Errata Sheet (dated 4/11/2007)
FDA Background Package for
April 18, 2007
Cardiovascular and Renal Drugs Advisory Committee Meeting
AVALIDE (irbesartan + hydrochlorothiazide) NDA 20-758/S-037
For Clinical Review, Efficacy Discussion Document, and Safety Discussion Document

Clinical Review: clarifications

1. Page 10, Section 1.3.3, Safety (Electronic pdf document Page 12)
   Page 26, Section 6.1.3.3, Overall Incidence of Adverse Events (Electronic pdf document Page 28)
   Page 47, Section 8.1, Conclusions (Electronic pdf document Page 49)

   Although patients receiving irbesartan/HCTZ had more adverse events than those receiving irbesartan monotherapy in Study CV131176 and had more adverse events than those receiving irbesartan monotherapy or hydrochlorothiazide monotherapy in Study CV131185, this difference in the number of adverse events is expected, given the 2:1 randomization in Study CV131176 and the 3:1:1 randomization in Study CV131185.

   Nevertheless, hypotension appears to be underreported in these studies, since vital signs were not recorded in a number of symptomatic patients.

2. Page 8, Section 1.2, Recommendation on Postmarketing Actions (Electronic pdf document Page 10)
   Page 47, Section 8.3, Recommendation on Postmarketing Actions (Electronic pdf document Page 49)
   Page 47, Section 8.3.1, Risk Management Activity (Electronic pdf document Page 49)

   No formal postmarketing studies are being requested of the sponsor at this time. Instead, the sponsor was asked to address elevations in creatine phosphokinase in their pharmacovigilance program.

Efficacy Discussion Document

1. Date of document changed from October 6, 2006 to April 6, 2007

2. Page 4, Table 1, Sponsor's Analysis: Proportion of Subjects Controlled (SeDBP < 90 mm Hg) by Week (Study CV131176) (Electronic pdf document Page 123)
   a. 95% Confidence Interval (CI) for Estimated Difference: values corrected
      i. Week 1, Irbesartan/HCTZ: 95% CI changed from (0.007, 0.113) to (0.7, 11.3)
      ii. Week 3, Irbesartan/HCTZ: 95% CI changed from (0.073, 0.224) to (7.3, 22.4)
      iii. Week 5, Irbesartan/HCTZ: 95% CI changed from (0.061, 0.220) to (6.1, 22.0)
      iv. Week 7, Irbesartan/HCTZ: 95% CI changed from (0.113, 0.271) to (11.3, 27.1)

Errata Sheet (dated 4/11/2007)
NDA 20-758 Avalide for Clinical Review, Efficacy Discussion Document and Safety Discussion Document

3. Page 5, Table 2, Sponsor's Analysis: Treatment Comparison of Proportions Controlled During Double-Blind Period by Week (CV131176) (Electronic pdf document Page 124)
    a. 95% Confidence Interval for Estimated Difference: values corrected
        i. Week 1, Irbesartan/HCTZ: 95% CI changed from (0.008, 0.089) to (0.8, 8.9)
        ii. Week 3, Irbesartan/HCTZ: 95% CI changed from (0.116, 0.242) to (11.6, 24.2)
        iii. Week 5, Irbesartan/HCTZ: 95% CI changed from (0.084, 0.224) to (8.4, 22.4)
        iv. Week 7, Irbesartan/HCTZ: 95% CI changed from (0.092, 0.236) to (9.2, 23.6)

4. Page 6, Table 3, Sponsor's Analysis: Mean Changes from Baseline in Trough SeDBP by Week (CV131176) (Electronic pdf document Page125)
    a. Week 1, Baseline Mean (mm Hg) (SD), Irbesartan/HCTZ: 113 (3.7) corrected to 113.4 (3.7)

5. Page 7, Table 4, Sponsor's Analysis: Mean Changes from Baseline in Trough SeSBP by Week (CV131176) (Electronic pdf document Page 126)
    a. Week 3, Baseline Mean (mm Hg) (SD), Irbesartan: 171.5 (17.6) corrected to 171.5 (16.6)

6. Page 8, Table 5, Sponsor's Analysis: Mean Changes from Baseline in Trough SeSBP by Week (CV131185) (Electronic pdf document Page 127)
    a. Week 8, Irbesartan
        i. P- Value for Combo and Mono Group Comparison corrected from < 0.0001 to 0.0016
    b. Week 8, HCTZ
        i. Baseline Mean (mm Hg) (SD) corrected from 161.7 (10.70) to 161.6 (10.75)
        ii. On Therapy Mean (mm Hg) (SD) corrected from 147.8 (11.95) to 145.9 (13.61)
        iii. Adjusted Mean Change from Baseline (mm Hg) (SE) corrected from -13.9 (1.26) to -15.7 (1.36)
        iv. Estimated Difference Between Combo and Mono Group (mm Hg) corrected from -10.9 to -11.3
        v. 95% Confidence Interval for Estimated Difference corrected from (-13.8, -8.1) to (-14.4, -8.3)

7. Page 10, Table 7, Sponsor's Analysis: Proportion of Subjects Controlled by Week (CV131185) (Electronic pdf document Page 129)
    a. 95% Confidence Interval for Estimated Difference: values corrected
        i. Week 2, Irbesartan: 95% CI changed from (-0.039, 0.155) to (-3.9, 15.5)
        ii. Week 2, HCTZ: 95% CI changed from (0.032, 0.210) to (3.2, 21.0)
        iii. Week 4, Irbesartan: 95% CI changed from (0.044, 0.261) to (4.4, 26.1)
        iv. Week 4, HCTZ: 95% CI changed from (0.175, 0.369) to (17.5, 36.9)
        v. Week 8, Irbesartan: 95% CI changed from (0.014, 0.242) to (1.4, 24.2)
        vi. Week 8, HCTZ: 95% CI changed from (0.231, 0.432) to (23.1, 43.2)
        vii. Week 12, Irbesartan: 95% CI changed from (0.107, 0.330) to (10.7, 33.0)

viii. Week 12, HCTZ: 95% CI changed from (0.203, 0.413) to (20.3, 41.3)

8. References provided for Tables 1 through 7 (Electronic pdf document Pages 123-129):

Table 1 - Page 4:
*Primary Endpoint
Reproduced from Sponsor, Clinical Study Report, Table 10.2, pages 67-68. Source: Appendix 10A.
Supplemental Tables S.10.1A, S.10.1B, S.10.2.
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

Table 2- Page 5:
Reproduced from Sponsor, Clinical Study Report, Table 10.2, pages 67-68. Source: Appendix 10A.
Supplemental Tables S.10.1A, S.10.1B, S.10.2.
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

Table 3 - Page 6:
Reproduced from Sponsor, Clinical Study Report, Table 10.3, pages 71-72. Source: Appendix 10A, Appendix 6.
Supplemental Tables S.10.3A.1, S.10.3B.
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

Table 4 - Page 7:
Reproduced from Sponsor, Clinical Study Report, Table 10.3, pages 71-72. Source: Appendix 10A, Appendix 6.
Supplemental Tables S.10.3A.1, S.10.3B.
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

Table 5 - Page 8:
*Primary Efficacy Endpoint
Reproduced from Sponsor, Clinical Study Report, Table 10.1.2A, pages 71-72. Source: Appendix 10A, 6.0.
Supplemental Tables S.10.1A, S.10.1E
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

Table 6 - Page 9
Reproduced from Sponsor, Clinical Study Report, Table 10.1.2B, pages 73-74. Source: Appendix 6.0, Appendix 10A.
Supplemental Tables S.10.1A, S.10.1E
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

Table 7 - Page 10
Reproduced from Sponsor, Clinical Study Report, Table 10.2, pages 77-78. Source: Appendix 6.0, Appendix 10A.
Supplemental Tables S.10.2A
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

Errata Sheet (dated 4/11/2007)
NDA 20-758 Avalide for Clinical Review, Efficacy Discussion Document and Safety Discussion Document

Safety Discussion Document

1. Date of document changed from October 6, 2006 to April 6, 2007

2. Page 2, Table 3, Sponsor's Analysis: Most Common Adverse Events as Reported by at Least 1% of Subjects in Either Treatment Group During Double-Blind Period, by Preferred Term (Study CV131176): clarified that this table was the sponsor's analysis and provided references (Electronic pdf document Page 132)

3. Page 2, Table 4, Number (Percent) of Subjects with Pre-Specified Adverse Events During Double-Blind Period by Adverse Event and Preferred Term (Study CV131176): provided references (Electronic pdf document Page 132)

4. Page 3, Table 5, Sponsor's Analysis: Summary of Subjects Discontinued during Period B and Reason for Discontinuation (CV131185): clarified that this table was the sponsor's analysis (Electronic pdf document Page 133)

5. Page 3, Table 6, Sponsor's Analysis: Overview of Adverse Events During Period B (CV131185): clarified that this table was the sponsor's analysis (Electronic pdf document Page 133)