Erratum to the FDA Briefing Document
Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
January 14, 2020

This erratum contains corrections to FDA's briefing information for the January 14, 2020, joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee. At this meeting, the committee will discuss oxycodegol tablets, submitted by Nektar Therapeutics, Inc., for the management of chronic low back pain (CLBP) in adult patients with pain severe enough to require daily, around-the clock, long-term opioid treatment and for which alternative treatment options are inadequate. Changes are **bolded** and underlined.

1. On Page 17, third sentence:

   "NKTR-181 showed lower mu-opioid receptor binding affinity than that of oxycodone and morphine (15-fold and 28-fold less, respectively) and lower functional activity (i.e., the ability to inhibit the cellular signal transduction) than these opioids."

   Should be revised to read (changes **bolded** and underlined):

   NKTR-181 showed lower mu-opioid receptor binding affinity than that of oxycodone and morphine (15-fold and 28-fold less, respectively) and **consequently** lower **potency ~~functional activity~~ ~~(i.e., the ability to inhibit the cellular signal transduction)~~ in cell-based assays ~~than these opioids~~**.

2. On Page 19, Section 7:

   "Subjects with severe renal impairment or ESRD-HD had higher exposure to the NKTR-181 and metabolite oxycodol; however, exposure to the metabolite oxycodone was similar among renal function groups."

   Should be revised to read (changes **bolded** and underlined):

   "Based on dose-normalization, ~~S~~**s**ubjects with severe renal impairment ~~or ESRD HD~~ had higher exposure to ~~**the**~~ **both** NKTR-181 and **the** metabolite oxycodol, **compared to the normal renal function group**; however, exposure to the metabolite oxycodone was similar among renal function groups."

3. On Page 22, Subsection 2:

   "Study 12-181-15 utilized supratherapeutic doses (600 mg and 1200 mg) of NKTR-181 for the assessment of oral abuse potential."

   Should be revised to read (change **bolded** and underlined):

   "**Study ~~12~~15-181-15** utilized supratherapeutic doses (600 mg and 1200 mg) of NKTR-181 for the assessment of oral abuse potential."

4. On Page 22, item #3:

   "The results of the physical dependence evaluations are difficult to interpret because assessments using the withdrawal scales were conducted outside of the time window when withdrawal symptoms are most likely to occur"

   Should be revised to read (change **bolded** and underlined).

   "The results of the physical dependence evaluations are difficult to interpret**. ~~because assessments using the withdrawal scales were conducted outside of the time window when withdrawal symptoms are most likely to occur."~~ According to the Sponsor, Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) data from study 14-181-07 were similar between NKTR-181 and placebo. However, the COWS data would not have captured withdrawal-related AEs because they were assessed 7 days after the stopping of drug; the onset of withdrawal is likely to be much shorter (e.g., 2-4 days given the half-life of NKTR-181 is 14 hours). In addition, patients had access to opioid rescue medications during the assessment period, which would have suppressed withdrawal-related symptoms.**

   Although, in the same study, SOWS data were collected daily after randomization, rescue medications, including opioids, were allowed and were taken more often by placebo-treated subjects, which likely confounded the assessment of opioid withdrawal."

5. On Page 27, **Demographic Characteristics:**

   "Of the 610 randomized subjects, 58.5% were female and 41.5% were male; the mean age was 51.4 years (range: 20 to 75 years). Four-hundred-one subjects (65.7%) were white, 188 subjects (30.8 %) were Black/African American, 6 subjects (1%) Asian, 6 subjects (1%) American Indian or Alaska Native, 2 subjects (0.3%) Native Hawaiian or Other Pacific Islander, and the rest of the subjects 7 (1.2%) of not reported or multiple race. Forty-two subjects (6.9%) were Hispanic or Latino, 562 (92.1%) were Not Hispanic or Latino, and 6 subjects (1%) of not

reported or unknown ethnicity. The mean BMI was 30.5 kg/m2. The mean (SD) screening pain score was 6.73 (0.95) and the mean time from the onset of low back pain was 13.2 years (range: 0.5 to 55.3 years). Out of 1190 enrolled subjects, 123 reported prior opioid use. Overall there were no relevant differences in medical history and medication history between the two groups. Demographics and baseline characteristics were comparable between the NKTR-181 and placebo groups. Of the 1189 treated subjects, 58.4% were female and 41.6% were male; the mean age was 51.0 years (range: 19 to 75 years), two thirds were Caucasian."

Should be revised to read (change **bolded** and underlined):

Of the 610 randomized subjects, 58.5% were female and 41.5% were male; the mean age was 51.4 years (range: 20 to 75 years). Four-hundred-one subjects (65.7%) were white, 188 subjects (30.8 %) were Black/African American, 6 subjects (1%) Asian, 6 subjects (1%) American Indian or Alaska Native, 2 subjects (0.3%) Native Hawaiian or Other Pacific Islander, and the rest of the subjects 7 (1.2%) of not reported or multiple race. Forty-two subjects (6.9%) were Hispanic or Latino, 562 (92.1%) were Not Hispanic or Latino, and 6 subjects (1%) of not reported or unknown ethnicity. The mean BMI was 30.5 kg/m2. The mean (SD) screening pain score was 6.73 (0.95) and the mean time from the onset of low back pain was 13.2 years (range: 0.5 to 55.3 years). **~~Out of 1190 enrolled subjects, 123 reported prior opioid use.~~** **Out of 1189 subjects who received at least one dose of study medication, the Applicant reports that 111 patients reported prior opioid use**. Overall there were no relevant differences in medical history and medication history between the two groups. Demographics and baseline characteristics were comparable between the NKTR-181 and placebo groups. Of the 1189 treated subjects, 58.4% were female and 41.6% were male; the mean age was 51.0 years (range: 19 to 75 years), two thirds were Caucasian.

6. On Page 32, Table 8:

Improvement from Screening	**NKTR-181 (N=309)**	**Placebo (N=301)**
30%	72%	57%
50%	58%	31%

On the last row, "58%" should be revised to "51%" and "31%" should be revised to "38%" (changes **bolded** and underlined):

Improvement from Screening	**NKTR-181 (N=309)**	**Placebo (N=301)**
30%	72%	57%
50%	**~~58~~ 51%**	**~~31~~ 38%**

7. On Page 42, the first paragraph:

   "The tables below show the most frequently reported TEAEs that lead to treatment discontinuation in Pool 1. In the open-label titration phase nausea, constipation, somnolence, vomiting, and dizziness were the most frequently reported TEAEs that led to treatment discontinuation. In the double-blind phase, constipation was the most frequently reported TEAE that led to treatment discontinuation, followed by fatigue, nausea, somnolence, vomiting, and drug withdrawal syndrome."

   Should be revised to read (change **bolded** and underlined):

   "The **~~tables below show~~** **following text describes** the most frequently reported TEAEs that lead to treatment discontinuation in Pool 1. In the open-label titration phase nausea, constipation, somnolence, vomiting, and dizziness were the most frequently reported TEAEs that led to treatment discontinuation. In the double-blind phase, constipation was the most frequently reported TEAE that led to treatment discontinuation, followed by fatigue, nausea, somnolence, vomiting, and drug withdrawal syndrome."

8. On Page 42, Table 14:

   The "*" in the table denotes a revision to the Applicant's originally submitted table in the Integrated Summary of Safety (ISS) to include one additional subject that was determined to have discontinued due to "Hepatic enzyme increased" based on FDA analysis.

9. On Page 49, the last paragraph, first sentence:

   "There were 16 subjects who the Applicant reports were discontinued from the clinical studies 14-181-07 and 14-181-08 for abnormal hepatic studies."

   Should be revised to read (change **bolded** and underlined):

"There were ~~**16**~~ **18** subjects who the Applicant reports were discontinued from the clinical studies 14-181-07 and 14-181-08 for abnormal hepatic studies."

10. On Page 50, the following patients should be added to the list of patients discontinued for abnormal LFTs in Study 07:

    - Subject (b) (6) was a 76-year-old woman with a past medical history significant for chronic low back pain, hyperlipidemia, osteoarthritis of the bilateral knees, and a benign brain neoplasm. Her concomitant medications included acetaminophen, aspirin, ibuprofen and rosuvastatin. She initiated treatment with oxycodegol and was titrated to 200 mg approximately nine days later. On the same day she was titrated to 200 mg, she developed elevations of her hepatic enzymes, with an ALT of 4.63x ULN and AST of 2.11x ULN. Four days later her ALT was 4.5x ULN and her AST was 2.73x ULN. Her laboratory values trended down over the next several days and the ALT and AST elevations had resolved by approximately two weeks after the initial elevation. Both transaminase elevations were reported as adverse events, and the study drug was reported as discontinued due to the abnormalities.

    - Subjec (b) (6) was a 43-year-old woman with a past medical history significant for chronic low back pain, familial hereditary neutropenia, and hypertension. Her concomitant medications included naproxen, cyclobenzaprine, and lisinopril. She initiated treatment with oxycodegol and remained on 100 mg without further titration for 8 days, after which she developed an elevation of her hepatic enzymes, with an ALT of 2.7x ULN and an AST of 3.4x ULN. The transaminase elevations were reported as an adverse event resulting in discontinuation of study drug. Both the ALT and AST were within normal limits 11 days later.

11. On Page 53, the last paragraph, second sentence:

    "The percentage of subjects with abnormal findings across studies and pools is very low and does not appear to be dose-dependent, however, the frequency of abnormalities occurring in the placebo group is zero."

    Should be revised to read (change **bolded** and <u>underlined</u>):

    "The percentage of subjects with abnormal findings across studies and pools is very low and does not appear to be dose-dependent, however, the frequency of abnormalities occurring in the ~~**placebo**~~ **<u>100 mg</u>** group is zero."

12. On Page 55, the first paragraph, third sentence:

    "A total of 17 patients, all of whom were on oxycodegol, were discontinued for LFT abnormalities."

Should be read (change bolded and underlined):

“A total of ~~**17**~~ **19** patients, all of whom were on oxycodegol, were discontinued for LFT abnormalities.”