,598	02/27/01
6,193,033	09/056,104	02/27/01
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6,193,074	09/186,179	02/27/01
6,193,080	09/442,448	02/27/01
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6,193,085	09/244,634	02/27/01
6,193,087	09/269,162	02/27/01
6,193,093	09/414,009	02/27/01
6,193,094	09/227,049	02/27/01
6,193,097	09/512,925	02/27/01
6,193,106	09/406,970	02/27/01
6,193,108	09/381,114	02/27/01
6,193,110	09/288,198	02/27/01
6,193,119	09/506,990	02/27/01
6,193,124	09/298,550	02/27/01
6,193,125	09/483,271	02/27/01

6,193,127	09/500,961	02/27/01
6,193,132	09/197,704	02/27/01
6,193,139	09/137,724	02/27/01
6,193,148	09/320,137	02/27/01
6,193,153	09/059,733	02/27/01
6,193,157	09/122,903	02/27/01
6,193,162	09/055,884	02/27/01
6,193,170	09/479,131	02/27/01
6,193,171	09/247,205	02/27/01
6,193,178	09/290,860	02/27/01
6,193,179	09/304,794	02/27/01
6,193,183	09/128,696	02/27/01
6,193,187	09/224,190	02/27/01
6,193,189	09/371,663	02/27/01
6,193,193	09/053,178	02/27/01
6,193,194	09/146,927	02/27/01
6,193,197	09/472,426	02/27/01
6,193,203	09/243,256	02/27/01
6,193,204	09/353,350	02/27/01
6,193,211	09/431,925	02/27/01
6,193,217	09/373,725	02/27/01
6,193,230	09/497,144	02/27/01
6,193,231	09/245,522	02/27/01
6,193,234	09/362,879	02/27/01
6,193,236	09/240,624	02/27/01
6,193,245	09/391,504	02/27/01
6,193,250	09/471,772	02/27/01
6,193,252	09/420,226	02/27/01
6,193,254	09/303,459	02/27/01

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6,193,258	09/191,654	02/27/01
6,193,260	09/388,688	02/27/01
6,193,261	09/404,244	02/27/01
6,193,267	09/089,196	02/27/01
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6,193,276	09/365,044	02/27/01
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6,193,280	09/416,440	02/27/01
6,193,281	09/163,007	02/27/01
6,193,282	09/405,875	02/27/01
6,193,286	09/258,173	02/27/01
6,193,290	09/229,274	02/27/01
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6,193,299	09/545,387	02/27/01
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6,193,338	09/293,241	02/27/01
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6,193,367	09/516,217	02/27/01
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6,193,454	09/301,832	02/27/01
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6,193,539	09/312,767	02/27/01
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6,193,542	09/246,165	02/27/01
6,193,553	09/304,211	02/27/01
6,193,556	09/040,756	02/27/01
6,193,562	09/414,560	02/27/01
6,193,567	09/405,763	02/27/01
6,193,578	09/426,057	02/27/01
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6,193,602	09/234,698	02/27/01
6,193,615	09/188,453	02/27/01

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6,193,624	09/375,194	02/27/01
6,193,625	09/273,727	02/27/01
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6,193,641	09/291,451	02/27/01
6,193,642	09/493,463	02/27/01
6,193,643	09/171,971	02/27/01
6,193,646	09/246,466	02/27/01
6,193,649	09/391,350	02/27/01
6,193,654	09/195,892	02/27/01
6,193,657	09/224,026	02/27/01
6,193,661	09/287,982	02/27/01
6,193,662	09/251,563	02/27/01

6,193,667	09/440,429	02/27/01
6,193,690	09/422,158	02/27/01
6,193,695	09/483,225	02/27/01
6,193,697	09/289,056	02/27/01
6,193,712	09/359,664	02/27/01
6,193,724	09/200,127	02/27/01
6,193,726	09/232,272	02/27/01
6,193,730	09/440,060	02/27/01
6,193,739	09/128,968	02/27/01
6,193,742	08/966,328	02/27/01
6,193,767	09/406,881	02/27/01
6,193,776	08/985,962	02/27/01
6,193,780	08/983,003	02/27/01
6,193,794	09/260,726	02/27/01
6,193,800	09/401,802	02/27/01
6,193,806	09/347,725	02/27/01
6,193,811	09/261,700	02/27/01
6,193,812	09/435,687	02/27/01
6,193,818	09/077,841	02/27/01
6,193,832	08/900,406	02/27/01
6,193,834	09/117,237	02/27/01
6,193,844	09/395,493	02/27/01
6,193,865	09/268,250	02/27/01
6,193,866	09/212,622	02/27/01
6,193,870	08/847,085	02/27/01
6,193,876	09/147,537	02/27/01
6,193,877	08/918,640	02/27/01
6,193,887	09/372,057	02/27/01
6,193,896	09/507,082	02/27/01
6,193,897	08/887,456	02/27/01
6,193,899	09/105,056	02/27/01
6,193,902	09/371,441	02/27/01
6,193,904	09/041,220	02/27/01
6,193,905	08/380,312	02/27/01
6,193,921	09/379,967	02/27/01
6,193,924	09/169,363	02/27/01
6,193,928	09/026,548	02/27/01
6,193,930	09/084,660	02/27/01
6,193,935	09/133,433	02/27/01
6,193,937	09/264,911	02/27/01
6,193,962	09/180,134	02/27/01
6,193,967	08/947,037	02/27/01
6,193,968	09/057,490	02/27/01
6,193,973	08/917,022	02/27/01
6,193,976	09/318,665	02/27/01
6,193,994	09/180,480	02/27/01
6,194,001	09/230,978	02/27/01
6,194,007	09/215,885	02/27/01
6,194,008	09/601,818	02/27/01
6,194,011	09/400,536	02/27/01
6,194,015	09/419,989	02/27/01

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6,194,024	08/469,449	02/27/01
6,194,025	09/493,867	02/27/01
6,194,026	09/174,716	02/27/01
6,194,027	09/184,356	02/27/01

6,194,029	09/243,491	02/27/01
6,194,039	09/425,589	02/27/01
6,194,041	08/654,569	02/27/01
6,194,046	09/244,200	02/27/01
6,194,048	09/165,637	02/27/01
6,194,049	08/720,629	02/27/01
6,194,050	09/340,927	02/27/01
6,194,053	09/031,234	02/27/01
6,194,056	09/349,601	02/27/01
6,194,057	09/191,211	02/27/01
6,194,058	09/126,929	02/27/01
6,194,066	08/229,962	02/27/01
6,194,067	09/254,190	02/27/01
6,194,068	08/966,126	02/27/01
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6,194,070	09/288,903	02/27/01
6,194,075	09/095,755	02/27/01
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6,194,087	09/209,343	02/27/01
6,194,091	09/160,908	02/27/01
6,194,093	09/203,285	02/27/01
6,194,096	09/101,349	02/27/01
6,194,102	09/231,943	02/27/01
6,194,123	09/310,824	02/27/01
6,194,127	09/085,048	02/27/01
6,194,129	09/173,164	02/27/01
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6,194,135	09/425,591	02/27/01
6,194,147	09/000,805	02/27/01
6,194,155	09/305,408	02/27/01
6,194,179	09/357,541	02/27/01
6,194,183	09/017,612	02/27/01
6,194,184	09/294,139	02/27/01
6,194,190	09/202,832	02/27/01
6,194,192	09/117,122	02/27/01
6,194,196	09/329,999	02/27/01
6,194,210	08/634,011	02/27/01
6,194,211	08/646,301	02/27/01
6,194,218	09/235,472	02/27/01
6,194,230	09/073,601	02/27/01
6,194,231	09/259,840	02/27/01
6,194,242	09/340,263	02/27/01
6,194,253	09/167,693	02/27/01
6,194,268	09/183,926	02/27/01
6,194,301	09/352,318	02/27/01
6,194,320	08/908,636	02/27/01
6,194,325	08/552,030	02/27/01
6,194,343	09/266,562	02/27/01
6,194,344	09/414,288	02/27/01
6,194,349	09/327,845	02/27/01
6,194,351	09/274,491	02/27/01
6,194,352	08/553,184	02/27/01
6,194,353	08/323,065	02/27/01
6,194,354	09/156,152	02/27/01
6,194,355	09/248,310	02/27/01
6,194,385	09/206,499	02/27/01
6,194,386	09/334,254	02/27/01
6,194,390	09/497,700	02/27/01
6,194,393	09/013,922	02/27/01

6,194,421	09/000,801	02/27/01
6,194,422	09/341,703	02/27/01

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6,194,427	09/259,244	02/27/01
6,194,428	09/238,569	02/27/01
6,194,433	09/166,703	02/27/01
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6,194,442	09/460,483	02/27/01
6,194,443	09/284,225	02/27/01
6,194,446	09/216,471	02/27/01
6,194,450	09/121,188	02/27/01
6,194,451	09/355,315	02/27/01
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6,194,455	09/321,946	02/27/01
6,194,458	09/422,499	02/27/01
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6,194,463	09/380,022	02/27/01
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6,194,482	09/444,740	02/27/01
6,194,483	09/436,365	02/27/01
6,194,485	09/285,198	02/27/01
6,194,500	09/323,961	02/27/01
6,194,501	09/155,053	02/27/01
6,194,528	09/020,936	02/27/01
6,194,536	09/308,787	02/27/01
6,194,539	08/560,110	02/27/01
6,194,541	09/307,113	02/27/01
6,194,542	08/976,161	02/27/01
6,194,543	09/096,411	02/27/01
6,194,546	08/841,650	02/27/01
6,194,550	09/197,649	02/27/01
6,194,555	08/659,254	02/27/01
6,194,558	09/130,242	02/27/01
6,194,564	09/136,341	02/27/01
6,194,566	09/400,993	02/27/01
6,194,578	09/348,449	02/27/01
6,194,581	09/218,214	02/27/01
6,194,583	09/525,394	02/27/01
6,194,584	09/555,503	02/27/01
6,194,588	09/251,242	02/27/01
6,194,590	09/509,911	02/27/01
6,194,601	09/397,975	02/27/01
6,194,608	09/194,019	02/27/01
6,194,611	09/051,688	02/27/01
6,194,615	09/335,196	02/27/01
6,194,619	08/116,938	02/27/01
6,194,621	08/663,038	02/27/01
6,194,623	09/371,848	02/27/01
6,194,624	09/444,316	02/27/01
6,194,627	09/308,189	02/27/01
6,194,632	09/215,098	02/27/01

6,194,633	09/013,687	02/27/01
6,194,643	09/387,395	02/27/01
6,194,645	09/238,816	02/27/01
6,194,646	09/270,144	02/27/01
6,194,660	09/340,803	02/27/01
6,194,668	09/211,806	02/27/01
6,194,679	09/370,083	02/27/01
6,194,683	09/484,783	02/27/01
6,194,695	09/141,621	02/27/01
6,194,701	09/287,078	02/27/01
6,194,709	09/179,020	02/27/01
6,194,730	09/186,865	02/27/01
6,194,731	09/197,540	02/27/01

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6,194,733	09/054,977	02/27/01
6,194,749	09/120,466	02/27/01
6,194,755	09/102,471	02/27/01
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6,194,779	08/254,667	02/27/01
6,194,781	09/023,432	02/27/01
6,194,785	09/023,554	02/27/01
6,194,790	09/444,984	02/27/01
6,194,798	09/172,524	02/27/01
6,194,801	09/419,062	02/27/01
6,194,804	09/132,701	02/27/01
6,194,819	09/112,891	02/27/01
6,194,823	09/115,941	02/27/01
6,194,824	09/116,357	02/27/01
6,194,825	09/168,088	02/27/01
6,194,834	09/142,788	02/27/01
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6,194,846	09/288,397	02/27/01
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6,194,849	09/068,746	02/27/01
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6,194,868	09/483,919	02/27/01
6,194,875	09/414,432	02/27/01
6,194,877	09/365,986	02/27/01
6,194,899	09/251,488	02/27/01
6,194,904	09/082,291	02/27/01
6,194,905	09/516,354	02/27/01
6,194,911	09/309,620	02/27/01
6,194,921	09/492,190	02/27/01
6,194,925	09/039,344	02/27/01
6,194,929	08/883,525	02/27/01
6,194,959	09/516,362	02/27/01
6,194,967	09/099,081	02/27/01
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6,194,978	09/125,990	02/27/01
6,194,998	09/299,518	02/27/01
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6,195,027	09/302,744	02/27/01
6,195,032	09/373,472	02/27/01
6,195,033	09/408,729	02/27/01
6,195,036	09/284,439	02/27/01

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6,195,078	09/000,300	02/27/01
6,195,085	09/056,255	02/27/01
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6,195,097	08/889,727	02/27/01
6,195,114	09/294,393	02/27/01
6,195,123	09/047,898	02/27/01
6,195,125	08/695,233	02/27/01
6,195,128	09/011,973	02/27/01
6,195,130	09/136,509	02/27/01
6,195,132	09/345,489	02/27/01
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6,195,147	09/126,857	02/27/01
6,195,152	09/436,993	02/27/01
6,195,154	09/323,042	02/27/01
6,195,155	09/418,204	02/27/01
6,195,175	09/124,679	02/27/01
6,195,177	09/299,791	02/27/01
6,195,184	09/336,542	02/27/01
6,195,187	09/111,004	02/27/01
6,195,188	09/083,386	02/27/01
6,195,199	09/178,735	02/27/01
6,195,205	08/390,807	02/27/01

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6,195,215	09/124,535	02/27/01
6,195,219	09/175,814	02/27/01
6,195,225	09/266,308	02/27/01
6,195,238	09/274,788	02/27/01
6,195,240	09/127,254	02/27/01
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6,195,262	09/118,027	02/27/01
6,195,264	09/195,389	02/27/01
6,195,266	09/282,838	02/27/01
6,195,270	09/596,800	02/27/01
6,195,276	09/172,954	02/27/01
6,195,280	09/521,352	02/27/01
6,195,284	09/579,320	02/27/01
6,195,328	09/061,354	02/27/01
6,195,329	09/048,272	02/27/01
6,195,331	08/989,686	02/27/01
6,195,335	09/110,917	02/27/01
6,195,339	08/996,547	02/27/01
6,195,348	09/012,075	02/27/01
6,195,350	09/007,179	02/27/01
6,195,356	08/991,614	02/27/01
6,195,359	08/951,842	02/27/01
6,195,361	08/957,366	02/27/01
6,195,363	09/092,998	02/27/01
6,195,366	09/065,416	02/27/01
6,195,367	09/002,036	02/27/01
6,195,391	08/251,730	02/27/01
6,195,400	09/048,884	02/27/01
6,195,401	09/064,507	02/27/01

6,195,407	09/296,029	02/27/01
6,195,410	09/491,956	02/27/01
6,195,412	09/266,055	02/27/01
6,195,420	08/670,926	02/27/01
6,195,438	08/925,318	02/27/01
6,195,440	09/193,468	02/27/01
6,195,442	09/384,901	02/27/01
6,195,449	08/858,102	02/27/01
6,195,471	09/047,084	02/27/01
6,195,472	09/096,369	02/27/01
6,195,474	09/085,508	02/27/01
6,195,476	09/493,036	02/27/01
6,195,480	09/129,844	02/27/01
6,195,490	09/307,527	02/27/01
6,195,496	09/364,814	02/27/01
6,195,499	09/399,230	02/27/01
6,195,500	08/196,658	02/27/01
6,195,504	08/974,512	02/27/01
6,195,505	09/037,121	02/27/01
6,195,512	08/599,261	02/27/01
6,195,523	09/317,274	02/27/01
6,195,544	09/157,538	02/27/01
6,195,590	09/022,251	02/27/01
6,195,603	08/514,180	02/27/01
6,195,605	09/407,290	02/27/01
6,195,619	09/363,159	02/27/01
6,195,620	09/129,515	02/27/01
6,195,628	08/816,579	02/27/01
6,195,643	09/370,745	02/27/01
6,195,644	09/317,975	02/27/01
6,195,653	09/482,595	02/27/01
6,195,666	08/990,246	02/27/01
6,195,677	09/088,675	02/27/01
6,195,682	09/179,466	02/27/01
6,195,691	08/714,990	02/27/01

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6,195,693	08/972,875	02/27/01
6,195,695	09/181,138	02/27/01
6,195,702	08/980,581	02/27/01
6,195,707	09/181,826	02/27/01
6,195,722	09/013,776	02/27/01
6,195,723	09/213,055	02/27/01
6,195,729	09/024,317	02/27/01
6,195,733	09/176,413	02/27/01
6,195,745	09/080,492	02/27/01
6,195,749	09/501,888	02/27/01
6,195,769	09/105,541	02/27/01
6,195,772	08/850,790	02/27/01

PATENTS WHICH EXPIRED ON March 1, 2009  
DUE TO FAILURE TO PAY MAINTENANCE FEES

Patent Number	Application Number	Issue Date
6,859,939	10/277,118	03/01/05

6,859,940	10/725,646	03/01/05
6,859,943	10/621,021	03/01/05
6,859,948	10/244,487	03/01/05
6,859,949	10/639,870	03/01/05
6,859,953	10/242,816	03/01/05
6,859,960	10/753,932	03/01/05
6,859,961	10/629,328	03/01/05
6,859,973	10/804,150	03/01/05
6,859,977	10/214,042	03/01/05
6,859,978	10/374,080	03/01/05
6,859,982	10/388,003	03/01/05
6,859,983	10/246,200	03/01/05
6,859,984	10/234,338	03/01/05
6,859,991	10/078,190	03/01/05
6,859,998	10/121,989	03/01/05
6,860,001	10/275,729	03/01/05
6,860,002	09/961,386	03/01/05
6,860,005	10/735,878	03/01/05
6,860,007	10/647,228	03/01/05
6,860,010	10/146,251	03/01/05
6,860,013	10/319,690	03/01/05
6,860,021	10/624,239	03/01/05
6,860,024	09/853,241	03/01/05
6,860,027	10/151,735	03/01/05
6,860,028	10/427,497	03/01/05
6,860,030	09/713,434	03/01/05
6,860,031	10/327,150	03/01/05
6,860,032	10/341,719	03/01/05
6,860,034	09/827,933	03/01/05
6,860,038	10/629,140	03/01/05
6,860,043	10/602,204	03/01/05
6,860,051	10/144,629	03/01/05
6,860,052	10/672,872	03/01/05
6,860,055	10/925,677	03/01/05
6,860,057	10/088,116	03/01/05
6,860,060	10/419,292	03/01/05
6,860,071	10/112,733	03/01/05
6,860,072	10/443,370	03/01/05
6,860,076	09/939,295	03/01/05
6,860,085	10/680,926	03/01/05
6,860,096	10/300,876	03/01/05
6,860,104	10/181,410	03/01/05
6,860,111	10/706,399	03/01/05
6,860,118	10/179,704	03/01/05
6,860,120	10/473,701	03/01/05
6,860,125	10/676,853	03/01/05

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6,860,136	10/364,770	03/01/05
6,860,140	10/868,069	03/01/05
6,860,141	10/868,158	03/01/05
6,860,154	10/047,627	03/01/05
6,860,163	10/463,811	03/01/05
6,860,164	10/224,123	03/01/05
6,860,166	10/309,734	03/01/05
6,860,168	10/412,253	03/01/05
6,860,179	10/162,528	03/01/05

6,860,180	10/699,216	03/01/05
6,860,181	09/747,126	03/01/05
6,860,182	09/837,111	03/01/05
6,860,210	10/166,540	03/01/05
6,860,215	10/469,750	03/01/05
6,860,216	10/792,752	03/01/05
6,860,222	10/169,312	03/01/05
6,860,223	10/633,330	03/01/05
6,860,230	10/842,693	03/01/05
6,860,236	10/774,217	03/01/05
6,860,248	10/286,725	03/01/05
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6,860,263	10/619,952	03/01/05
6,860,266	10/054,069	03/01/05
6,860,268	10/066,562	03/01/05
6,860,272	10/051,363	03/01/05
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6,860,298	10/234,475	03/01/05
6,860,316	10/338,543	03/01/05
6,860,319	10/454,054	03/01/05
6,860,322	10/088,303	03/01/05
6,860,324	10/466,917	03/01/05
6,860,336	10/372,441	03/01/05
6,860,342	10/863,052	03/01/05
6,860,347	10/291,071	03/01/05
6,860,354	10/277,077	03/01/05
6,860,363	10/190,447	03/01/05
6,860,364	10/351,652	03/01/05
6,860,382	10/449,895	03/01/05
6,860,384	10/381,848	03/01/05
6,860,385	10/320,727	03/01/05
6,860,388	10/251,098	03/01/05
6,860,389	10/112,553	03/01/05
6,860,390	10/076,297	03/01/05
6,860,401	10/361,405	03/01/05
6,860,402	10/296,169	03/01/05
6,860,415	10/316,646	03/01/05
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6,860,435	10/164,985	03/01/05
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April 21, 2009

US PATENT AND TRADEMARK  
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1341 OG 136

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April 21, 2009

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# ATTACHMENT

C

Mary J. Morry  
Assistant Counsel  
Intellectual Property Litigation  
Fax 732 594 6200  
Tel 732 594 1935  
Email mary\_morry@merck.com

Merck & Co., Inc.  
P. O. Box 2000  
126 Lincoln Avenue  
Rahway, NJ 07065-0907



April 10, 2008

**VIA COURIER**

Shashank Upadhye, Esq.  
Vice-President, Global Intellectual Property  
Apotex Corp.  
150 Signet Drive  
Toronto, Ontario M9L 1T9  
Canada

Re: Apotex Notification of Certification  
Regarding U.S. Patent No. 5,608,075  
ANDA No. 90-150 for Hydrochlorothiazide/ Losartan Potassium  
12.5mg/50mg; 12.5mg/100mg and 25mg/100mg

Dear Mr. Upadhye,

We are in receipt of your letter of March 19, 2008 in connection with the above-referenced ANDA.

This is to inform you that Merck will not bring suit against Apotex Corp. based on the above mentioned U.S. Patent No. 5,608,075. As noted in your letter, and as reflected in the publicly accessible records of the USPTO, Merck and DuPont disclaimed this patent on April 28, 2005. After that date, neither this patent nor any exclusionary right under it continued to exist. Accordingly, Merck and DuPont have forever relinquished any right to sue any entity, including Apotex, for infringement of this patent. Furthermore, in 2005 Merck made a request to the FDA that it remove this patent from the Orange Book.

Very truly yours,

  
Mary J. Morry  
MJM:emh

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA- (b) (4)	ORIG-1	(b) (4)	LOSARTAN POTASSIUM
ANDA-91652	ORIG-1	MYLAN PHARMACEUTICALS INC.	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-91629	ORIG-1	AUROBINDO PHARMA LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-91617	ORIG-1	ALEMBIC LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-91590	ORIG-1	MYLAN PHARMACEUTICALS INC.	LOSARTAN POTASSIUM
ANDA-91541	ORIG-1	MICRO LABS LIMITED	LOSARTAN POTASSIUM
ANDA-91497	ORIG-1	HUAHAI US INC	LOSARTAN POTASSIUM
ANDA-91129	ORIG-1	COBALT LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-90790	ORIG-1	APOTEX CORP	LOSARTAN POTASSIUM
ANDA-90544	ORIG-1	UPSHER SMITH LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-90528	ORIG-1	TORRENT PHARMACEUTICALS LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-90467	ORIG-1	TORRENT PHARMACEUTICALS LTD	LOSARTAN POTASSIUM
ANDA-90428	ORIG-1	ALEMBIC LTD	LOSARTAN POTASSIUM
ANDA-90382	ORIG-1	ACTAVIS PHARMA MANUFACTURING PRIVATE LTD	LOSARTAN POTASSIUM
ANDA- (b) (4)	ORIG-1	(b) (4)	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-90150	ORIG-1	APOTEX CORP	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-90083	ORIG-1	AUROBINDO PHARMA LTD	LOSARTAN POTASSIUM
ANDA-78385	ORIG-1	ZYDUS PHARMACEUTICALS USA INC	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-78245	ORIG-1	LUPIN LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-78243	ORIG-1	ZYDUS PHARMACEUTICALS USA INC	LOSARTAN POTASSIUM
ANDA-78232	ORIG-1	LUPIN LTD	LOSARTAN POTASSIUM

ANDA-77948	ORIG-1	LEK PHARMACEUTICA L AND CHEMICAL CO DD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-77732	ORIG-1	ROXANE LABORATORIES INC	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-77459	ORIG-1	ROXANE LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-77424	ORIG-1	LEK PHARMACEUTICA LS D D	LOSARTAN POTASSIUM
ANDA-77157	ORIG-1	TEVA PHARMACEUTICA LS USA	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-76958	ORIG-1	TEVA PHARMACEUTICA LS USA INC	LOSARTAN POTASSIUM
ANDA-200180	ORIG-1	COBALT LABORATORIES INC	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE

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

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/s/

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GARY J BUEHLER  
03/11/2010

March 15, 2010

Office of Generic Drugs  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Sir or Madam,

**Re: GRATUITOUS AMENDMENT – Patent Amendment AND Request For Final Approval For ANDA 90790 Losartan Potassium Tablets 25mg, 50mg and 100mg.**

Apotex Corp. is hereby submitting a Gratuitous Amendment to ANDA 90790 Losartan Potassium Tablets 25mg, 50mg and 100mg. Subsequent to the update of the patent information for US 5608075 in the electronic orange book, this amendment provides for a revised patent certification to the US Patent 5608075. Apotex submits a paragraph II certification for US 5608075.

Apotex's ANDA contains a Paragraph III certifications to U.S. Patent Nos. 5,138,069 (the '069 patent) and 5,153,197 (the '197 patent) and a method of use certification to US 5210079. This request for final approval is submitted in the anticipation of the expiration of patents and their associated pediatric exclusivities for the reference listed drug Cozaar Tablets on April 6, 2010.

This amendment is filed through the Electronic Submission Gateway (ESG) and a letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted and therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form 356h has been provided in section 1.1.2.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at (954) 984-3986 by fax at (866)392-1774, or alternatively please do not hesitate to contact me at (416) 401-7889, by fax at (416) 401-3809 or via email at [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,





SENT VIA TELEFAX

Docket No. FDA-2010-N-0134

Dear ANDA Applicant:

This is a follow-up to our letter of March 11, 2010, in which we asked for comment on legal and regulatory issues pertaining to 180-day exclusivity as described in section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act for abbreviated new drug applications (ANDAs) for losartan potassium tablets and losartan potassium-hydrochlorothiazide tablets.

As noted in that letter, Merck Research Laboratories (Merck) holds the NDAs for Cozaar (losartan potassium) tablets and Hyzaar (potassium-hydrochlorothiazide) tablets, the reference listed drugs for these ANDAs. Merck submitted U.S. Patent No. 5,608,075 (the '075 patent) to FDA for listing for the Cozaar and Hyzaar NDAs 20-386 and 20-387, respectively. Merck requested in March 2005 that FDA delist the patent for these drug products. The patent has remained listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for Cozaar and Hyzaar as a placeholder for any exclusivity that may result from an ANDA applicant's paragraph IV certification to the patent.

At the time of our March 11, 2010 letter, the Orange Book listing for the '075 patent showed a patent expiration date of March 4, 2014. **We are writing now to inform you that the Orange Book has been updated to show additional information submitted by Merck pertaining to the '075 patent: the expiration date of the '075 patent is March 4, 2009.** This change in the expiration date for the '075 patent is for both the Cozaar and Hyzaar NDAs.

If you have any questions regarding this correspondence, please contact Dave Read, Regulatory Counsel, Office of Generic Drugs, at 240-276-9310.

Sincerely,

{See appended electronic signature page}

Gary J. Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA- (b) (4)	ORIG-1	(b) (4)	LOSARTAN POTASSIUM
ANDA-200180	ORIG-1	COBALT LABORATORIES INC	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-91652	ORIG-1	MYLAN PHARMACEUTICALS INC	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-91629	ORIG-1	AUROBINDO PHARMA LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-91617	ORIG-1	ALEMBIC LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-91590	ORIG-1	MYLAN PHARMACEUTICALS INC	LOSARTAN POTASSIUM
ANDA-91541	ORIG-1	MICRO LABS LIMITED	LOSARTAN POTASSIUM
ANDA-91497	ORIG-1	HUAHAI US INC	LOSARTAN POTASSIUM
ANDA-91129	ORIG-1	COBALT LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-90790	ORIG-1	APOTEX CORP	LOSARTAN POTASSIUM
ANDA-90544	ORIG-1	UPSHER SMITH LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-90528	ORIG-1	TORRENT PHARMACEUTICALS LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-90467	ORIG-1	TORRENT PHARMACEUTICALS LTD	LOSARTAN POTASSIUM
ANDA-90428	ORIG-1	ALEMBIC LTD	LOSARTAN POTASSIUM
ANDA-90382	ORIG-1	ACTAVIS PHARMA MANUFACTURING PRIVATE LTD	LOSARTAN POTASSIUM
ANDA- (b) (4)	ORIG-1	(b) (4)	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-90150	ORIG-1	APOTEX CORP	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-90083	ORIG-1	AUROBINDO PHARMA LTD	LOSARTAN POTASSIUM
ANDA-78385	ORIG-1	ZYDUS PHARMACEUTICALS USA INC	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-78245	ORIG-1	LUPIN LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE

ANDA-78243	ORIG-1	ZYDUS PHARMACEUTICA LS USA INC	LOSARTAN POTASSIUM
ANDA-78232	ORIG-1	LUPIN LTD	LOSARTAN POTASSIUM
ANDA-77948	ORIG-1	LEK PHARMACEUTICA L AND CHEMICAL CO DD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-77732	ORIG-1	ROXANE LABORATORIES INC	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-77459	ORIG-1	ROXANE LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-77424	ORIG-1	LEK PHARMACEUTICA LS D D	LOSARTAN POTASSIUM
ANDA-77157	ORIG-1	TEVA PHARMACEUTICA LS USA	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-76958	ORIG-1	TEVA PHARMACEUTICA LS USA INC	LOSARTAN POTASSIUM

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/s/

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GARY J BUEHLER  
03/16/2010



SENT VIA TELEFAX

Docket No. FDA-2010-N-0134

Dear ANDA Applicants:

This letter addresses whether the March 4, 2009 expiration of U.S. Patent No. 5,608,075 ('075 patent) affects the first applicant's eligibility for 180-day exclusivity for generic versions of Merck's Cozaar and Hyzaar drug products, and supplements the March 11, 2010 letter to ANDA applicants that was posted at [www.regulations.gov](http://www.regulations.gov) in Docket No. FDA-2010-N-0134. As explained below, in light of the Court of Appeals' decision in Teva Pharms., USA, Inc. v. Sebelius, No. 09-5281 (D.C. Cir. Mar. 2, 2010) ("Teva slip op."), we have concluded that the expiration of the '075 patent does not result in a forfeiture of the first applicant's eligibility for exclusivity for ANDAs referencing Cozaar and Hyzaar.

## Background

FDA has pending before it ANDAs referencing Cozaar (losartan potassium) Tablets and Hyzaar (losartan potassium and hydrochlorothiazide) Tablets. Among the patents submitted to FDA for Cozaar and Hyzaar, and thus relevant to the approval date for these ANDAs, is the '075 patent. FDA's Orange Book shows that the '075 patent was submitted by Merck, and that Merck later requested delisting of the patent. Merck has also recently informed FDA that the expiration date for the '075 patent should be revised from March 4, 2014, to March 4, 2009.<sup>1</sup> The Orange Book currently displays the March 4, 2009 expiration date for the '075 patent.

The timing of approval of ANDAs referencing Cozaar and Hyzaar will be affected by, among other things, any 180-day exclusivity under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act) available to a first applicant to challenge the '075 patent.<sup>2</sup> Under the Act, as amended by the MMA, a 180-day exclusivity period will not delay approval of any ANDA referencing Cozaar or Hyzaar if the exclusivity has been forfeited by the first applicant. See section 505(j)(5)(D)(i). The delisting of the '075 patent by Merck and the March 4, 2009 patent expiration date implicate two distinct 180-day exclusivity forfeiture provisions in the Act, sections 505(j)(5)(D)(i)(I) and (VI), respectively.

<sup>1</sup> Apotex notified FDA on March 9, 2010, that records of the U.S. Patent and Trademark Office (PTO) showed that the '075 patent had expired no later than March 30, 2009, due to non-payment of fees. Pursuant to the procedure described in 21 C.F.R. § 314.53(f), FDA sought information from Merck regarding the correct expiration date for the '075 patent. By letters of March 12, 2010, Merck stated that the correct expiration date for the '075 patent is March 4, 2009.

<sup>2</sup> The 180-day exclusivity for ANDAs referencing Cozaar and Hyzaar is governed by section 505(j)(5)(B)(iv) and related provisions, as modified by the Access to Affordable Pharmaceuticals provisions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003) (the MMA).

## **Delisting of the '075 Patent**

The U.S. Court of Appeals for the D.C. Circuit recently considered the effect of the delisting of the '075 patent on a first applicant's claim to 180-day exclusivity arising from a paragraph IV certification to that patent. Teva slip op. The court reviewed the delisting provision, section 505(j)(5)(D)(i)(I)(bb)(CC). The Agency had applied this provision in previous adjudications such that delisting of the patent for any reason by the NDA holder could result in forfeiture. Teva had asserted that FDA's interpretation of the delisting provision, although applied by FDA only in adjudications involving other drugs and different parties, was both subject to immediate review by the court and not supported by the statute.<sup>3</sup> The court, in a 2-1 decision, agreed with Teva on both grounds, and ruled that Merck's delisting of the '075 patent could not be the basis for forfeiture of exclusivity by the first applicant for generic Cozaar and Hyzaar. Slop. op at 29.

The D.C. Circuit, in response to a request from Teva, issued the mandate on an expedited basis on March 12, 2010, and remanded the case to the district court.<sup>4</sup> On March 26, 2010, the district court amended an order it had issued on March 16, 2010, to clarify that Teva has not forfeited its 180-day exclusivity under the Failure to Market provision, section 505(j)(5)(D)(i)(I). The district court stated that forfeiture due to patent expiration under section 505(j)(5)(D)(i)(VI) was not raised in Teva's Complaint and was not addressed by the D.C. Circuit in either its March 2, 2010 Opinion or in the March 12, 2010 issuance of the mandate. The district court ordered FDA to file a notice of its decision on the '075 patent expiration issue by 5 p.m. on March 26, 2010.

## **Expiration of the '075 Patent**

When Teva first raised the question of 180-day exclusivity for ANDAs referencing Cozaar and Hyzaar before the district court in June 2009, FDA's records showed a March 4, 2014 expiration date for the '075 patent, and no outside party had brought any other expiration date for the patent to the Agency's attention. It was only after the March 2, 2010 Teva decision that FDA was notified by Apotex that the Patent and Trademark Office records showed that the '075 patent had expired for failure to pay fees. Now that Merck has confirmed to FDA that the '075 patent expired on March 4, 2009, FDA is addressing whether the patent expiration is a separate basis, apart from the delisting, for forfeiture of exclusivity.<sup>5</sup> To obtain comment from interested parties on the effect of the revised patent expiration date, FDA sent a letter to ANDA applicants on March 11, 2010, and opened a public docket for submission of comments (FDA-2010-N-0134).

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<sup>3</sup> On July 31, 2009, the U.S. District Court for the District of Columbia found that it had jurisdiction to review the matter, but granted judgment in favor of the government on the merits. Teva Pharms. USA, Inc. v. Sebelius, 638 F. Supp. 2d 42 (D.D.C. 2009).

<sup>4</sup> The Solicitor General is considering seeking rehearing of the Court of Appeals' decision. If rehearing is sought by the government and granted, the mandate would be recalled.

<sup>5</sup> In Teva, the government argued that the court should not address the dispute concerning 180-day exclusivity being pressed by plaintiff Teva until FDA had decided that issue. One basis for the government's position was the potential that factual and/or legal issues specific to the circumstances associated with the Teva claim would require an FDA analysis that would, at a minimum, be useful to the court in its decision-making. The court rejected that position. FDA believes that the new and complicated issues raised by the expiration of the patent at issue in this case provide a good example of why courts should await an agency decision in a particular matter rather than anticipate an agency's decision based on previous rulings in similar matters.

FDA has considered these submissions, as well as the relevant statutory provisions, regulations, and case law, in developing the views described in this response.<sup>6</sup>

Neither the district court nor the D.C. Circuit addressed the effect of the expiration of the '075 patent on the first applicant's eligibility for 180-day exclusivity, nor could they have done so because, as noted, when the courts ruled, neither they nor FDA was aware of the fact that the '075 patent had expired. Therefore, FDA is addressing the matter here. First, the Agency analyzes the issue as if it were writing on a clean slate, and interpreting and applying the statute without reference to the recent Teva decision. Second, the Agency describes the effect of the Court of Appeals' reasoning in the Teva delisting decision on the outcome in this particular patent expiration matter.

Merck, the NDA holder, has notified FDA that the sole patent giving rise to a claim of 180-day exclusivity for ANDAs referencing Cozaar and Hyzaar, the '075 patent, has expired. The patent information provided to FDA by the NDA holder controls for patent certification purposes. Teva Pharms., USA, Inc. v. Leavitt, 548 F.3d 103, 106 (D.C. Cir. 2008) ("FDA operates in a purely ministerial role, relying on NDA holders to provide the Agency with accurate patent information."). Therefore, in assessing the first applicant's claim to exclusivity, FDA will rely on Merck's statement that the '075 patent has expired.

The effect of a patent expiration on exclusivity is specifically addressed in the 180-day exclusivity provisions applicable to the ANDAs referencing Cozaar and Hyzaar. Section 505(j)(5)(B)(iv) of the Act, as amended by the MMA, states:

Subject to subparagraph (D), if the application contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

"Subparagraph (D)" describes how a first applicant will forfeit its 180-day exclusivity period upon the occurrence of different types of a "forfeiture event" with respect to that applicant. Section 505(j)(5)(D). Among the defined events resulting in forfeiture is "Expiration of All Patents," which occurs when "[a]ll of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired." Section 505(j)(5)(D)(i)(VI). If this forfeiture event applies to a first applicant, the applicant forfeits exclusivity immediately upon the expiration of all patents as to which it qualified as a first

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<sup>6</sup> Due to the limited amount of time remaining before April 6, 2010, when one or more ANDAs referencing Cozaar and Hyzaar are expected to be eligible for final approval, FDA initiated its request for comment on the effect of a March 4, 2009 expiration date for the '075 patent before it had received the confirmation from Merck of the correct expiration date. Further, because of the exceptional circumstances of this case, FDA is making a decision on 180-day exclusivity before April 6, 2010. Because of the possibility that relevant facts will change, it is FDA's usual practice to wait until at least one ANDA is otherwise eligible for final approval before the Agency makes decisions regarding 180-day exclusivity. Among other considerations underlying FDA's decision to address the patent expiration at this time is the Teva court's decision on 180-day exclusivity based on events involving the same patent at issue in the current matter.

applicant.<sup>7</sup> If there is only one patent that serves as a basis for 180-day exclusivity, when that patent expires, there will be no exclusivity for the drug product, and the Agency may approve any otherwise approvable ANDA.

Under FDA's longstanding interpretation, once a patent expires, eligibility for 180-day exclusivity based on that patent is extinguished. This is true under both the pre-MMA 180-day exclusivity provisions and the MMA exclusivity provisions applicable to the ANDAs referencing Cozaar and Hyzaar. The pre-MMA exclusivity provisions did not explicitly address whether 180-day exclusivity could survive the expiration of the patent. In addressing that statutory gap, FDA stated that once a patent expires, the correct certification to the patent is a "paragraph II" certification pursuant to section 505(j)(2)(A)(vii)(II) ("that such patent has expired"). Once the application no longer contains a paragraph IV certification to the patent, the applicant no longer has a basis to obtain exclusivity as to that patent. This was held to be a reasonable interpretation of the pre-MMA exclusivity provision. Dr. Reddy's Labs., Inc. v. Thompson, 302 F. Supp. 2d 340, 356-57 (D.N.J. 2003). Moreover, even when the D.C. Circuit found in Ranbaxy Labs. Ltd. v. Leavitt, 469 F.3d 120 (D.C. Cir. 2006), that the pre-MMA exclusivity provisions would not permit an NDA holder's delisting of a patent to defeat a first applicant's claim on exclusivity, the court noted that "as Ranbaxy and Teva acknowledged at oral argument, the text and the structure of the [pre-MMA] statute suggest a distinction between expiration and delisting such that the first generic applicant may no longer retain exclusivity when the patent has expired." Id. at 126 n.3 (citing, inter alia, Dr. Reddy's Labs.). The forfeiture provision at section 505(j)(5)(D)(i)(VI), enacted in the MMA, thus embodies the familiar principle that 180-day exclusivity does not survive patent expiration.<sup>8</sup>

The issue presented by the expiration of the '075 patent is not whether, as a general rule, exclusivity will be forfeited pursuant to section 505(j)(5)(D)(i)(VI) upon the expiration of a patent, but whether a patent expiration for failure to pay fees is an exception to this rule.<sup>9</sup> The

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<sup>7</sup> The forfeiture events described in sections 505(j)(5)(D)(i)(II)-(V) are similarly immediate in effect if they are found to apply to a first applicant. It is interesting to note the contrast between these "immediate" forfeiture events, which provide no opportunity for the first applicant to use its exclusivity period once the forfeiture event has occurred, and the "Failure to Market" forfeiture event described in 505(j)(5)(D)(i)(I), which provides that upon the occurrence of certain events, rather than face immediate forfeiture, the first applicant will have the opportunity to begin commercial marketing of the drug product and thus start the running of its 180-day exclusivity period. For each of the events set out in 505(j)(5)(D)(i)(I)(bb), the first applicant has 75 days from the date of the specified event to begin marketing and receive the benefits of exclusivity. These provisions describe events that could occur with respect to "the first applicant *or any other applicant*" (emphasis added), as well as the patent delisting provision interpreted by the court in Teva. Presumably, Congress structured this exclusivity forfeiture provision so that, even if it is an applicant other than a first applicant that triggers a forfeiture by, for example, obtaining a final decision of non-infringement, the first applicant will nevertheless have a limited opportunity to benefit from being the first to challenge the patent. It is reasonable for FDA to conclude that, once at least one applicant has obtained a final court decision or settlement stating that the patent at issue is invalid or not infringed - or the patent has been delisted by the NDA holder because it does not meet the patent listing requirements - Congress sought to balance the benefits derived from the exclusivity incentive against the delay in the availability of generic drugs resulting from that exclusivity, and thus established a limit on the length of time during which the exclusivity would be available. In the case of patent expiration, Congress concluded that not even a limited 180-day exclusivity barrier to approval was warranted once the patent expired.

<sup>8</sup> The MMA did not revise the descriptions of patent certifications set forth at section 505(j)(2)(A)(vii).

<sup>9</sup> Teva, for example, appears to acknowledge that forfeiture will occur upon "natural patent expiry." March 18, 2010 Comment from Teva at 3.

Agency's view is that, if it were writing on a clean slate, it would interpret the statute so that patent expiration for any reason is a patent expiration forfeiture event. FDA believes that interpretation is most consistent with the plain meaning of the words of the statute and with a workable and appropriate approach to administration of the statute.

The text of the patent expiration forfeiture event provision does not provide a basis to distinguish between "natural patent expiry" and expiration for some other reason.<sup>10</sup> Section 505(j)(5)(D)(i)(VI) refers broadly to forfeiture when "all of the patents ... have expired." There is no language qualifying the type of expiration the Agency is to consider relevant for forfeiture.<sup>11</sup> Thus, there is no apparent statutory basis for the Agency to conclude that only some patent expirations result in forfeiture.

Some of the comments noted a number of reasons why FDA should create an exception to patent expiration forfeiture when the patent expires because the patent owner has failed to pay applicable fees. Among these are concerns about the lack of certainty regarding the expiration when the patent expires due to non-payment of fees. The March 18, 2010 comments from Teva and from Olsson, Frank & Weeda (OFW) identify situations in which a patent that has expired can be "revived" through payment by the patent owner of fees. Teva comment at 2-3; OFW comment at 3-4, 9-10.

Although it may well be the case that a patent that has expired for failure to pay fees could, in certain circumstances, be revived, this possibility alone is an inadequate basis to maintain that a later expiration date must control. As an initial matter, FDA will not change the applicable patent expiration date unless the NDA holder tells the Agency to do so. If the NDA holder (who is also likely to be the patent owner or licensee) notifies FDA that the patent has expired due to failure to pay fees, it can be presumed to have resolved at least to a reasonable certainty the finality of the patent expiration. Further, the concerns about uncertainty of expiration would presumably extend to all situations in which a patent has expired due to failure to pay fees, including those in which, although 180-day exclusivity is not an issue, reliance on a later expiration date could delay generic drug approvals. For example, if an NDA holder notified FDA that a patent on a drug as to which no ANDA had yet been submitted had expired due to failure to pay fees, but FDA refused to accept the NDA holder's representation because of uncertainty that the patent would remain "expired," future ANDA applicants would be required to submit patent certifications for a patent that may have its natural patent expiration years in the future. If the NDA holder is sufficiently certain its patent has expired that it notifies FDA of that fact, FDA believes that generic drug applicants are entitled to rely on that patent expiration date in seeking approval for their drug products.

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<sup>10</sup> Teva's comment does not define "natural patent expiry." For example, that term presumably could encompass both the expiration of the original 17 or 20 year term of a patent and the expiration of the term of certain patent claims that have been extended under 35 U.S.C. § 156. FDA's requirements do not limit the type of patent expiration information that may be submitted to FDA. 21 C.F.R. § 314.53.

<sup>11</sup> Based on the lengthy list of patents that expired on March 4, 2009, that was submitted as Attachment B to the March 9, 2010 Apotex letter raising the '075 patent expiration issue, expiration for failure to pay fees is not uncommon. Nonetheless, FDA is not aware of any other case in which it has been notified by an NDA holder that a patent that had been submitted to FDA and listed in the Orange Book has expired due to non-payment of fees.

Finally, in assessing what expiration date should control for purposes of 180-day exclusivity, it is appropriate for FDA to continue to rely on the NDA holder's representations to FDA. Teva v. Leavitt, 548 F.3d at 106. In this case, for example, although Apotex brought the question of the correct expiration date for the '075 patent to FDA's attention, the Agency did not consider the patent expiration date to be March 4, 2009 (and publish that date in the Orange Book) until Merck notified FDA that March 4, 2009 was the correct date. Had Merck maintained that the patent expiration date remained March 4, 2014, FDA would have retained the March 4, 2014 date in its records and relied on that date for patent certification, exclusivity, and application approval purposes. As stated in FDA's regulations,

Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list [the Orange Book]. If the new drug application holder does not change the patent information submitted to FDA, ... an abbreviated new drug application under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent.

21 C.F.R. § 314.53(f). Even though information on patent expirations due to failure to pay fees is available from the PTO, it would not be an appropriate use of FDA resources for FDA to forgo its ministerial role in these matters and make its own assessments of patent expiration. In light of the commenters' concerns about the uncertain nature of these patent expirations, it would seem particularly important that the Agency continue to defer to the NDA holder's judgment regarding the expiration of its patent.

The expiration of a patent is a specific basis for forfeiture of exclusivity under the MMA, and it also necessitates a change in the ANDA applicants' patent certifications. The MMA patent certification provisions, like the pre-MMA provisions, state that the appropriate certification to an expired patent is a "paragraph II" (that such patent has expired). Section 505(j)(2)(A)(vii)(II). Upon expiration of a patent, a paragraph IV certification to the patent automatically becomes invalid. Ranbaxy Labs Ltd. v. FDA 96 Fed. Appx. 1 (D.C. Cir. 2004) (unpublished). Thus, a paragraph IV certification to the expired '075 patent is invalid, and the appropriate certification to the patent is "paragraph II." The 180-day exclusivity provision at section 505(j)(5)(B)(iv) directs that FDA determine whether an ANDA "contains a [paragraph IV] certification ... and is for a drug for which a first applicant has submitted an application containing such a certification." When a first applicant's ANDA does not contain a valid paragraph IV certification or a non-first applicant's ANDA no longer contains a paragraph IV certification, the 180-day exclusivity provision at section 505(j)(5)(B)(iv), by its own terms, does not apply.<sup>12</sup> Thus, permitting the first applicant to retain exclusivity as to an expired patent requires FDA to take an action that is not sanctioned by the words of the statute.

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<sup>12</sup> The MMA also defines a "first applicant" eligible for exclusivity as an applicant that, among other things "submits a substantially complete application that contains *and lawfully maintains* [a paragraph IV certification]." Section 505(j)(5)(B)(iv)(II)(bb) (emphasis added). An applicant cannot lawfully maintain a paragraph IV certification to a patent that has expired.

For the reasons described above, FDA concludes that if it were assessing this issue without reference to the Teva decision, it would find that, under the plain language of the statute, because the '075 patent will have expired by the time any ANDA referencing Cozaar or Hyzaar is ready for approval, any first applicant previously eligible for 180-day exclusivity as to the '075 patent forfeits that exclusivity. Moreover, even if the statutory language is considered ambiguous, FDA concludes loss of exclusivity under these circumstances is most consistent with the statute's text and goals, and provides the most reasonable way of administering the statute.

### **Effect of Teva Decision on Patent Expiration Forfeiture**

FDA does not believe it can assess the effect of expiration of the '075 patent due to nonpayment of fees on exclusivity for generic Cozaar and Hyzaar without consideration of the D.C. Circuit's Teva decision and the reasoning in that decision regarding the delisting of the '075 patent.

In Teva, the D.C. Circuit concluded that Teva is entitled to exclusivity, in spite of the fact that the NDA holder has requested delisting of the patent, based on the "structure" of the statute, regardless of the words of the statute.<sup>13</sup> Moreover, the court concluded that this analysis was appropriately considered under "Chevron step one," i.e., that there was no statutory ambiguity that FDA is free to resolve based on its understanding of the statute and the industry it regulates. Slip op. at 29. After rejecting Teva's "linguistic" argument, slip op. at 24, the court adopted a "structural argument" based on the pre-MMA Ranbaxy case. Slip op. at 24. It found that the structure of the MMA exclusivity provisions, as with the pre-MMA exclusivity provision considered in Ranbaxy, does not permit an NDA holder to "unilaterally" deprive the generic applicant of its exclusivity on the basis of delisting.<sup>14</sup> Slip op. at 5, 29. This reasoning thus appears to preclude a forfeiture of exclusivity on the basis of a patent expiration where the expiration is in the control of the NDA holder. Because the '075 patent expired due to Merck's

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<sup>13</sup> The D.C. Circuit specifically stated:

We see nothing in the 2003 amendments to the Food, Drug, and Cosmetic Act that changes the structure of the statute such that brand companies should be newly able to delist challenged patents, thereby triggering a forfeiture event that deprives generic companies of the period of marketing exclusivity they otherwise deserve. For that reason, the interpretation of the statute that the FDA has adopted in two recent adjudications, and that it regards itself as bound by law to apply to Teva's ANDAs for losartan products, fails at Chevron step one.

Slip op. at 29.

<sup>14</sup> The Teva court's decision suggests that it believed the statute would permit innovator companies to delist patents at will to deprive the first applicant of exclusivity, i.e., that "Brand manufacturers are . . . free to delist challenged patents whenever they please . . ." Slip op. at 24, 25. Patent listing is not optional. In fact, NDA holders are required by statute to provide patent information to FDA if, but only if, the patent claims the drug product or an approved use of the product, and if "a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." Section 505(b)(1). Thus, the patent holder may not simply withdraw or change patent information previously submitted to FDA because of some desire to interfere with the 180-day exclusivity of a potential generic competitor. It is, of course, true that FDA does not have the patent expertise to enforce the statutory requirement that appropriate patents be listed or delisted. Because the continued listing of an inappropriate patent, with the resulting blocking of competition, can place the NDA holder in jeopardy of antitrust damages, considerations of antitrust liability may well be factors in innovator decisions to withdraw patent information previously submitted. In fact, settlement of disputes between innovator companies and the Federal Trade Commission can result in patent delistings. See, e.g., Report, In the Matter of Bristol-Myers Squibb Co., Docket No. C-4076 (Federal Trade Comm'n, June 20, 2003) (describing delisting of patents for Serzone, Buspar, and Taxol). The Teva decision could affect the availability and effectiveness of delisting as a remedy.

failure to pay applicable fees, that expiration, consistent with the Court of Appeals' reasoning in Teva, is not a grounds for forfeiture of the first applicant's exclusivity. Although FDA believes this result is inconsistent with the plain language of the statute, as discussed above, it believes it is appropriate to apply the Court of Appeals' reasoning to the present facts. In the event the D.C. Circuit reconsiders and revises the decision in Teva, FDA reserves the right to revisit these conclusions regarding 180-day exclusivity for ANDAs referencing Cozaar and Hyzaar.

FDA thus finds that, consistent with the reasoning of the Court of Appeals, despite having been delisted by the patent owner and having expired, the '075 patent nevertheless must be considered to remain a basis for 180-day exclusivity. FDA will not approve any other ANDA referencing Cozaar or Hyzaar until the first applicant has received approval of its ANDA, begun commercial marketing, and the 180-day exclusivity period has expired.<sup>15</sup> The Agency makes this finding even though it is not the result that FDA, as the agency that administers the statute, believes is appropriate given the relevant statutory language or the policies underlying the statute.

### **Conclusion**

For the reasons described above, the Agency has concluded that, in light of the D.C. Circuit's decision in Teva, the March 4, 2009 expiration of the '075 patent for failure to pay applicable fees does not result in forfeiture of the first applicant's 180-day exclusivity for ANDAs referencing Cozaar and Hyzaar. If you have any questions regarding this decision, please contact Dave Read, Regulatory Counsel, Office of Generic Drugs at (240) 276-9310.

Sincerely,

{See appended electronic signature page}

Gary Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

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<sup>15</sup> We note that even though the Teva litigation has proceeded on the assumption that a first applicant will receive approval and begin marketing promptly after all applicable patent and exclusivity barriers expire, the rule derived from this case would presumably apply even if the first applicant did not promptly obtain approval and begin to market, e.g., because of changes in the application that required additional review, unsatisfactory inspections, or unavailability of materials. In such cases, FDA could be barred from approving otherwise approvable subsequent ANDAs until either the first applicant eventually triggered its exclusivity with commercial marketing and the 180-day period expired, or the delisted patent expired "naturally," with the result that competition from lower priced generic drugs would be delayed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA- (b) (4)	ORIG-1	(b) (4)	LOSARTAN POTASSIUM
ANDA-200180	ORIG-1	COBALT LABORATORIES INC	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-91652	ORIG-1	MYLAN PHARMACEUTICALS INC	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-91629	ORIG-1	AUROBINDO PHARMA LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-91617	ORIG-1	ALEMBIC LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-91590	ORIG-1	MYLAN PHARMACEUTICALS INC	LOSARTAN POTASSIUM
ANDA-91541	ORIG-1	MICRO LABS LIMITED	LOSARTAN POTASSIUM
ANDA-91497	ORIG-1	HUAHAI US INC	LOSARTAN POTASSIUM
ANDA-91129	ORIG-1	COBALT LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-90790	ORIG-1	APOTEX CORP	LOSARTAN POTASSIUM
ANDA-90544	ORIG-1	UPSHER SMITH LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-90528	ORIG-1	TORRENT PHARMACEUTICALS LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-90467	ORIG-1	TORRENT PHARMACEUTICALS LTD	LOSARTAN POTASSIUM
ANDA-90428	ORIG-1	ALEMBIC LTD	LOSARTAN POTASSIUM
ANDA-90382	ORIG-1	ACTAVIS PHARMA MANUFACTURING PRIVATE LTD	LOSARTAN POTASSIUM
ANDA- (b) (4)	ORIG-1	(b) (4)	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-90150	ORIG-1	APOTEX CORP	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-90083	ORIG-1	AUROBINDO PHARMA LTD	LOSARTAN POTASSIUM
ANDA-78385	ORIG-1	ZYDUS PHARMACEUTICALS USA INC	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-78245	ORIG-1	LUPIN LTD	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE

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ANDA-77732	ORIG-1	ROXANE LABORATORIES INC	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-77459	ORIG-1	ROXANE LABORATORIES INC	LOSARTAN POTASSIUM
ANDA-77424	ORIG-1	LEK PHARMACEUTICA LS D D	LOSARTAN POTASSIUM
ANDA-77157	ORIG-1	TEVA PHARMACEUTICA LS USA	LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE
ANDA-76958	ORIG-1	TEVA PHARMACEUTICA LS USA INC	LOSARTAN POTASSIUM

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/s/

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GARY J BUEHLER  
03/26/2010

OGD APPROVAL ROUTING SUMMARY

ANDA # 090790 Applicant Apotex Corp.

Drug Losartan Potassium Tablets, 25 mg, 50 mg, and 100 mg Strength(s)

APPROVAL  TENTATIVE APPROVAL  SUPPLEMENTAL APPROVAL (NEW STRENGTH)  OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. **Martin Shimer**

Chief, Reg. Support Branch

Date 26 February 2010 Date 4/6/10

Initials MHS

Initials rlw

Contains GDEA certification: Yes  No  Determ. of Involvement? Yes  No

(required if sub after 6/1/92)

Pediatric Exclusivity System

RLD = Cozaar NDA#20-386

Patent/Exclusivity Certification: Yes  No

Date Checked Granted

If Para. IV Certification- did applicant

Nothing Submitted

Notify patent holder/NDA holder Yes  No

Written request issued

Was applicant sued w/in 45 days: Yes  No

Study Submitted

Has case been settled: Yes  No

Date settled:

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes  No

Date of latest Labeling Review/Approval Summary \_\_\_\_\_

Any filing status changes requiring addition Labeling Review Yes  No

Type of Letter: Full Approval.

Comments: ANDA submitted on 8/29/2008, BOS=Cozaar NDA 20-386, PIII to '069 and '197, PIV to '075 and section viii to '079. ANDA ack for filing with PIV on 8/29/2008 (LO dated 10/23/2008). Patent Amendment submitted on 10/29/2008-notice was sent via Fed Ex to Merck and Co. in West Point PA, in Whitehouse Station NJ, and in Rahway NJ, all notices were delivered on 10/29/2008. Patent Amendment submitted on 11/3/2008-Merck and company submitted a letter dated 11/3/2008 to Apotex confirming that suit would not be brought on the '075 patent.

The '069 patent is now expired and the '197 patent will expire on 4/6/2010. The innovator firm has requested that the Agency delist the '075 patent as of January 2009. Delisting of a patent is one of several events that can lead to forfeiture of 180 day exclusivity. As things currently stand, the Agency considers the first Filer TEVA to have forfeited eligibility for 180 day exclusivity. A DC has ruled in the Agency's favor on this policy but TEVA has appealed the DC ruling.

Final recommendation: The Agency will prepare as if TEVA has forfeited exclusivity meaning that this ANDA will be eligible for Full Approval on 4/6/2010. However, prior to issuing any Full Approvals on 4/6/2010, OGD must check to see if TEVA prevailed in their appeal.

Update 4/6/2010-TEVA did prevail in their appeal and they are currently in position to be Fully Approved with 180 day exclusivity. This award of 180 day exclusivity would effectively preclude the Agency from Full Approving any other ANDAs for Losartan Potassium Tablets. Apotex has submitted a request for a TRO which if granted would likely preclude the Agency from approving any ANDAs for Losartan Potassium Tablets. If the court were to grant the TRO it would have no real impact on this ANDA as it is

currently eligible for TA only due to the appellate court ruling.  
As of 4:03 p.m. the OGD has not been informed of any change in litigation status or that a TRO was granted in response to Apotex's request. ANDA is eligible for TA only as indicated above.

2. **Project Manager**, Dat Doan Team1      Review Support Branch      Date 2/4/10      Date \_\_\_\_\_  
Initials sd      Initials \_\_\_\_\_

Original Rec'd date 12/1/08      EER Status    Pending  Acceptable  OAI   
Date Acceptable for Filing 12/1/08      Date of EER Status \_\_\_\_\_  
Patent Certification (type) IV, mou      Date of Office Bio Review \_\_\_\_\_  
Date Patent/Exclus. expires 4/6/10      Date of Labeling Approv. Sum \_\_\_\_\_  
Citizens' Petition/Legal Case Yes  No       Labeling Acceptable Email Rec'd Yes  No   
(If YES, attach email from PM to CP coord)      Labeling Acceptable Email filed Yes  No   
First Generic                              Yes  No       Date of Sterility Assur. App. \_\_\_\_\_  
Priority Approval                          Yes  No       Methods Val. Samples Pending    Yes  No   
(If yes, prepare Draft Press Release, Email      MV Commitment Rcd. from Firm    Yes  No   
it to Cecelia Parise)                      Modified-release dosage form: Yes  No   
Acceptable Bio review tabbed Yes  No       Interim Dissol. Specs in AP Ltr:    Yes   
Bio Review Filed Electronically: Yes  No   
Suitability Petition/Pediatric Waiver \_\_\_\_\_  
Pediatric Waiver Request Accepted  Rejected  Pending   
Previously reviewed and tentatively approved            Date \_\_\_\_\_  
Previously reviewed and CGMP def. /NA Minor issued            Date \_\_\_\_\_  
Comments: bio ac 2/16/10; labeling ac 2/25/10

EES acceptable 8/10/10

3. **Labeling Endorsement**  
Reviewer: \_\_\_\_\_      Labeling Team Leader: \_\_\_\_\_  
Date \_\_\_\_\_      Date 4/6/10  
Name/Initials \_\_\_\_\_      Name/Initials rlw/for      Comments: \_\_\_\_\_

From: Lee, Koung U  
Sent: Thursday, April 01, 2010 3:12 PM  
To: Barlow, James T; Doan, Dat  
Subject: RE: 90790/Apotex/Losartan

I concur.

Koung

From: Barlow, James T  
Sent: Thursday, April 01, 2010 2:21 PM  
To: Doan, Dat; Lee, Koung U

Subject: RE: 90790/Apotex/Losartan

I checked Drugs@FDA, OB and USP.

The labeling Approval Summary signed by Koung Lee on 2/25/10 remains acceptable.

The stability study for the suspension was deemed acceptable per chemistry review dated 3/16/10

Stability Data: Satisfactory

The available stability data and the results are summarized in the Review section P.8.1 Stability Summary and Conclusion.

Apotex provided stability data to demonstrate that its Losartan Potassium Tablets, USP 50 mg is stable under the conditions of preparation and storage of a suspension as described in the product labeling. A suspension consisting of 10 tablets in water/Ora-Plus/Ora-Sweet was prepared as

90-790 Rev #2 Page 34 of 37

CHEMISTRY REVIEW

described in the DOSAGE AND ADMINISTRATION section of the package insert and stored in a refrigerator for 4 weeks. Samples evaluated at one week intervals for appearance, potency, and impurity profile. There were no significant changes in these parameters over the 4-week period.

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From: Doan, Dat  
Sent: Thursday, April 01, 2010 1:51 PM  
To: Barlow, James T; Lee, Koung U  
Subject: 90790/Apotex/Losartan  
Importance: High

Hi Jim, Koung:

Can you please endorse this for me? Per Bob, since we still don't know the outcome of the legal situation, there is no need to look at the AP letter. Bob and Co. will make sure it is correct.

<< File: 90790.labeling.ap.summary.pdf >>

Thanks,

Dat

- |    |  |                     |
|----|--|---------------------|
| 4. | <b>David Read</b> (PP IVs Only) Pre-MMA Language included <input type="checkbox"/> | Date <u>5Apr10</u>  |
|    | OGD Regulatory Counsel, Post-MMA Language Included <input type="checkbox"/>        | Initials <u>DTR</u> |
|    | Comments: OK.  |                     |
| 5. | <b>Div. Dir./Deputy Dir.</b>   | Date <u>3/24/10</u> |
|    | Chemistry Div. I II OR III   | Initials <u>PS</u>  |
|    | Comments: CMC ok for approval.   |                     |

6. **Frank Holcombe** First Generics Only Date 4/6/10  
Assoc. Dir. For Chemistry Initials rlw/for Comments: (First generic drug  
review)  
N/A. Multiple ANDAs have been tentatively approved for this drug product.

7. Vacant Date \_\_\_\_\_ Deputy Dir., DLPS  
Initials \_\_\_\_\_  
RLD = Cozaar Tablets 25 mg, 50 mg and 100 mg  
Merck Research Laboratories NDA 20-286

8. **Peter Rickman** Date 8/11/10  
Director, DLPS Initials rlw/for Comments: Bioequivalence  
Para.IV Patent Cert: Yes  No ; Pending Legal Action: Yes  No ; Petition: Yes  No   
studies (fasting and non-fasting) on the 100 mg tablet  
strength found acceptable. In-vitro dissolution testing for all three tablet  
strengths also found acceptable. Waivers granted to the 25 mg and 50 mg tablet  
strengths under 21 CFR 320.22(d)(2). Bio study sites have acceptable DSI  
inspection histories. Office-level bio endorsed 1/28/10 and 2/16/10.  
Final-printed labeling (FPL) found acceptable for approval 4/1/10.  
CMC found acceptable for approval (Chemistry Review #3).

OR

8. **Robert L. West** Date 8/11/10  
Deputy Director, OGD Initials RLWest  
Para.IV Patent Cert: Yes  No ; Pending Legal Action: Yes  No ; Petition: Yes  No   
Press Release Acceptable   
Comments: Acceptable EEs dated 8/10/10. No "OAI" Alerts noted.

Apotex provided a paragraph IV certification to the '075 patent, but was not  
sued within the 45-day period. Apotex also provided a method-of-use statement  
to the '079 patent and has "carved-out" information pertaining to the use of the  
drug product for the treatment of chronic renal failure (U-496) from its labeling.  
This is acceptable. There are no additional patents or exclusivity listed in the  
current "Orange Book" for this drug product.

Final approval of this ANDa is currently blocked by TEVA's 180-day generic drug  
exclusivity due to expire on October 3, 2010.

This ANDA is recommended for tentative approval.

9. **Gary Buehler** Date 8/11/10  
Director, OGD Initials rlw/for  
Comments: Keith Webber, Ph.D. Deputy Director, OPS  
First Generic Approval  PD or Clinical for BE  Special Scientific or Reg.Issue   
Press Release Acceptable

10. Project Manager, Team Dat Doan Date 8/11/10  
Review Support Branch Initials dd

\_\_\_\_\_ Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

8/11/10 Date notified of approval by phone

8/11/10 Date approval letter faxed

FDA Notification:

8/11/10 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

8/11/10 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

ORANGE BOOK PRINT OFF :

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» [www.hhs.gov](http://www.hhs.gov)

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 **U.S. Food and Drug Administration**



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# Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020386 Product 003 in the OB\_Rx list.

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Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
<a href="#">N020386</a>	003	5138069	Aug 11, 2009				
<a href="#">N020386</a>	003	5138069*PE D	Feb 11, 2010				
<a href="#">N020386</a>	003	5153197	Oct 6, 2009			<a href="#">U - 3</a>	
<a href="#">N020386</a>	003	5153197*PE D	Apr 6, 2010			<a href="#">U - 3</a>	
<a href="#">N020386</a>	003	5210079	May 11, 2010			<a href="#">U - 496</a>	
<a href="#">N020386</a>	003	5210079*PE D	Nov 11, 2010			<a href="#">U - 496</a>	
<a href="#">N020386</a>	003	5608075*PE D	Sep 4, 2009				



There is no unexpired exclusivity for this product.

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**Additional information:**

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. \*\*\*\* The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.

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[View a list of all patent use codes](#)

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FDA/Center for Drug Evaluation and Research

Office of Generic Drugs

Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through June, 2010

Patent and Generic Drug Product Data Last Updated: August 10, 2010

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90790	----- ORIG-1	----- APOTEX CORP	----- LOSARTAN POTASSIUM

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/s/

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DAT T DOAN  
08/11/2010

# APOTEX

ADVANCING GENERICS

August 11, 2010

Office of Generic Drugs (HFD-600)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North VII  
7620 Standish Place  
Rockville, MD 20855

Dear Sir or Madam:

**Re: MINOR AMENDMENT – FINAL APPROVAL REQUESTED**

**Losartan Potassium Tablets, USP, 25 mg, 50 mg, and 100 mg; ANDA No. 090790**

Apotex is hereby submitting a Minor Amendment to ANDA No. 090790 to request final approval for its Losartan Potassium Tablets, USP, 25 mg, 50 mg, and 100 mg, which was tentatively approved on August 11, 2010. A copy of the tentative approval letter is appended to this cover letter.

The reference listed drug, Cozaar® Tablets, 25 mg, 50 mg, and 100 mg, is subject to periods of patent protection as follows: U.S. Patent No. 5,210,079 (the '079 patent) expires on November 11, 2010; U.S. Patent No. 5,608,075 (the '075 patent) expired on September 4, 2009. The '079 patent is a method of use patent and Apotex's ANDA contains a *section viii* statement regarding the indication protected by this patent. A paragraph IV certification to the '075 patent was included in the ANDA; on November 11, 2008 we notified the agency that no action for infringement was brought against Apotex within the statutory 45-day period. As listed in the "Orange Book", another applicant's losartan potassium tablets, 25 mg, 50 mg, and 100 mg, under ANDA 076958, is subject to a Patent Challenge (PC) exclusivity period which expires on October 3, 2010. Apotex therefore requests final approval of its ANDA for losartan potassium tablets, 25 mg, 50 mg, and 100 mg, on October 3, 2010. Apotex acknowledges that there have been no changes in the conditions under which its ANDA was tentatively approved.

This amendment is filed through the Electronic Submission Gateway (ESG). A Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted; therefore only an electronic copy of the cover letter is provided. A signed electronic Form FDA 356h is provided in section 1.1.2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (866) 392-1774.

Sincerely,



Bernice Tao  
Director, Regulatory Affairs US

**From:** Doan, Dat  
**Sent:** Monday, September 20, 2010 4:34 PM  
**To:** Doan, Dat  
**Subject:** Concerning your ANDA for Losartan Tablets USP

**Importance:** High  
Hi,

The RLD of Losartan Potassium Tablets USP has recently updated the drug product labeling. The 50 mg tablet of Merck's Cozaar (Losartan Potassium) Tablets is now scored, whereas the 25 mg and 100 mg tablets remain unscored. Please provide a commitment to update your ANDA **with respect to MAPP 5223.2** prior to marketing. Please also commit to demonstrate acceptable content uniformity of scored tablet segments (divided by hand) for the tablet batch manufactured with the score.

Thanks,

Dat Doan, R.Ph.  
LCDR, USPHS  
Project Manager, OGD, FDA  
7500 Standish Place  
MPN 2, HFD-617, Rm N147  
Rockville, MD 20855  
(p) 240-276-9336  
(f) 240-276-8440  
Email: dat.doan@fda.hhs.gov

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/s/

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DAT T DOAN  
09/20/2010



September 21, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North VII  
7620 Standish Place,  
Rockville, Maryland 20855

**Re: General Correspondence**  
**Losartan Potassium Tablets, USP 25 mg, 50 mg and 100 mg; ANDA No. 090790**

Dear Sir/Madam,

Reference is made to the September 20, 2010 email from Dat Doan, regarding the recent labeling update for the reference listed drug, Cozaar® (losartan potassium tablets), to provide for a scored 50 mg tablet.

Apotex commits to update ANDA No. 090790 in accordance with MAPP 5223.2 (Scoring Configuration of Generic Drug Products) prior to marketing a scored version of Losartan Potassium Tablets, 50 mg. Also, Apotex will demonstrate acceptable content uniformity of the scored tablet segments (divided by hand) for the tablet batch manufactured with the score.

This submission is filed through the Electronic Submission Gateway (ESG). A Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted; therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form FDA 356h has been provided in section 1.1.2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889.

Sincerely,

to  
Bernice Tao  
Director, Regulatory Affairs New Products

# **APOTEX**

**ADVANCING GENERICS**

September 24, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North VII  
7620 Standish Place,  
Rockville, Maryland 20855

To Whom It May Concern,

**Re: LABELING AMENDMENT**  
**Losartan Potassium Tablets, USP 25 mg, 50 mg and 100 mg: ANDA No. 090790**

Apotex Corp. is hereby submitting an amendment to ANDA No. 090970 for Losartan Potassium Tablets, USP 25 mg, 50 mg and 100 mg. The amendment is being filed based on the recent labeling update approved on September 21, 2010, for the reference listed drug, Cozaar®. This amendment provides for changes to the Prescribing Information - Drug Interactions section. Final printed labeling is provided in section 1.14.2.2; a side-by-side comparison of Apotex's labeling and the RLD labeling is provided in section 1.14.3.1.; and the labeling text is provided in Word format in section 1.14.2.3. Apotex commits to submit the content of labeling in SPL format within 14 days of the date of final approval.

This amendment is filed through the Electronic Submission Gateway (ESG) and a letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted and therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form 356h has been provided in section 1.1.2.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at (954) 384-3986 by fax at (866)392-1774.

Sincerely,



*ht*  
\_\_\_\_\_  
Bernice Tao  
Director, U.S. Regulatory Affairs

**From:** Doan, Dat  
**Sent:** Monday, September 27, 2010 5:02 PM  
**To:** Doan, Dat  
**Subject:** Losartan Update!!! Please send response ASAP!

**Importance:** High  
Hi,

As the 50 mg tablet of Merck's Cozaar® (Losartan Potassium) Tablets is now scored, the Office of Generic Drugs recommends the following actions be taken:

1. A commitment should be provided to supplement your ANDA with respect to MAPP 5223.2, within 3 months of receipt of approval.
2. Please also provide a commitment to demonstrate acceptable uniformity of scored tablet segments (divided by hand) for the 50 mg tablet batch manufactured with the scored configuration. Testing and criteria may follow the recommendations as found in USP <905> for uniformity of dosage.
3. Any unscored 50 mg tablets manufactured in anticipation of ANDA approval may be distributed, however, no new unscored 50 mg tablets batches should be manufactured without a change in the scoring configuration to match the RLD and subsequent approval of the related supplement.
4. The above mentioned commitments must be submitted and received in order to receive full approval.

If you've already sent in a commitment based on the email sent out September 21, 2010, please send in another commitment to these points ASAP to ensure that all criteria are met.

- Email me an electronic copy (pdf) of your response submission. [Dat.Doan@fda.hhs.gov](mailto:Dat.Doan@fda.hhs.gov)
- Make sure your submission includes some type of electronic format (i.e. Gateway or pdf copy on a disc, etc.)

Thank you,

Dat Doan, R.Ph.  
LCDR, USPHS  
Project Manager, OGD, FDA  
7500 Standish Place  
MPN 2, HFD-617, Rm N147  
Rockville, MD 20855  
(p) 240-276-9336  
(f) 240-276-8440  
Email: [dat.doan@fda.hhs.gov](mailto:dat.doan@fda.hhs.gov)

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/s/

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DAT T DOAN  
09/28/2010

# APOTEX

ADVANCING GENERICS

September 27, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North VII  
7620 Standish Place,  
Rockville, Maryland 20855

To Whom It May Concern,

**Re: GENERAL CORRESPONDENCE**  
**Losartan Potassium Tablets, USP 25 mg, 50 mg and 100 mg: ANDA No. 090790**

Please refer to the Labeling Amendment submitted on September 24, 2010, for Losartan Potassium Tablets, USP 25 mg, 50 mg and 100 mg, ANDA No. 090790, which provided for updated labeling (prescribing information) in accordance with the recent RLD labeling update. Reference is also made to the September 27, 2010 email from James Barlow.

Apotex hereby withdraws the amendment without prejudice. Furthermore, Apotex commits to re-submit the labeling update in a post-approval CBE supplement.

This correspondence is filed through the Electronic Submission Gateway (ESG). A letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted and therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form 356h is provided in section 1.1.2.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at (954) 384-3986 by fax at (866)392-1774.

Sincerely,



  
\_\_\_\_\_  
Bernice Tao  
Director, U.S. Regulatory Affairs

# APOTEX

ADVANCING GENERICS

September 28, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North VII  
7620 Standish Place,  
Rockville, Maryland 20855

To Whom It May Concern,

**Re: GENERAL CORRESPONDENCE**  
**Losartan Potassium Tablets, USP 25 mg, 50 mg and 100 mg: ANDA No. 090790**

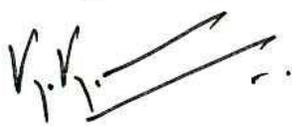
Reference is made to Apotex's September 21, 2010, commitment letter and the September 27, 2010, email from Dat Doan, regarding the change scoring of the 50 mg tablet of the reference listed drug, Merck's Cozaar®. In response, Apotex hereby commits to the following:

1. Apotex commits to update ANDA No. 090790 in accordance with MAPP 5223.2 (Scoring Configuration of Generic Drug Products), within 3 months of receipt of approval. The change in scoring configuration will be submitted as a "Supplement – Expedited Review Requested".
2. Apotex commits to demonstrate acceptable uniformity of the scored tablet segments (divided by hand) for the 50 mg tablet batch manufactured with the scored configuration. Testing and criteria will follow the recommendations as found in USP<905> for Uniformity of Dosage.
3. Apotex will distribute the unscored 50 mg tablets manufactured in anticipation of ANDA approval, however, no new unscored 50 mg tablet batches will be manufactured without a change in the scoring configuration to match the RLD and subsequent approval of the related supplement.

This amendment is filed through the Electronic Submission Gateway (ESG) and a letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted and therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form 356h has been provided in section 1.1.2.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at (954) 384-3986 by fax at (866)392-1774.

Sincerely,

  
\_\_\_\_\_  
Bernice Tao  
Director, U.S. Regulatory Affairs



ANDA 090790

Apotex Corp.  
U.S. Agent for: Apotex, Inc.  
Attention: Kiran Krishnan  
Associate Director, Regulatory Affairs  
2400 N. Commerce Parkway, Suite 400  
Weston, FL 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated August 27, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Losartan Potassium Tablets USP, 25 mg, 50 mg and 100 mg.

Reference is also made to the tentative approval letter issued by this office on August 11, 2010 and to your amendments dated February 1, August 12, September 21 and September 28, 2010.

The reference listed drug (RLD), Cozaar, was approved for new labeling on September 23, 2010. The 180-days generic exclusivity is scheduled to expire on October 3, 2010. FDCA Section 505(j)(10) (added by Section 10609 of the Patient Protection and Affordable Care Act) permits the FDA to approve an ANDA with labeling that differs from that of the RLD provided the change to the RLD labeling is approved within 60 days of the expiration of a patent, an exclusivity period, or 30-month stay, and the labeling changes do not include a change to the WARNINGS section, the Agency has determined that the continued presence of the labeling in effect before the revision will not adversely impact the safe use of the drug, and the applicant agrees to submit revised labeling of the drug not later than 60 days after being notified of the required changes.

Under Section 505(j)(10), we can approve your losartan tablet ANDA provided you commit to supplementing your application with updated labeling reflecting the change to the Cozaar labeling within 60 days of your receipt of notification, i.e., of today's date. Your commitment must be in writing, in a letter addressed to:

Office of Generic Drugs (HFD-600)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North VII  
7620 Standish Place  
Rockville, MD 20855

Please note that this commitment letter must be received before full approval of your drug product can be granted. Thank you in advance for your prompt attention regarding this matter.

Sincerely Yours,

{ See appended electronic signature page }

Wm Peter Rickman

Director

Division of Labeling and Program Support

Office of Generic Drugs

Center for Drug Evaluation and Research

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/s/

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JAMES T BARLOW  
10/01/2010

KOUNG U LEE  
10/01/2010  
For Wm Peter Rickman

October 1, 2010

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North VII  
7620 Standish Place,  
Rockville, Maryland 20855

**Re: General Correspondence**  
**Losartan Potassium Tablets, USP 25 mg, 50 mg and 100 mg; ANDA No. 090790**

Dear Sir/Madam,

Reference is made to the October 1<sup>st</sup>, 2010 communication from Dat Doan, regarding the recent labeling changes for the reference listed drug, Cozaar® (losartan potassium tablets) and to provide for a commitment to revise Apotex's labelling within 60 days from October 1<sup>st</sup>, 2010.

Apotex hereby commits to update the label for ANDA 90790 to reflect the changes made to the Cozaar labeling within 60 days from October 1<sup>st</sup>, 2010.

This submission is filed through the Electronic Submission Gateway (ESG). A Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted; therefore only an electronic copy of the cover letter is provided. A signed electronic copy of Form FDA 356h has been provided in section 1.1.2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889.

Sincerely,



H  
\_\_\_\_\_  
Bernice Tao  
Director, Regulatory Affairs New Products

**Memorandum to File**

**Determination if ANDAs may be approved with different labeling under section 505(j)(10) of the Federal Food, Drug, and Cosmetic Act (the Act)**

Have revision(s) to the reference listed drug (RLD) labeling been approved within 60 days of the expiration of a patent, an exclusivity period, or a 30-month stay that delayed ANDA approval: ✓ Yes  No

- 1. NDA #: 020386/S-052
- 2. NDA Name : Cozaar (losartan potassium tablets, USP)
- 3. Date RLD revised labeling was approved: 9/23/2010
- 4. Expiration date (and type) of patent, exclusivity period, or 30-month stay delaying ANDA approval:  
October 4, 2010 (180-day exclusivity)

Does the approved revision to the RLD labeling include a change to the Warnings section?  Yes  No

Has the sponsor of the application agreed to submit revised labeling of the drug to reflect the change in the labeling of the RLD not later than 60 days after receiving notification that the changes are required? ✓ Yes  No

Has the Agency determined that the continued presence of the labeling in effect before the revision will adversely impact the safe use of the drug?  Yes  No  
**If yes, please explain:**

**FINAL DECISION: Can ANDAs be approved with different labeling, as permitted under section 505(j)(10) of the Act?** ✓ Yes  No

**Background information**

FDCA Section 505 (j)(10) (added to the statute by Section 10609 of the Patient Protection and Affordable Care Act) permits the FDA to approve an ANDA with labeling that differs from that of the RLD provided the change to the RLD labeling is approved within 60 days of the expiration of a patent, an exclusivity period, or 30-month stay, and the labeling changes do not include a change to the WARNINGS section, the sponsor of the application agrees to submit revised labeling of the drug not later than 60 days after notification that such changes to labeling are required, and the Agency has not determined that the continued presence of the labeling in effect before the revision will adversely impact the safe use of the drug.

For Cozaar, FDA approved a change to the PRECAUTIONS section on September 23, 2010. The labeling change addresses risks related to renal toxicity in patients taking

Cozaar who might require combination therapy with a diuretic and NSAIDs. A summary of the changes is provided below.

S-052, Approved 9/23/2010
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists (including losartan) may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving losartan and NSAID therapy.  The antihypertensive effect of angiotensin II receptor antagonists, including losartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Merck submitted final printed labeling on September 24, 2010, for the changes approved on September 23, 2010. In its cover letter, Merck states “Final printed Labeling will be used on or before 01-May-2011 in all packages sold or distributed from the Company’s manufacturing facilities.”

Teva is currently the only ANDA approved for the 25 mg, 50 mg, and 100 mg strengths of losartan tablets (ANDA 76-958). Their 180-day generic exclusivity is scheduled to expire on October 4, 2010. (As of September 27, 2010, Teva has not updated its losartan labeling to contain the change.)

Implementation of the labeling change by the RLD may not occur for over 7 months. Upon approval of other losartan ANDAs on October 4, 2010, the labeling for these ANDAs will be the same as that of the RLD and Teva currently in the marketplace. Apotex committed to supplement its ANDA with revised labeling within 60 days of their commitment letter dated October 1, 2010.

*{see appended electronic signature}*

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Labeling Reviewer

Supervisory Comment/Concurrence:

*{see appended electronic signature}*

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Team Leader

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

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/s/

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JAMES T BARLOW  
10/04/2010

KOUNG U LEE  
10/04/2010  
For Wm Peter Rickman

# ROUTING SHEET

APPROVAL    TENTATIVE APPROVAL    SUPPLEMENTAL APPROVAL (NEW STRENGTH)    CGMP

Division: **IV**   Team: **1**   PM: **Dat Doan**

Electronic ANDA:  
Yes  No

ANDA #: **090790**

Firm Name: **Apotex**

ANDA Name: **Losartan Potassium Tablets USP, 25 mg, 50 mg and 100 mg**

RLD Name: **NDA Number: 020386/S-049 NDA Drug Name: Cozaar® Tablets NDA Firm: Merck & Co. Inc.**

## Electronic AP Routing Summary Located:

**V:\Chemistry Division 4\Team 41\Electronic AP Summary**

## AP/TA Letter Located:

**V:\Chemistry Division 4\Team 41\Final Version For DARRTS Folder**

## Project Manager Evaluation:

Date: **9/20/10** Initials: **dd**

- Previously reviewed and tentatively approved --- Date 8/11/10  
 Previously reviewed and CGMP Complete Response issued -- Date \_\_\_\_\_

Original Rec'd date <u>8/29/08</u>	Date of Application <u>8/27/08</u>	Date Acceptable for Filing <u>10/23/08</u>
Patent Certification (type) <u>IV</u>	Date Patent/Excl. expires <u>10/3/10</u>	Citizens' Petition/Legal Case? Yes <input type="checkbox"/> No <input type="checkbox"/> (If YES, attach email from PM to CP coord)
First Generic Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> DMF#: _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Comment: Prepared Draft Press Release sent to Cecelia Parise Yes <input type="checkbox"/> No <input type="checkbox"/> Date:	
<input type="checkbox"/> Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted <input type="checkbox"/> Rejected <input type="checkbox"/> Pending <input type="checkbox"/>	

EER Status:  Pending  Acceptable  OAI   *EES Date Acceptable: 8/10/10*    Warning Letter Issued; Date:  
Has there been an amendment providing for a Major change in formulation since filing? Yes  No  Comment:  
Date of Acceptable Quality (Chemistry) 9/29/10   Addendum Needed: Yes  No  Comment:  
Date of Acceptable Bio 2/16/10   Bio reviews in DARRTS: Yes  No  (Volume location: \_\_\_\_\_)  
Date of Acceptable Labeling 2/25/10   Attached labeling to Letter: Yes  No  Comment:  
Date of Acceptable Sterility Assurance (Micro) \_\_\_\_\_

Methods Val. Samples Pending: Yes  No ; Commitment Rcvd. from Firm: Yes  No

Post Marketing Agreement (PMA): Yes  No  (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes  No  (If yes, enter dissolution information in Letter)

## Routing:

Labeling Endorsement, Date emailed: \_\_\_\_\_   REMS Required: Yes  No    REMS Acceptable: Yes  No

Regulatory Support

Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: \_\_\_\_\_

Division

1<sup>st</sup> Generic Review

Bob West / Peter Rickman

Keith Webber

Filed AP Routing Summary in DARRTS

Notified Firm and Faxed Copy of Approval Letter

Sent Email to "CDER-OGDAPPROVALS" distribution list

**OGD APPROVAL ROUTING SUMMARY**

1. **Regulatory Support Branch Evaluation**

**Martin Shimer**

Date: 9/28/2010

Chief, Reg. Support Branch

Initials: MHS

Contains GDEA certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> (required if sub after 6/1/92)	Determ. of Involvement? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
Patent/Exclusivity Certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Was applicant sued w/in 45 days: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Has case been settled: Yes <input type="checkbox"/> No <input type="checkbox"/> Date settled: Is applicant eligible for 180 day	Pediatric Exclusivity System RLD = <u>Cozaar</u> NDA# <u>20-386</u> Date Checked _____ Nothing Submitted <input type="checkbox"/> Written request issued <input type="checkbox"/> Study Submitted <input type="checkbox"/>
Generic Drugs Exclusivity for each strength: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Type of Letter: <input checked="" type="checkbox"/> APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH) <input type="checkbox"/> CGMP <input type="checkbox"/> OTHER:	
Comments: This ANDA was previously TA'd on 8/11/2010. At the time of the TA the firm had PIV certs to the '075, PIII to the '069 and '197 and a section viii to the '079. At this point in time the only unexpired patent is the '079 to which the applicant has provided a section viii statement- therefore this patent is not a barrier to approval of this ANDA. The last remaining regulatory barrier to the approval of this ANDA is TEVA's (76958) eligibility for 180 day exclusivity which will expire on 10/3/2010. This Application is eligible for Full Approval on or after 10/3/2010.	

2. **Labeling Endorsement**

Reviewer, \_\_\_\_\_ :  
Date \_\_\_\_\_  
Initials \_\_\_\_\_

Labeling Team Leader, \_\_\_\_\_ :  
Date 10/5/10  
Initials rlw/for

REMS required?  Yes  No  
REMS acceptable?  Yes  No  n/a

Comments:

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From: Lee, Koung U  
Sent: Wednesday, September 29, 2010 12:26 PM  
To: Barlow, James T; Doan, Dat  
Cc: Wu, Ruby (Chi-Ann); Rickman, William P  
Subject: RE: 90790/Apotex/Losartan  
Importance: High

Dat,

I concur.  
Koung

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From: Barlow, James T  
Sent: Wednesday, September 29, 2010 12:13 PM  
To: Doan, Dat; Lee, Koung U  
Subject: RE: 90790/Apotex/Losartan

I checked Drugs@FDA, OB and USP.

The labeling Approval Summary signed by Koung Lee on 2/25/10 remains acceptable. Please note that the suspension stability was found acceptable in 3/16/10 chemistry review.

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From: Doan, Dat  
Sent: Wednesday, September 29, 2010 11:39 AM  
To: Barlow, James T; Lee, Koung U  
Subject: 90790/Apotex/Losartan  
Importance: High

Hi Jim, Koung:

Please endorse this for me.

<< File: 90790.ap.letter.DOC >>

<< File: 90790.labeling.ap.summary.pdf >>

Thanks,

Dat Doan, R.Ph.

3. ***Paragraph IV Evaluation***

**PIV's Only**

David Read

OGD Regulatory Counsel

Pre-MMA Language included

Post-MMA Language Included

Comments: Apotex provided a method-of-use statement to the '079 patent. There are no other unexpired patents currently listed in the "Orange Book".

Date **10/5/10**

Initials **rlw/for**

4. ***Quality Division Director /Deputy Director Evaluation***

Date **10/5/10**

Chemistry Div. **SELECT DIV #**

Initials **rlw/for**

Comments: This approval package was endorsed on 10/4/10 by Robert Iser, Acting Director, Division of Chemistry IV. (approval routing summary).

5. ***First Generic Evaluation***

**First Generics Only**

Frank Holcombe

Assoc. Dir. For Chemistry

Comments: (First generic drug review)

**N/A. TEVA's ANDA 76-958 for this drug product was approved on 4/6/10.**

Date **10/5/10**

Initials **rlw/for**

***OGD Office Management Evaluation***

6. **Peter Rickman**

Date **10/5/10**

Director, DLPS

Initials **rlw/for**

Para.IV Patent Cert: Yes  No

Pending Legal Action: Yes  No

Petition: Yes  No

Comments: This ANDA was granted tentative approval on August 11, 2010. Final approval was blocked at that time by TEVA's eligibility for 180-day generic drug exclusivity. Refer to the administrative sign-off form created at that time. TEVA's eligibility expired on 10/3/10.

CMC found acceptable for final approval (Project Manager's Regulatory Assessment) 9/29/10. Apotex has provided a commitment to provide for a scored 50 mg tablet as requested. This is acceptable.

Final-printed labeling (FPL) remains acceptable for approval (see above). Apotex has provided a commitment to update its final-printed labeling to be consistent with the newly approved changes to the RLD labeling. This is

acceptable. Memorandum to the record filed in DARRTS to address this issue.

AND/OR

7. **Robert L. West**

**Date 10/5/10**  
**Initials RLWest**

Deputy Director, OGD

Para.IV Patent Cert: Yes  No

Pending Legal Action: Yes  No

Petition: Yes  No

Press Release Acceptable

Date PETS checked for first generic drug \_\_\_\_\_

Comments: Acceptable EES dated 8/10/10 (Verified 10/5/10). No "OAI" Alerts noted.

Apotex has provided a method-of-use statement to the '079 patent and has deleted reference to the use of the drug product for the treatment of chronic renal failure from its labeling. This is acceptable. There are no additional patents or exclusivity listed in the current "Orange Book" for this drug product.

With the expiration of TEVA's 180-day generic drug exclusivity, this ANDA is recommended for final approval.

8. ***OGD Director Evaluation***

Keith Webber

Deputy Director, OPS

Comments: RLWest for Keith Webber, Ph.D. 10/5/10.

First Generic Approval

PD or Clinical for BE

Special Scientific or Reg.Issue

Press Release Acceptable

Comments:

9. Project Manager

**Date 10/6/10**

**Initials dd**

Check Communication and Routing Summary into DARRTS

Orange Book Report:

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 U.S. Department of Health & Human Services

 **U.S. Food and Drug Administration**



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# Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020386 Product 003 in the OB\_Rx list.



Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
<a href="#">N020386</a>	003	5138069	Aug 11, 2009				
<a href="#">N020386</a>	003	5138069*PED	Feb 11, 2010				
<a href="#">N020386</a>	003	5153197	Oct 6, 2009			<a href="#">U - 3</a>	
<a href="#">N020386</a>	003	5153197*PED	Apr 6, 2010			<a href="#">U - 3</a>	
<a href="#">N020386</a>	003	5210079	May 11, 2010			<a href="#">U - 496</a>	
<a href="#">N020386</a>	003	5210079*PED	Nov 11, 2010			<a href="#">U - 496</a>	
<a href="#">N020386</a>	003	5608075*PED	Sep 4, 2009				



**There is no unexpired exclusivity for this product.**

**Additional information:**

- 1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).**
- 2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.**
- 3. \*\*\*\* The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.**

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

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/s/

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DAT T DOAN  
10/08/2010