CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204760Orig1s000

OTHER REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 16, 2014

FROM: Julie Beitz, MD

SUBJECT: Approval Action

TO: NDA 204760 Movantik (naloxegol) tablets
AstraZeneca Pharmaceuticals LP

Summary

Naloxegol is an antagonist of opioid binding at the mu-opioid receptor. When administered at the recommended dose levels, naloxegol functions as a peripherally-acting opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids.

Naloxegol is a PEGylated derivative of naloxone and a new molecular entity. Pegylation confers the following properties: naloxegol has reduced passive permeability across membranes compared to naloxone; naloxegol is a P-glycoprotein (P-gp) efflux transporter substrate; and naloxegol is orally bioavailable. The reduced passive permeability and P-gp efflux transporter properties limit CNS entry of naloxegol compared to naloxone.

This memo documents my concurrence with the Division of Gastroenterology and Inborn Errors Product's recommendation for approval of NDA 204760 for Movantik (naloxegol) tablets for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

Discussions regarding product labeling, and postmarketing study requirements and commitments have been satisfactorily completed. There are no inspectional issues that preclude approval.

Dosing

The recommended dose of Movantik (naloxegol) tablets is 25 mg taken once daily in the morning on an empty stomach. Patients who do not tolerate this dose, may reduce the dose to 12.5 mg once daily.

Maintenance laxatives should be discontinued prior to initiation of therapy with Movantik. Laxatives can be used as needed if the response to Movantik is not optimal.

Movantik has been shown to be efficacious in patients who have taken opioids for at least 4 weeks. Sustained exposure to opioids prior to starting Movantik may increase the patient's sensitivity to the effects of Movantik.

Regulatory History

On October 22, 2007, Nektar Therapeutics submitted IND 078781 for naloxegol (NKTR-118), a PEGylated derivative of naloxone for the treatment of opioid induced constipation. On January 12, 2010, the IND was transferred to AstraZeneca Pharmaceuticals LP.

An End-of-Phase 2 meeting was held on January 26, 2010; during the meeting, eligibility criteria and definitions for clinical response in phase 3 trials were discussed.

On April 26, 2010, the sponsor was informed in an Advice Letter that, as a derivative of thebaine, naloxegol is a Schedule II controlled substance under the Federal Controlled Substances Act, and that sufficient data to evaluate its abuse potential and dependence-producing properties would need to be submitted. If nonclinical studies suggest that naloxegol has opioid agonist or partial agonist activity, a human abuse potential study would be required to support possible rescheduling. In written comments issued on October 12, 2011, the sponsor was informed that based on the available data presented, a human abuse potential study would not be required.

On October 8, 2012, the Division provided preliminary written comments to the sponsor in advance of a planned pre-NDA meeting. These comments described the Division's concerns regarding the potential for opioid withdrawal and related adverse cardiovascular outcomes that may be associated with the class of peripherally acting opioid receptor antagonists, including naloxegol. The meeting was cancelled but subsequently held on April 23, 2013. The Division provided advice on specific analyses that should be included in the NDA regarding the occurrence of opioid withdrawal and adverse cardiovascular outcomes in clinical trials, as well as, effects of drug exposure on opioid analgesia and hemodynamic parameters.

AstraZeneca agreed to include as part of the NDA filing the additional analyses requested but also noted that these further analyses will not change their conclusions regarding the cardiovascular safety of naloxegol. The sponsor stated that adjudicated major adverse cardiovascular events, or MACE[1], were balanced between naloxegol, placebo, and usual care across the program, and that no MACE were associated with gastrointestinal or other adverse events typically associated with opioid withdrawal.

In the final minutes for the April 23, 2013 meeting, dated May 22, 2013, the Division further clarified that results from a cardiovascular outcomes trial (or CVOT) would not be required prior to NDA filing. Additional recommendations regarding analyses of potential opioid withdrawal symptoms to be submitted in the NDA were provided in an Advice Letter dated August 9, 2013.

On September 16, 2013, AstraZeneca submitted NDA 204760 for naloxegol. The application was granted a standard review and reviewed under the Program. The Late Cycle Meeting was held on June 18, 2014. There were no substantive review issues identified for discussion at this meeting.

FDA Advisory Committee Meeting. On June 11-12, 2014, a meeting of the Anesthesia and Analgesia Drug Products Advisory Committee (AADPAC) was convened to discuss the assessment of cardiovascular safety for five peripherally acting opioid receptor antagonists in various stages of development for the treatment of OIC in patients with chronic non-cancer pain, including Cubist's Entereg (alvimopan), Salix's Relistor (methylnaltrexone bromide), and AstraZeneca's Movantik (naloxegol).

The views of Committee members were split regarding whether the imbalance in myocardial infarctions seen with Entereg relative to placebo in a single 12-month trial in OIC patients with chronic non-cancer pain represented a real cardiovascular signal.[2] Those who believed it was a signal described it as weak, at best, but not ignorable given the seriousness of the adverse event (i.e., myocardial infarction). These members also acknowledged that 1) the finding had not been

[1] MACE is defined as the occurrence of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.

[2] In this trial there were 538 patients randomized to Entereg and 267 to placebo (i.e., randomization was 2:1). Cardiovascular disease and risk factors were assessed retrospectively in half of the patients. Of those assessed, baseline risk factors and conditions (e.g., diabetes, hypertension, hyperlipidemia, and prior myocardial infarction) were balanced between treatment groups. At day 360, 33% (177/538) of Entereg-treated patients and 28% (74/267) of placebo-treated patients remained on treatment, providing 388 and 183 patient years of exposure, respectively. During the course of the trial, seven myocardial infarctions were identified in the Entereg treatment group, and none on placebo; these events all occurred in the first four months of the trial.

replicated in a second Entereg trial, and 2) there was insufficient evidence to establish a biologic mechanism by which Entereg or other opioid receptor antagonists could cause myocardial infarction in chronic opioid users.

Although symptoms had been reported in peripherally acting opioid receptor antagonist development programs that were potentially indicative of opioid withdrawal, reasons for the occurrence of such symptoms were not readily apparent. Analyses of potential withdrawal symptoms in Entereg and Relistor users suggested a greater incidence when gastrointestinal symptoms were included, consistent with their peripheral antagonist effects on opioid receptors in the gastrointestinal tract, the intended effect.[3] Salix also noted that the incidence of anxiety, hot flushes, hyperhidrosis, piloerection and tremor reported with Relistor use in OIC trials in patients with chronic non-cancer pain (Study 3356 and Study 3358) was similar to that reported for extended-release opioids, suggesting that these symptoms are likely attributable to chronic opioid therapy.[4] Importantly, although there were reports of potential withdrawal symptoms occurring in temporal relation to cardiovascular symptoms or signs such as palpitations, chest pain or increased blood pressure, direct attribution of cardiovascular adverse effects to opioid withdrawal could not be established.

Although some AADPAC members thought a CVOT would be needed prior to approval of Entereg, the majority of Committee members (17 of 24) voted against the need for pre-approval CVOTs for other members of the class of peripherally acting opioid receptor antagonists intended to treat OIC in patients with non-cancer pain in the absence of a worrisome signal. Committee members noted that interpretable CVOTs would be feasible but would pose major challenges, including: 1) large sample sizes would be required to study a population that is not enriched with patients at higher cardiovascular risk, 2) population enrichment could reduce the sample size required but could also slow enrollment, 3) high treatment discontinuation rates can be expected, 4) patient dropouts can perhaps be minimized if randomized treatments are equally efficacious, to the extent this is possible, 5) prescribers and patients need to be motivated to remain compliant with protocol requirements in the long-term, and 6) substantial resources are required to successfully conduct and complete such trials.

There was general consensus that a 12-month controlled trial of modest size, similar in size to that of the Entereg trial, would be a useful addition to the safety database of new members of the class, although it was recognized that such a trial could not detect modest increases in MACE risk. Committee members advised that such a trial be designed to prospectively assess and adjudicate cardiovascular adverse events, and provide for careful follow-up of trial drop-outs. They recognized that a trial of this size could detect only large increases in MACE risk, and then only if patients with higher cardiovascular risk were included. Most AADPAC members also supported the use of post-marketing observational studies to further quantify the potential risk of MACE associated with use of these drugs in real-world settings and with large numbers of patients.

Product Quality Considerations

Naloxegol is a PEGylated derivative of naloxone. The NDA applicant has provided sufficient information to assure the identity, strength, purity, and quality of naloxegol.

[3] Slide C-32 of Cubist's presentation at the June 2014 AADPAC meeting reported that in OIC trials of Entereg the incidence of withdrawal symptom clusters (at least 2 events on the same day) was 8.6% in Entereg-treated patients and 6.3% in placebo-treated patients when gastrointestinal symptoms were included; in contrast, withdrawal symptom clusters excluding gastrointestinal symptoms were reported in <1% of patients in both groups. Slide CS-56 of Salix's presentation reported rates of potential opioid withdrawal symptoms in Study 3358 including and excluding gastrointestinal symptoms as 5.1 per 100 patient years and 1.3 per 100 patient years, respectively. Symptom reports were based on either investigator reports or DSM-V criteria.

[4] Slide CS-54 of Salix's presentation at the June 2014 AADPAC meeting showed that the incidence of potential withdrawal symptoms in Relistor Study 3356 and Study 3358 was within the range expected with extended-release opioids (0-10%).

The proposed drug substance, naloxegol oxalate, is a white to off-white [redacted] (b) (4) powder, highly soluble in water in the pH range of 1 to 7.5. Phase 3 clinical trials were conducted with naloxegol free base, but the naloxegol oxalate salt will be commercialized. *In vivo* bioequivalence was established between the two formulations.

The commercial product will be formulated as an immediate release, film-coated tablet and marketed in two strengths, 12.5 mg and 25 mg (containing 14.2 mg and 28.5 mg of naloxegol oxalate, respectively). Both tablet strengths will be available in 30 and 90 count bottles and in blister packs.

Clinical Pharmacology

Based on membrane binding assay data, naloxegol's affinity for the mu-opioid receptor is similar to that for the kappa-opioid receptor, and much greater than that for the delta-opioid receptor. Naloxegol exposures at 25 mg are sufficient to antagonize mu- and kappa-opioid receptors and are unlikely to antagonize delta-opioid receptors.

Following oral administration of naloxegol, the C_{max} is achieved within 0.5 to 2 hours. In a majority of subjects, a secondary plasma concentration peak of naloxegol was observed approximately 0.4 to 3 hours after the first peak which may be due to enterohepatic recirculation of the drug. Across the range of doses evaluated, AUC increased in a dose-proportional manner and C_{max} increased in a slightly more than dose-proportional manner. Accumulation was minimal following multiple daily doses of naloxegol.

Since naloxegol is PEGylated naloxone, formation of naloxone by complete separation of the 7-pegylated side chain is a theoretical possibility. Based on the information available, naloxone concentrations ≥ 0.25 ng/mL (LLOQ for the assay) can be ruled out. Neither the presence of naloxone at concentrations below 0.25 ng/mL nor the potential of such concentrations to cause central opioid antagonism is known.

Food effects. A high-fat meal increased the extent and rate of naloxegol absorption. The C_{max} and AUC were increased by approximately 30% and 45%, respectively. In clinical trials, naloxegol was dosed on an empty stomach approximately 1 hour prior to the first meal in the morning; product labeling will recommend dosing on an empty stomach.

QT prolongation potential. In a randomized, double-blind, 4-way cross-over thorough QTc study with moxifloxacin as a positive control, there was no QT prolonging effect observed for either the therapeutic (25 mg) or a supratherapeutic dose (150 mg dose) of naloxegol.

Effect of age. Overall, in clinical trials of naloxegol, 11% of subjects were over 65 years of age. No differences in safety or effectiveness were observed in these subjects compared with younger subjects. Naloxegol pharmacokinetic profiles were assessed in 6 young and 6 elderly healthy Japanese subjects. Following multiple daily doses of 25 mg naloxegol, C_{max} and AUC_{tau} were approximately 45% and 54% greater at steady state in the older subjects compared with the younger subjects.

Renal impairment. The effect of renal impairment on the pharmacokinetics of a single oral dose of naloxegol 25 mg was studied in subjects with renal impairment classified as moderate (n=8), severe (n=4), or end-stage renal disease (ESRD) not yet on dialysis (n=4), and compared with healthy subjects (n=6). Most renally impaired subjects had plasma naloxegol pharmacokinetic profiles comparable to those of healthy subjects. The remaining individuals with renal impairment demonstrated higher naloxegol exposures (up to 10-fold) compared to the healthy subjects; the reason for these high exposures is unknown. A lower starting dose of naloxegol (12.5 mg) is recommended for subjects with a creatinine clearance < 60 mL/min.

Plasma concentrations of naloxegol in 8 subjects with ESRD on hemodialysis were similar to healthy subjects with normal renal function, when drug was administered either pre- or post-hemodialysis. The fraction of dose in dialysate was very minor however, suggesting that dialysis did not aid in the removal of naloxegol. Product labeling will state that naloxegol is not dialyzable.

Hepatic impairment. Naloxegol pharmacokinetics were assessed in subjects with mild (n=8) or moderate (n=8) hepatic impairment (Child-Pugh Classes A or B) and compared to normal healthy subjects (n=8). Following administration of a single 25 mg dose of naloxegol, subjects with mild or moderate hepatic impairment showed slightly decreased AUC values (16 to 17 %) based on geometric mean data, while C_{max} was comparable to controls. No dosage adjustment is recommended for subjects with mild or moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naloxegol was not evaluated.

Drug interactions

Naloxegol is metabolized primarily by the CYP3A enzyme system and is a substrate of the P-gp efflux transporter. Therefore, drugs, herbal products or foods that are inhibitors or inducers of these systems are likely to modulate naloxegol pharmacokinetics. Naloxegol does not appear to be a substrate for other major CYP 450 enzymes or transporters.

Strong CYP 3A4 and P-gp inhibitors. The effects of once daily oral dosing of 400 mg ketoconazole, a strong inhibitor of CYP 3A4 and P-gp, on the pharmacokinetics of 25 mg naloxegol were studied in 22 healthy subjects. The C_{max} and AUC of naloxegol increased 9.6- and 12.9-fold, respectively. Product labeling will contraindicate concomitant use of naloxegol with strong CYP 3A4 inhibitors. Concomitant use with grapefruit or grapefruit juice, which can be a strong CYP3A inhibitor when consumed in large quantities or in double strength, was not formally evaluated; product labeling will recommend that consumption of grapefruit or grapefruit juice be avoided due to the potential for increased drug exposure.

Moderate CYP 3A4 and P-gp inhibitors. The effects of once daily oral dosing of 240 mg diltiazem, a moderate inhibitor of CYP 3A4 and P-gp, on the pharmacokinetics of 25 mg naloxegol were evaluated in 43 healthy subjects. The C_{max} and AUC of naloxegol increased 2.9- and 3.4-fold, respectively. Product labeling will recommend that concomitant use with moderate CYP 3A4 inhibitors be avoided. If dosing with moderate CYP 3A4 inhibitor drugs cannot be avoided, a daily dose of 12.5 mg is recommended.

***P-gp Inhibitors*.** The effects of once daily oral dosing of 600 mg quinidine, a strong P-gp inhibitor but weak CYP 3A4 inhibitor, on the pharmacokinetics of 25 mg naloxegol were studied in 36 healthy subjects. The C_{max} and AUC of naloxegol increased 2.5- and 1.4-fold, respectively. Dosing recommendations for concomitant use of P-gp inhibitors follow the recommendations for the drug's CYP 3A4 inhibitor potential. Thus, P-gp inhibitors which are also strong CYP 3A4 inhibitors are contraindicated. When naloxegol is used with P-gp inhibitors that are also weak CYP 3A4 inhibitors no dose adjustment is needed.

***CYP 3A4 and P-gp* inducers.** The effects of once daily oral dosing of 600 mg rifampicin, a strong inducer of CYP 3A4 and P-gp, on the pharmacokinetics of 25 mg naloxegol were assessed in 22 healthy subjects. The C_{max} and AUC of naloxegol were reduced by 76% and 89%, respectively. Product labeling will contraindicate concomitant use of naloxegol with strong CYP 3A4 inducers due to the potential for loss of efficacy. Physiologically-based pharmacokinetic (PBPK) simulations suggested that naloxegol exposures after co-administration of a single 25 mg dose with efavirenz, a moderate CYP 3A4 inducer, are similar to those after administration of 12.5 mg naloxegol alone.

Naloxegol did not appear to alter morphine pharmacokinetics or morphine-induced pupillary constriction (miosis).

Postmarketing Commitment. The applicant has agreed to further study the time-dependent/mechanism-based inhibition potential of naloxegol on the hepatic CYP 2C8 enzyme *in vitro* as a postmarketing commitment. Sufficient data regarding this potential interaction were not submitted in the NDA.[5]

Efficacy

The efficacy of Movantik in patients with OIC and chronic non-cancer pain was evaluated in two replicate double-blind, placebo-controlled trials. Patients receiving an opioid morphine equivalent daily dose of 30 to 1000 mg for at least four weeks before enrollment and who self-reported OIC[6] were eligible. During these trials, patients were prohibited from using laxatives other than bisacodyl rescue laxatives (if they had not had a bowel movement for 72 hours), or a one-time use of an enema (if after 3 doses of bisacodyl, they still did not have a bowel movement).

A total of 652 and 700 patients were enrolled in the two trials, respectively. Patients were randomized 1:1:1 to receive Movantik 12.5 mg, Movantik 25 mg, or placebo once daily for 12 weeks. The mean age of trial participants was 52 years; the majority were female and Caucasian. Participants were taking a wide range of opioids for an average of 3.6 and 3.7 years, respectively. The mean baseline opioid morphine equivalent daily dose prior to enrollment was 140 and 136 mg, respectively; back pain was the most common reason for pain. Use of one or more laxatives on at least one occasion within two weeks prior to enrollment was reported by 71% of patients in both trials.

The primary endpoint was response defined as at least 3 spontaneous bowel movements per week, and a change from baseline of at least 1 spontaneous bowel movement for at least 9 of the 12 study weeks, and for 3 of the last 4 weeks.

In the first trial, responses in both Movantik treatment groups were significantly better compared to the placebo group. In the second trial, response in the Movantik 25 mg treatment group was significantly better than placebo. Response in the Movantik 12.5 mg treatment group was numerically higher than placebo but the difference did not reach statistical significance.

Several secondary endpoints were protocol-specified and are described below. Analysis of secondary endpoints for the Movantik 12.5 mg dose in the second trial was not performed because the primary endpoint was not met.

Laxative users with OIC symptoms comprised 55 and 53% of participants in the two trials, respectively. These patients (identified using an investigator-administered questionnaire) had reported using laxatives at least 4 out of the 14 days prior to enrollment and at least one of the following OIC symptoms of moderate, severe or very severe intensity: incomplete bowel movements, hard stool, straining, or sensation of needing to pass a bowel movement but unable to do so. Among these patients, 42 and 50% reported using laxatives daily. In the first trial, responses among patients on Movantik 25 mg and 12.5 mg were significantly better compared to patients on the placebo group. In the second trial, response in the Movantik 25 mg treatment group was significantly better than placebo.

The time to first post-dose spontaneous bowel movement was significantly shorter in patients treated with Movantik 25 mg compared to placebo-treated patients (with median times of 6 vs. 36 hours and 12 vs. 37 hours in the two trials, respectively). The time to first post-dose spontaneous bowel movement

[5] See *FDA's Draft Guidance for Industry: Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*, dated February 2012.

[6] Opioid induced constipation was confirmed during a 2-week run-in period and was defined as < 3 spontaneous bowel movements per week on average with at least 25% of these bowel movements associated with one or more of the following: straining, hard or lumpy stools, or having a sensation of incomplete evacuation.

was also shorter in patients treated with Movantik 12.5 mg compared to placebo-treated patients in the first trial (with a median time of 20 vs. 36 hours).

The change from baseline in the mean number of days per week with at least 1 but no more than 3 spontaneous bowel movements was evaluated among treatment groups. There was a significant difference in the number of days per week with 1 to 3 spontaneous bowel movements per day on average over 12 weeks between the Movantik 25 mg (in both trials) and Movantik 12.5 mg (in the first trial) groups as compared to placebo.

Based on the results of these trials, the recommended starting dose of Movantik is 25 mg for most patients. The 12.5 mg Movantik dose may be used as a starting dose in selected populations.

Safety

A total of 1497 patients received Movantik in clinical trials, including 537 patients exposed for greater than 6 months, and 320 patients exposed for 12 months.

In the two 12-week efficacy trials, the most common adverse events reported in at least 3% of patients were: abdominal pain, diarrhea, nausea, flatulence, vomiting, headache and hyperhidrosis. Abdominal pain in particular was reported more frequently in patients treated with Movantik 25 mg compared to those treated with 12.5 mg (21% vs. 12%).

A randomized, 52-week, open-label safety trial was also conducted in 844 patients, with 534 randomized to Movantik 25 mg and 270 patients to a usual care control group. The overall adverse event profile for Movantik 25 mg in this trial was similar to that observed in the 12-week efficacy trials.

Cardiovascular safety assessment. There were no direct effects of naloxegol on the cardiovascular system in nonclinical testing. In clinical trials, mean changes from baseline in vital signs and the pattern and frequency of vital sign outliers were similar across treatment groups.

In the 52-week safety trial, the incidence of adjudicated MACE was low and similar across treatment groups. In the Movantik 25 mg group, there were two MACE, one cardiovascular death and one non-fatal myocardial infarction, for 0.5 events per 100 patient years. In the usual care group, there were two MACE, one cardiovascular death and one non-fatal stroke, for 0.9 events per 100 patient years.[7]

In the entire Phase III program (including the two efficacy trials and the 52-week safety trial), three non-fatal myocardial infarctions were reported among 1386 patients on Movantik (12.5 or 25 mg), for 0.45 (95% CI: 0.09, 1.32) events per 100 patient years.[8] This event rate compares favorably to the myocardial infarction rate among 700 patients treated with placebo or usual care (0.56; 95% CI: 0.07, 2.04), and to the published myocardial infarction rate of 0.60 (95% CI: 0.57, 0.64) among chronic opioid users (excluding patients with a myocardial infarction within the past six months).[9]

Opioid withdrawal. Given the mechanism of action of peripherally acting opioid receptor antagonists such as naloxegol, opioid withdrawal symptoms could be expected to result from the action of these drugs on peripheral opioid receptors (e.g., in the gastrointestinal tract) but not in the CNS. As noted above, gastrointestinal adverse events and hyperhidrosis were commonly reported in association with naloxegol use.

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[7] *See* AstraZeneca's briefing document for the June 2014 AADPAC meeting, Table 8.
[8] *Ibid.,* Table 9.
[9] Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiol Drug Saf 2011; 20:754-62.

Clusters of symptoms potentially related to opioid withdrawal (i.e., at least 3 symptoms occurring on the same day and not all related to the gastrointestinal system), occurred in less than 1% (1/444) of placebo-treated patients, in 1% (5/441) of patients receiving Movantik 12.5 mg, and in 3% (14/446) of patients receiving Movantik 25 mg in the two efficacy trials. Symptoms included, but were not limited to, hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning. Patients on chronic methadone for their pain condition were observed to have a higher frequency of gastrointestinal adverse reactions than patients receiving other opioids (39% vs. 26% in the Movantik 12.5 mg group; and 75% vs. 34% in the Movantik 25 mg group).

No association was seen between symptoms potentially related to opioid withdrawal and adverse cardiovascular events. No patient experiencing opioid withdrawal symptoms had a report of MACE.

Although patients suspected of having clinically important disruptions to the blood-brain barrier were not enrolled in clinical trials of Movantik, these patients may be at increased risk for opioid withdrawal or reduced analgesia.

Gastrointestinal perforation. The **Warnings and Precautions** section of product labeling will state that cases of gastrointestinal perforation have been reported with use of another peripherally acting opioid receptor antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity of the wall of the gastrointestinal tract (e.g., gastrointestinal malignancies, peritoneal metastases, peptic ulcer disease, or diverticular disease).

Abuse Potential

Naloxegol will be labeled as a Schedule II drug under the Controlled Substances Act, based on a provision in the Act that places all derivatives of opium and opioids, including thebaine, into Schedule II.

CDER's Controlled Substances Staff concluded, based on review of the nonclinical and clinical abuse-related data submitted in the NDA, that naloxegol is primarily a full mu-opioid receptor antagonist with limited CNS activity. Naloxegol therefore does not have abuse potential that is similar to controlled substances in the Act, and could be recommended for decontrol under the Act.

In an Advice Letter dated September 5, 2014, the Division informed AstraZeneca that they could request a waiver under 21 CFR 314.90 from the requirement to submit a prior approval supplement post-approval to propose revised language in the Highlights section of labeling regarding scheduling.

Pregnancy Considerations

Movantik will be classified as a Category C drug. There are no adequate and well-controlled studies with Movantik in pregnant women. The use of Movantik during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier. No effects on embryo-fetal development were observed following administration of naloxegol in pregnant rats during the period of organogenesis at doses up to 1452 times the human AUC at the maximum recommended human dose. No effects on embryo-fetal development were observed following administration of naloxegol in pregnant rabbits during the period of organogenesis at doses up to 409 times the human AUC at the maximum recommended human dose.

It is unknown whether Movantik is present in human milk; however, naloxegol is present in rat milk and is absorbed in nursing rat pups. Because of the potential for serious adverse reactions, including opioid withdrawal, in nursing infants, product labeling will reflect that a decision should be made to discontinue nursing or discontinue Movantik, taking into account the importance of the drug to the mother.

Pediatric Considerations

Pediatric Use. The **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state that the safety and effectiveness of Movantik have not been established in pediatric patients.

Required Pediatric Studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new acting ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

FDA will waive the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Based on the available literature, few pediatric patients receive round-the-clock opioids for greater than 4 weeks. There is also a lack of consensus on the use of opioids for the treatment of chronic non-cancer pain in pediatric patients.

Tradename Review

The applicant's proposed tradename "Movantik" is acceptable from both a promotional and safety perspective. The applicant was informed of this determination on November 1, 2013.

Postmarketing Requirements under 505(o)

The applicant will be required to conduct the following postmarketing study to identify an unexpected serious risk of MACE in patients with chronic non-cancer pain taking Movantik (naloxegol) for OIC:

> An observational study comparing Movantik (naloxegol) to other available therapies for the treatment of opioid induced constipation in patients with chronic non-cancer pain.

The study will be designed around a testable hypothesis to assess, with sufficient sample size and power, the risk of MACE among naloxegol users relative to comparator(s) taking into account important potential confounders including lifestyle risk factors and use of OTC medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. The study will be designed to ensure an adequate number of patients with at least 12 months of naloxegol exposure at the end of the study.

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/s/

JULIE G BEITZ
09/16/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204760
Product Name: Movantik (naloxegol)

PMR/PMC Description: 2779-1

A post-marketing, observational epidemiologic study comparing MOVANTIK (naloxegol) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to MOVANTIK (naloxegol)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among MOVANTIK (naloxegol) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the MOVANTIK (naloxegol)-exposed and comparator(s), clearly define the new user clean period, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least 12 months of MOVANTIK (naloxegol) exposure at the end of the study. .

PMR/PMC Schedule Milestones:

Final Protocol Submission:	May 2015
Study/Trial Completion:	December 2021
Final Report Submission:	December 2023
Other: interim reporting	June 2018

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected

X Theoretical concern
☐ Other

The drug's safety profile has been adequately assessed in the pre-approval program. However, a potential signal of cardiovascular risk was detected in Entereg (alvimopan), another drug in the same class of peripherally active mu opioid receptor antagonists (PAMORAs). On June 11 and 12, 2014, the Anesthetic and Analgesic Drug products Advisory Committee recommended that sponsors assess the potential for a cardiovascular risk through postmarketing requirements (PMR) observational studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

DEPI-I believes that the theoretical cardiovascular risk for naloxegol, given that it is in the same class as Entereg (alvimopan) which has a potential signal for cardiovascular risk, is adequate to indicate an unexpected serious risk related to naloxegol use. Although there was no clear increase in cardiovascular risk based on the clinical data, longer term data is necessary to achieve the study's goal, that is, to assess the unexpected serious risk of major adverse cardiac events (MACE) defined as acute myocardial infarction (AMI), stroke, and cardiovascular death in the postmarketing setting.

DEPI-I has determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risks of MACE (AMI, stroke, cardiovascular death) related to the use of naloxegol. DEPI-I therefore requests a required post-marketing safety study (PMR) under section 901 of FDAAA 2007 Title IX to identify an unexpected serious risk when available data indicates the potential for a serious risk related to the use of naloxegol.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  ☐ Accelerated Approval (subpart H/E)
  ☐ Animal Efficacy Rule
  ☐ Pediatric Research Equity Act
  X FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  ☐ Assess a known serious risk related to the use of the drug?
  ☐ Assess signals of serious risk related to the use of the drug?
  X Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

X Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A post-marketing, observational epidemiologic study comparing MOVANTIK (naloxegol) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to MOVANTIK (naloxegol)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among MOVANTIK (naloxegol) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the MOVANTIK (naloxegol)-exposed and comparator(s), clearly define the new user clean period, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least 12 months of MOVANTIK (naloxegol) exposure at the end of the study.

Required

X Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?
X Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

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/s/

MAUREEN D DEWEY
09/12/2014

JOYCE A KORVICK
09/12/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204760
Product Name: Movantik (naloxegol)

PMC Description: **2779-2**
An in vitro study to evaluate the time-dependent/mechanism-based inhibition potential of naloxegol on the hepatic CYP2C8 enzyme.

PMC Schedule Milestones:		
	Final Protocol Submission:	12/2014
	Study/Trial Completion:	03/2015
	Final Report Submission:	04/2015
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

We request the applicant to conduct an in vitro study to evaluate the time-dependent/mechanism-based inhibition potential of naloxegol on CYP2C8 enzyme, as this interaction has not been assessed in this NDA submission. Please refer to the FDA Draft Guidance for Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Please see above

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An in vitro study to evaluate the time-dependent/mechanism-based inhibition potential of naloxegol on the hepatic CYP2C8 enzyme.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
In vitro drug-drug interaction study

5. Is the PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

MAUREEN D DEWEY
09/12/2014

JOYCE A KORVICK
09/12/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 22, 2014
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	MOVANTIK (naloxegol)
Dosage Form and Route:	tablets, for oral use, C-II
Application Type/Number:	NDA 204760
Applicant:	AstraZeneca Pharmaceuticals LP

1 INTRODUCTION

On September 16, 2013, AstraZeneca Pharmaceuticals LP submitted for the Agency's review New Drug Application (NDA) 204760 for MOVANTIK (naloxegol) tablets, with the proposed indication for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on November 20, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for MOVANTIK (naloxegol) tablets.

2 MATERIAL REVIEWED

- Draft MOVANTIK (naloxegol) tablets MG received on September 16, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 11, 2014.
- Draft MOVANTIK (naloxegol) tablets Prescribing Information (PI) received on September 16, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on OPDP on August 11, 2014.
- Approved RELISTOR (methylnaltrexone bromide) Subcutaneous Injection comparator labeling dated August 23, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
08/22/2014

MEETA N PATEL
08/22/2014

BARBARA A FULLER
08/22/2014

LASHAWN M GRIFFITHS
08/22/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: August 20, 2014

To: Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 204760
OPDP Comments for draft Movantik (naloxegol) tablets, for oral use PI

OPDP has reviewed the proposed Movantik (naloxegol) tablets, for oral use PI and have no additional comments.

Thank you for the opportunity to comment on the proposed PI. Comments on the proposed Medication Guide will be submitted under separate cover in collaboration with DMPP.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
08/20/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 18, 2014
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 204760
Product Name and Strength:	Movantik (naloxegel) tablets 12.5 mg and 25 mg
Submission Date:	August 4, 2014
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
OSE RCM #:	2013-2139
DMEPA Primary Reviewer:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Kendra Worthy, PharmD

1 PURPOSE OF MEMO

DGIEP requested that we review the revised label, labeling, and full prescribing information for Movantik (naloxegel) tablets 12.5 mg and 25 mg (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised Full Prescribing Information is acceptable from a medication error perspective. The revised carton and container label and labeling is unacceptable from a medication error perspective. We note that some areas of the carton and container labels could be revised (b) (4)

[1] Calderon M. Label and Labeling Review for Movantik (NDA 204760). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 Nov. 07. 32 p. OSE RCM No.: 2013-2139.

(b) (4)

We recommend (b) (4)

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/s/

MATTHEW J BARLOW
08/18/2014

KENDRA C WORTHY
08/18/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Review of Qualitative Research Protocol for Movantik: Assessing the Content Validity of a Stool Symptom Screener in Patients with Chronic Opioid-Induced Constipation

Date:	August 14, 2014
Reviewer:	Shelly Harris, M.P.H. REMS Assessment Analyst Division of Risk Management
Team Leader:	Doris Auth, Pharm.D. Division of Risk Management
Associate Director:	Mary Willy, Ph.D. Division of Risk Management
OND Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Drug Name(s):	Movantik (naloxegol)
Therapeutic Class:	Peripherally-acting mu-opioid antagonist
Dosage and Route:	25 mg daily/oral
Application Type/Number:	NDA 204760
Applicant/sponsor:	AstraZeneca Pharmaceuticals LP
OSE RCM #:	2014-1026

1 INTRODUCTION

This review is in response to a consult request by the Division of Gastroenterology and Inborn Errors Products (DGIEP) for the Division of Risk Management (DRISK) to review the qualitative research protocol for Movantik to determine if the Baseline Laxative Response Status Questionnaire (BLSRQ) and the two week recall period are appropriate to define the laxative inadequate responder (LIC) subpopulation.

1.1 Background

Movantik, a peripherally-acting mu-opioid receptor antagonist (PAMORA) and pegylated derivative of the mu-opioid antagonist naloxone, is proposed for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. Movantik primarily exerts its pharmacologic activity in the gastrointestinal tract, to decrease opioid-induced constipation without affecting opioid-mediated analgesia in the central nervous system (CNS). As a pure (full) antagonist at mu-opioid receptors (highest binding affinity), antagonist at delta-opioid receptors and weak partial agonist at kappa-opioid receptors, Movantik's pharmacologic profile is unique in the class of PAMORAs.

The laxative inadequate responder (LIR) subpopulation category was designed to represent conventional laxative users who continued to have moderate to very severe OIC symptoms at study entry. To define these patients, the Applicant developed the BLRSQ that was to be administered by the investigator at screening. A patient was classified as a LIR during the screening period based on the results of the BLRSQ. For this classification, patients had to report 1) a minimum frequency of laxative use of at least four times over a two-week period and 2) reported at least moderate OIC symptoms over the previous two weeks. There is currently no accepted method of defining patients with an inadequate response to laxatives; therefore the Applicant developed the BLRSQ in conjunction with a board of external experts. DGIEP requested a consult to determine if the laxative inadequate responder (LIR) subgroup was appropriately defined by the Applicant using the BLSRQ.

The Applicant reports that during a January 24, 2012 meeting, FDA recommended additional qualitative research to gain a better understanding of the Stool Symptom Screener items (a subset of questions in the BLRSQ), the two-week recall period for the Stool Symptom Screener, the response options as well as the two-week recall period for laxative use, and a stratified analysis of the LIR and non-LIR groups to assess if this understanding differed by patient groups.

In the Late-Cycle Meeting Background Package sent the Applicant on June 6, 2014, DGIEP provided the following comments to the Applicant:

We have the following comments about the labeling language for your first-ranked secondary endpoint (assessed in a subgroup identified using an investigator-administered questionnaire):

a) We are currently reviewing the qualitative study report/protocol (for the investigator-administered questionnaire), and will determine if it is acceptable to report results in the subgroup identified using this instrument in the labeling.

b) Even if the instrument is acceptable, we do not agree with the term [redacted] We propose describing the subgroup as follows: [redacted] patients (identified using an investigator-administered questionnaire) [redacted] prior to enrollment, had [redacted] reported [redacted] these laxatives at least 4 out of the past 14 days [redacted]."

2 REVIEW MATERIALS AND METHODS

2.1 Material Reviewed

- August 6, 2013, Clinical Overview: Naloxegol for the Treatment of Opioid Induced Constipation (OIC)
- September 16, 2013, Assessing the Content Validity of a Stool Symptom Screener in Patients with Chronic Opioid-Induced Constipation: Exploratory Study Report
- September 2013, Draft Highlights of Prescribing Information for Movantik
- June 6, 2014, Late-Cycle Meeting Background Package
- June 10, 2014, Risk Evaluation and Mitigation Strategy (REMS) Review (N. Booker)
- July 17, 2014, Response to Information Request Regarding Bowel Movements, Laxative Use, and Laxative-inadequate Response Status

2.2 Review Methods

A health science evaluator reviewed the sponsor's Qualitative Research Study Report and appendices.

3 RESULTS OF REVIEW

3.1 Study Objectives and Key Findings

The objective of this qualitative study was to evaluate the content validity of the Stool Symptom Screener, an interviewer-administered measure that assesses the severity of four constipation symptoms, and to assess participant's perception of a two-week recall period for bowel movements, laxative use, and constipation symptoms. The study also assessed if there were differences between two patient sub-groups, laxative inadequate responders (LIRs) defined as OIC patients who take laxatives at least four times over a two-week period and report at least moderate or greater severity on at least one item of the Stool Symptom Screener, and non-LIRs defined as patients who take laxatives with less frequency or not at all and report a range of severity on the Stool Symptom Screener items.

In the initial protocol for the study, patients were classified as LIR or laxative adequate responders (LAR) based on how satisfied they were with the amount of relief received from the laxative used. In the revised protocol, the criteria were changed to LIR and non-LIR.

3.2 Key Findings

Key findings as listed in the report included:

- The Stool Symptom Screener items were well-understood and considered relevant by participants
- Most participants reported no difficulties with a two-week recall of bowel movements, laxative use, and constipation symptoms.
- There was no difference found between LIRs and non-LIRs in terms of understanding of the Stool Symptom Screener and their response options, and reported lack of difficulty with two-week recall of bowel movements, laxative use and constipation symptoms. The only difference between the groups was the frequency and regularity by which they take laxatives, ranging from not at all to at least four times in the past two weeks.

4 CONCLUSION AND RECOMMENDATION

The reviewer has the following conclusions and recommendations:

1. The qualitative research study report focused on the Stool Symptom Screener (four constipation symptom questions that are a part of the BLSRQ) and not the entire BLSRQ. The reviewer is not able to assess if the BLSRQ is appropriate for defining the laxative inadequate responder (LIR) population since only the content validity of the four questions was assessed in the qualitative exploratory study report. The entire instrument for the BLSRQ was not assessed with this qualitative research study.

2. The reviewer is unable to determine if the sub-population is appropriately categorized as LIRs (laxative inadequate responders) from the qualitative research report. The criteria used to determine classification into the LIR group was taking laxatives at least four times in a two week period and rating one of four constipation symptoms as moderate, severe, or very severe. There is no additional data that suggests that this is an inadequate response to laxatives.

   In addition, patients in the non-LIR group (patients who did not take laxatives in the past two weeks or patients that took laxatives less than four times in the past two weeks) could be considered inadequate responders to laxatives. The majority of patients in the non-LIR group were classified as laxative unknown responders (LUR). In additional clinical studies (Studies 4 and 5-Intent to treat analysis set), patients in the LUR group that did not currently take laxatives were asked why they did not use them. Despite low response rates, 31% (Study 4) and 30% (Study 5) of participants stated it was because of inadequate relief of constipation when using laxatives.

   In the initial protocol, participants were classified as laxative inadequate responders (LIR) or laxative adequate responders (LAR), based on the response to the question:

a. Were you satisfied with the amount of symptom relief provided from the laxative(s)?
b. □ Yes (classify as laxative adequate responder)
c. □ No (classify as laxative inadequate responder)

In the revised protocol, the criteria were changed to LIR and non-LIR based on the definitions above. Participants were still asked if they were satisfied with the amount of symptom relief they received from the laxative. Therefore, participants classified as LIR could still report satisfaction with the symptom relief received from the laxative.

3. Overall, participants stated that they would be able to remember the specific constipation symptoms included in the Stool Symptom Screener, over a two-week time period. Participants stated that the two-week time period was reasonable to assess number of bowel movements and number of laxatives used. In the interview guide, participants were also asked what time frame would be best for them to remember constipation symptoms, number of bowel movements, and number of laxatives used. In a response to Information Request, the Sponsor reported that the majority of participants (85% or more) stated that two weeks was a reasonable time frame to remember these items.

4. We are concerned that the two-week recall period may be too long in terms of the entire BLSRQ. The Stool Symptom Screener is adapted from the Patient Assessment of Constipation Symptoms (PAC-SYM), a 12-item questionnaire developed to measure patient's experience of symptoms and symptom severity in constipation over time. The PAC-SYM uses a two-week recall period but this instrument only focuses on symptoms and severity of symptoms. Patients are not required to report items such as number of times symptoms occurred, number of bowel movements, or number of times laxatives are used. Other instruments that have been validated in OIC populations use shorter recall periods ranging from daily to the prior week[1234]. One study reported significant differences between data collected from questionnaires and data collected from a daily diary about bowel habits based on the patient's recall even after only a few days[5]. Another

[1] Constipation Assessment Scales (CAS) (prior week); Bowel Function Index (1 week); Bowel Function Diary (daily recording of the number and type of bowel movements)

[2] Coffin B. and Causse C. Constipation assessment scales in adults: a literature review including the new Bowel Function Index (2011) Expert Reviews. Gastroenterology. Hepatology. 5(5), 601-613.

[3] Camilleri et al. (2010) Validation of a Bowel Function Diary for Assessing Opioid-Induced Constipation. The American Journal of Gastroenterology. 106; 497-506.

[4] Ducrott, P. and Causse, C. (2012) The Bowel Function Index: A new validated scale for assessing opioid-induced constipation. Current Medical Research and Opinion. 28 (3); 457-466.

[5] Bellini et al. (2010) The daily diary and the questionnaire are not equivalent for the evaluation of bowel habits. Digestive and Liver Disease 42; 99-102

study reported that symptoms for IBS-C (constipation-predominant IBS) would best be assessed in a 7-day time period[6].

5. DRISK is not the appropriate group to determine if it is acceptable to report results in the labeling.

[6] Norquist et al. (2012). Choice of recall period for patient-reported outcome (PRO) measures: criteria for consideration. Quality of Life Research. 21 (6); 1013-1020.

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/s/

SHELLY L HARRIS
08/14/2014

MARY E WILLY
08/14/2014
I concur

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 26, 2014

TO: Donna Griebel, M.D.
Director,
Division of Gastroenterology and Inborn Errors
Office of Drug Evaluation III

FROM: Chase H. Bourke, Ph.D.
Pharmacologist, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Charles Bonapace, Pharm.D.
Acting Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR covering NDA 204-760, Naloxegol oxalate, sponsored by AstraZeneca Pharmaceuticals LP, USA

Table of Contents

1. Summary

At the request of the Division of Gastroenterology and Inborn Errors (DGIEP), the Division of Bioequivalence and GLP Compliance (DBGLPC) inspected the following study:

D3820C00018: "A Phase I, randomized, open-label, three-way cross-over study in healthy volunteers to demonstrate the bioequivalence of the naloxegol 25 mg commercial and Phase III formulations and to assess the effect of food administration on the pharmacokinetics of the commercial formulation"

Inspection of the clinical portion of the study was conducted at the following site:

Quintiles Drug Research Unit, London, UK

Inspection of the analytical portion of the study was conducted at the following site:

(b) (4)

2. Recommendations

Following evaluation of the inspectional findings and the analytical site's response to Form FDA 483, these DBGLPC reviewers recommend the following:

- The data generated by Quintiles Drug Research Unit (clinical site) and (b) (4) (analytical site) were found to be reliable. Therefore, these reviewers recommend that data generated at these sites should be accepted for Agency review.

3. Inspectional Findings by Site

3.1. Quintiles Drug Research Unit, London, UK

Following the inspection of the clinical site by Laura E. Garcia (ORA, FDA San Juan District Office) during March 31 - April 4, 2014 at Quintiles Drug Research Unit, London, UK, no Form FDA 483 was issued. However, the investigator noticed that the subjects' food menu contained flavonoid-rich foods such as berries, apples, and peas. The study protocol states that flavonoid-rich foods must be avoided. The site reported the issue as a note to file instead of a protocol deviation. The

issue was communicated to management as a discussion item during the close-out meeting.

In the opinion of these reviewers, consumption of the specific flavonoid-rich foods is unlikely to have an effect on the study outcome. However, naloxegol is a substrate of CYP3A4; thus, consumption of fruits which inhibit CYP3A4, such as grapefruit and star fruit (although not on the food menu), could have affected the metabolism of naloxegol and impacted the study outcome.

3.2. (b) (4)

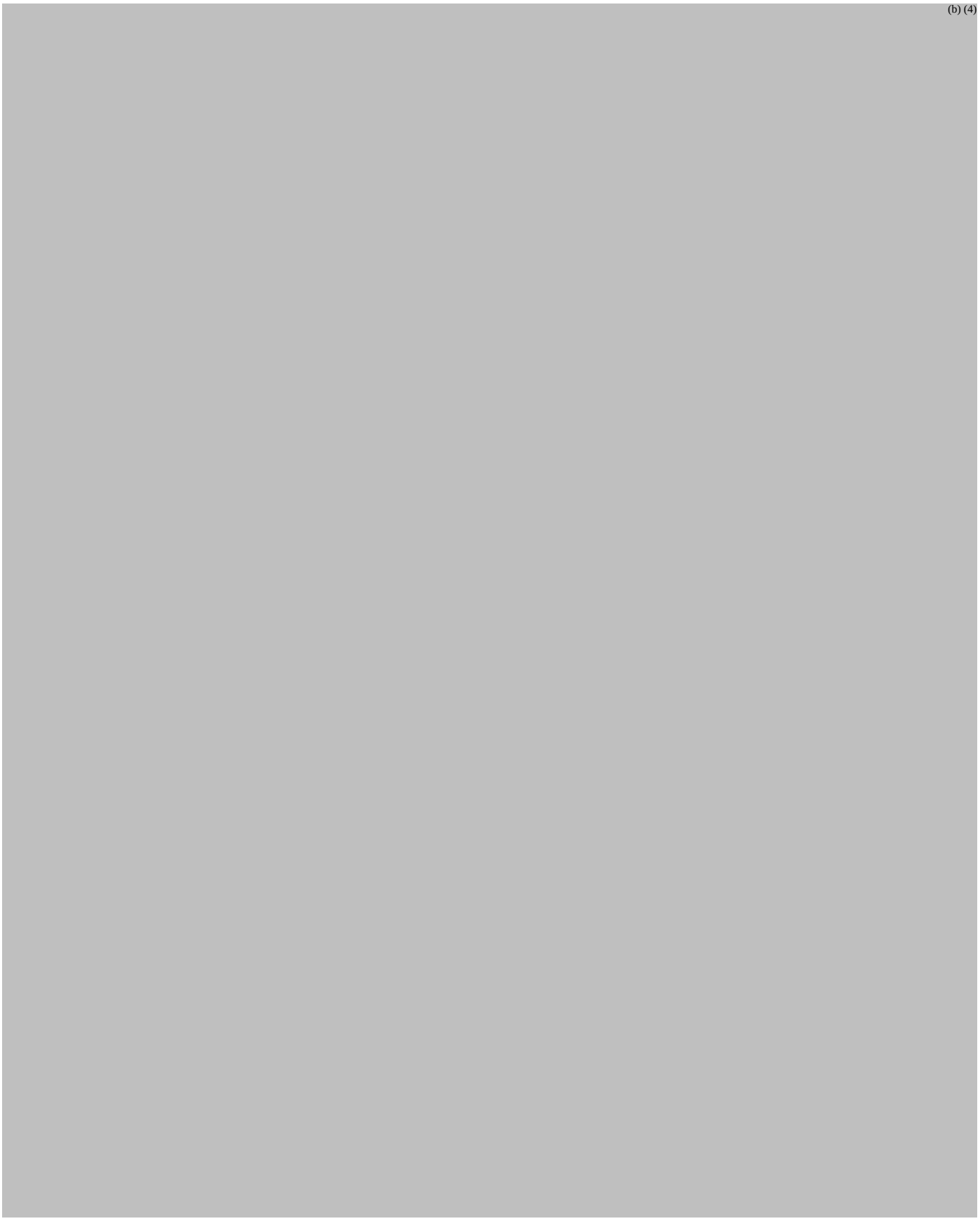
The inspection of the analytical portion of the study was conducted (b) (4)

Following the inspection of the analytical site, Form FDA 483 was issued (**Attachment 5.1**). The response to Form FDA 483 was received on March 11, 2014 (**Attachment 5.2**).

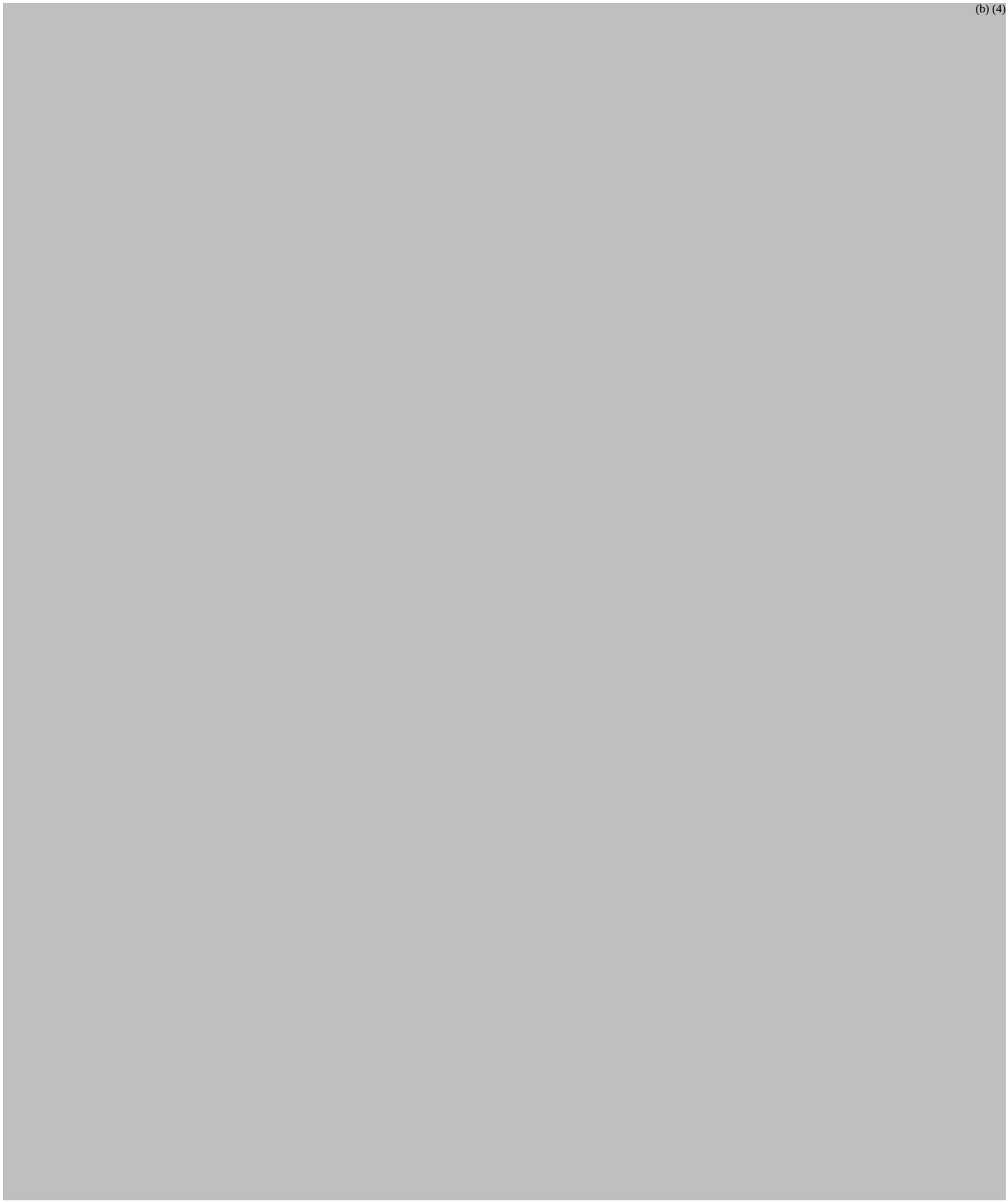
The Form FDA 483 observations, the firm's response to the Form FDA 483 observations, and our evaluation follow.

(b) (4)

(b) (4)



(b) (4)



(b) (4)

4. Final Site Classifications

NAI – Quintiles Drug Research Unit, London, UK
FEI: 3008488237

VAI – (b) (4)
FEI: (b) (4)

cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Bonapace/Dasgupta/Bourke/Dejernett/
OSI/DBGLPC/Fenty-Stewart
OND/ODEIII/DGIEP/Scherer/Griebel
OPS/ONDQA/Riviere
ORA/ (b) (4)
ORA/ (b) (4)

Draft: CHB 06/24/2014
Edit: CRB 06/26/2014
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Quintiles Drug Research Unit, London, UK/NDA 204-760_Naloxegol oxalate
Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites (b) (4) /NDA 204-760_Naloxegol oxalate
OSI FiLE# BE6584; O:\BE\assigns\bio204760 ast nal.doc
FACTS: 8742013

5. Attachments

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/s/

CHASE H BOURKE
06/27/2014

CHARLES R BONAPACE
06/27/2014

WILLIAM H TAYLOR
06/27/2014

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: June 2, 2014

To: Donna Griebel, M.D., Director
Division of Gastroenterology and Inborn Error Products

Through: Silvia Calderon, Ph.D., Team Leader
Michael Klein, Ph.D., Director
Controlled Substance Staff (CSS)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Evaluation of Abuse-Related Studies
Naloxegol (12.5 and 25 mg tablets)
NDA 204,760
Indication: Treatment of Opioid-Induced Constipation
Sponsor: Astra Zeneca Pharmaceuticals
PDUFA Goal Date: September 16, 2014

Materials reviewed: Abuse-related preclinical and clinical data in NDA (submission #000, September 16, 2013)

Table of Contents

1. Background

This memorandum responds to a consult request to CSS by the Division of Gastroenterology and Inborn Error Products (DGIEP) to evaluate abuse-related preclinical and clinical data submitted in NDA 205,760 for naloxegol.

Naloxegol oxalate (NKTR-118) is a new molecular entity with mu, kappa and delta opioid antagonist properties. Naloxegol is covalently bonded to a polyethylene glycol (PEG) side-chain, which prevents its passage across the blood brain barrier. The Sponsor states that the chemistry restricts naloxegol's site of action to the blockade of peripheral μ-opioid receptors. Thus, the Sponsor characterizes naloxegol as "predominantly peripherally-acting mu opioid antagonist". Notably, PEGylation does not prevent interaction of naloxegol with peripheral mu opioid receptors, which allows for the compound to act as an antagonist at these sites.

Naloxegol is derived from the mu opioid antagonist, naloxone, and is proposed for the treatment of opioid-induced constipation (OIC), which occurs through activation of mu opioid receptors in the gastrointestinal (GI) tract. Although naloxone and other opioid antagonists can reduce this AE, they can simultaneously block the intended therapeutic effects of opioids, which rely on central nervous system activity. Through PEG conjugation of naloxone, creating naloxegol, the opioid antagonism is restricted to the periphery where it can directly block OIC without compromising analgesia.

The Sponsor for this drug is Astra Zeneca Pharmaceuticals, under a license from Nektar Therapeutics. Naloxegol is not currently marketed in any country, although clinical trials are being conducted with the drug in 19 countries.

Naloxegol is currently a Schedule II drug under the Controlled Substances Act (CSA), based on a provision in the CSA that places all derivatives of opium and opioids, including thebaine, into Schedule II. Although naloxone (an unscheduled compound under the CSA) is a chemical intermediate of naloxegol, naloxone itself is a derivative of thebaine. Any opium derivative may be rescheduled or decontrolled if sufficient evidence exists to support this action. In 1971, naloxone was decontrolled under the CSA when data demonstrated that it was an opioid antagonist.

(b) (4)

(b) (4)

Our final determination of the abuse potential of naloxegol is found in the present document, which details our review of all abuse-related data (nonclinical and clinical) submitted in the NDA.

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 204,760 for naloxegol (a Schedule II substance under the CSA) and concludes that it is primarily a full opioid antagonist with limited CNS activity. As such, naloxegol does not have abuse potential that is similar to controlled substances in the CSA. These conclusions are based on the following:

- Naloxegol has limited central nervous system activity, but its primary activity is interaction with peripheral mu-opioid receptors. The peripheral activity of naloxegol is due to its derivation through the attachment of a seven unit ethylene oxide side chain (also known as a polyethylene oxide or polyethylene glycol (PEG) side chain) (b) (4) The PEG side chain restricts penetration of naloxegol across the blood brain barrier, limiting its action on the central nervous system.

- Distribution studies show that naloxegol has little brain and spinal cord penetration. Low central activity suggests that a drug has little possibility for abuse potential.

- Naloxegol acts primarily as a full mu opioid antagonist. In receptor binding studies with 327 sites, naloxegol showed high affinity for mu opioid (7-34 nM), kappa opioid (9-187 nM) and delta opioid (54-203 nM) receptors, but no other sites. Second messenger studies that evaluated [^{35}S]GTPγS binding at opioid receptors showed that naloxegol is a full mu and delta opioid antagonist, but has no mu opioid agonist activity and limited partial kappa opioid agonist activity.

- Naloxegol does not produce opioid-like behaviors. In toxicological studies, naloxegol did not produce general behavioral changes that were different from those induced by vehicle in a 28-day rat study and in 14-day and 28-day beagle studies. Similarly, in the Irwin test (a dedicated general behavioral test), naloxegol did not produce alterations in behavior compared to vehicle.

- Naloxegol does not produce opioid-like analgesic responses. In two tests of analgesia (grid stimulation test and a hotplate test), naloxegol did not produce any behavioral changes different from those produced by vehicle. In contrast, morphine produced expected opioid-like analgesia in these tests.

- Naloxegol does not produce an opioid-like interoceptive cue. In a drug discrimination test with animals trained to discriminate morphine from saline, naloxegol by itself generalized to saline. When naloxegol was given as a pretreatment prior to morphine administration, naloxegol blocked the ability of morphine to induce a response on the morphine-associated lever, demonstrating its ability to act centrally as an opioid antagonist.

- Naloxegol does not produce opioid-like rewarding properties. In animals trained to self-administer cocaine, exposure to naloxegol produced the same level of self-administration as that of saline. In contrast, exposure to morphine produced the expected high level of self-administration compared to saline, showing that it has rewarding properties.

- Chronic administration of naloxegol does not produce physical dependence. In animals treated with naloxegol for 14-30 days, there were no behavioral changes upon drug discontinuation compared to saline. In contrast, morphine produced a classic opioid withdrawal syndrome following chronic administration and subsequent discontinuation of the drug.

- Human pharmacokinetic studies show that naloxegol is rapidly absorbed (Tmax = 1.5-2.0 hours), with a half-life of 7-9 hours. The majority of naloxegol (81%) is eliminated intact in urine. There are no active metabolites.

- Naloxegol does not produce abuse-related adverse events in healthy individuals. In 14 Phase 1 pharmacokinetic, safety and tolerability studies in which healthy individuals received naloxegol at doses ranging from 8 to 1000 mg, no adverse events representative of any euphoria-related signs or symptoms were reported. Few individuals in these studies experienced any nervous system or psychiatric disorders, which were generally limited to dizziness (0-25%), headache (0-25%), and paresthesia (0-13%).

- It is not possible to determine if naloxegol produces abuse-related AEs from efficacy studies conducted in patients. All patients in the Phase 2/3 efficacy and safety studies received opioids for pain management and then received naloxegol to determine if naloxegol could prevent opioid-induced constipation. Since opioids produce abuse-related AEs, it is not possible to attribute abuse-related AEs to naloxegol administration.

- Naloxegol does penetrate the human brain sufficiently to produce withdrawal symptoms in patients taking opioids for analgesia. In Phase 2/3 studies, the overall incidence of naloxegol-induced withdrawal was low, but slightly higher than that of placebo (2% vs. 1%, respectively). There was a greater incidence of opioid withdrawal in patients receiving the higher 25 mg dose of naloxegol (14/446=3%) compared to those receiving the lower 12.5 mg dose of naloxegol (5/441=1%). It is unclear from the data whether the withdrawal signs in humans are mediated through central or peripheral mechanisms, but the animal drug discrimination data show that naloxegol can antagonize a centrally-mediated behavioral response.

3. Recommendations

CSS recommends that:

- The Sponsor-proposed text for Section 9.0 (Drug Abuse and Dependence) be accepted.
- Naloxegol be recommended for decontrol under the Controlled Substances Act.

4. Discussion

A. Chemistry of Naloxegol

Naloxegol oxalate ((5α,6α)-17-allyl-6-(2,5,8,11,14,17,20-heptaoxadocosan-22-yloxy)-4,5-epoxymorphinan-3,14-diol oxalate) is a white to off-white (b) (4) powder and is highly soluble in aqueous media (with solubilities exceeding 50 mg/mL) over the pH range of 1 to 7.5. Naloxegol oxalate is also soluble in water, dilute acids and organic solvents. The Phase 3 clinical program was conducted using a tablet formulation of naloxegol as free base. Naloxegol free base is a viscous liquid and is soluble in a variety of media, such as water, dilute acids and organic solvents.

Synthesis of naloxegol involves (b) (4) (see B.1.a. Brain Permeability Study (below) for information regarding the selection of 7 PEG units for final naloxegol formulation).

B. Pharmacology of Naloxegol

1. Preclinical Pharmacokinetics

a. Brain Permeability Study (Study # RD00001811.00)

The effect of PEG length on the rate of brain uptake was investigated with a series of PEG-naloxone conjugates. This study used an *in situ* brain perfusion technique that utilizes intact rat brain to determine drug permeation across the blood-brain barrier under normal physiological conditions. Naloxone and naloxegol were both tested in the perfusate solutions.

The opioid antagonist, naloxone, readily entered the brain at a rate with mean brain uptake rate of 60 pmole/gm brain/sec. (b) (4)

The Sponsor selected (b) (4) for development, based on these data and results of in vitro and in vivo pharmacological experiments.

b. Tissue Distribution Study (Study #192601)

There was differential absorption and distribution of oral naloxegol (50 mg/kg) between male and female rats. For female rats, Tmax in the majority of tissues was observed at 0.5 hours post-dose, while Tmax was at 1 hour post-dose for male rats. Tissue concentrations were higher in the female rats than in the male rats at the same timepoints. The tissues with highest radioactivity were liver and kidney, with high levels in glandular tissues (adrenals, Harderian, pituitary, preputial, salivary and thyroid glands) and pigmented tissues potentially due to an affinity with the melanin proteins. There was poor distribution of radioactivity to the tissues of the central nervous system (CNS) (brain and spinal cord).

In both sexes, elimination of radioactivity was rapid, with the majority of tissues having undetectable levels by the 24 hour post-dose timepoint.

2. Receptor Binding and Second Messenger System Studies

a. Receptor Binding Studies (Study #1012SY, PAIN.000-229-304 and RD00001536.00)

Naloxegol was tested at 10 μM for affinity at a total of 327 receptor sites, channels and enzymes. In these tests, naloxegol has high affinity for human cloned mu opioid (7-34 nM), kappa opioid (9-187 nM) and delta opioid (54-203 nM) receptors. Comparatively, the opioid antagonist, naloxone, has higher affinity at mu (2 nM), kappa (4 nM) and delta (10 nM) opioid receptors. Another opioid antagonist, methylnaltrexone, has similar or higher affinity at mu receptors (7-9 nM), similar affinity at kappa receptors (11-130 nM) and lower affinity at delta receptors (239-1900 nM).

In contrast to the high affinity for opioid receptors, naloxegol does not have significant affinity (> 50% inhibition) for other CNS sites, including: dopamine, serotonin, glutamate (NMDA, PCP), GABA (benzodiazepine, GABA, GABA channel), sigma, acetylcholine (muscarinic and nicotinic subtypes), norepinephrine ($alpha_1$, $alpha_2$, $beta_1$, $beta_2$), cannabinoid (CB-1, CB-2), histamine (H1 and H2 subtypes), and monoamine transporters (dopamine, serotonin and norepinephrine). Additionally, naloxegol does not have significant affinity for the calcium channel or the potassium channel.

b. Second Messenger System Studies (Study # hMOR GTP NKTR-118, PAIN.000-229-304 and 1022SY)

The activity of naloxegol at mu, kappa and delta opioid receptors was assessed using [^{35}S]GTPγS functional assays to determine whether naloxegol is an agonist or antagonist at these receptors. This assay measures binding of [^{35}S]GTPγS on the human embryonic kidney 293 (HEK-293S) cell line that stably expresses mu, kappa and delta opioid receptors. Naloxegol was tested over 12 concentrations in a single, half-log dilution series up to a maximum of 100 μM.

When naloxegol and naloxone were tested alone, neither of them displayed any significant effect on [^{35}S]GTPγS binding associated with the mu opioid receptor. However, both naloxegol and naloxone inhibited the mu agonist activity of DAMGO and morphine activity with a mean relative Imax of 86% for both agonists following pretreatment with both antagonists. These two tests suggest naloxegol is a full mu opioid antagonist.

Naloxegol alone induced a concentration-dependent increase in the binding of [^{35}S]GTPγS in the kappa opioid receptor functional assay up to 39% of the binding produced by the positive control kappa agonist, U-69593. Naloxegol also inhibited the response binding produced by U-69593, but maximum inhibition was 68%. This suggests naloxegol is a weak partial kappa opioid agonist, with antagonist effects against a kappa opioid agonist.

Naloxegol alone had no effect on the binding of [^{35}S]GTPγS in the delta opioid receptor functional assay. However, naloxegol decreased the response to the reference delta agonist, DPDPE, in a concentration-dependent manner with an IC50 value of 0.866μM, consistent with antagonism at this receptor. This suggests naloxegol is a full delta opioid antagonist.

3. Preclinical Behavioral Studies

a. Behavioral Observations in Rat and Beagle Toxicology Studies (Study #LS-2007-011, LS-2005-031, LS-2007-012)

Three toxicology studies were conducted in which behavior was monitored following naloxegol administration: one study with rats for 28 days and two studies with beagle dogs for 14 and 28 days (with recovery). The doses selected were based on evaluating a full toxicological range of doses. These studies show that naloxegol produces only limited behavioral changes, either during drug administration or following drug discontinuation. These data suggest that naloxegol is not centrally active and does not produce physical dependence.

Rat Study (28 Day)

Male and female rats (n =10/group) received oral doses of vehicle or naloxegol (50, 150 and 500 mg/kg) for 28 days. During the treatment period when rats were observed on a daily basis, there were no differences in clinical signs, eye afflictions, functional (neurological) observations, body weights or food consumption between rats treated with vehicle or with naloxegol at any dose.

Beagle Dog Study (14 Day)

Male and female beagle dogs (n =3/group) received oral doses of vehicle or naloxegol (25, 75, or 200 mg/kg) for 14 days. Animals were observed daily for changes in clinical signs and body weight between rats treated with vehicle or with naloxegol at any dose. During drug administration, soft stool and/or diarrhea were observed at all three naloxegol doses in males, with increasing frequency. Two male dogs that received 25 mg/kg naloxegol were observed with emesis on Day 1. Female dogs exhibited occasional diarrhea, soft stool, and emesis at the 75 and 200 mg/kg naloxegol doses. The study report states these changes are expected and

similar to those produced by naloxone (no data provided). There were no significant changes in body weight compared to vehicle.

Beagle Dog Study (28 Day Plus Recovery)

Male and female beagle dogs (n =20/group) received oral doses of vehicle or naloxegol 50, 150 and 500 mg/kg) for 28 days, followed by a 14 day recovery period (n = 2/sex/ group). During the treatment period when rats were observed on a daily basis, there were no differences in clinical signs, eye afflictions, functional (neurological) observations, body weights or food consumption between rats treated with vehicle or with naloxegol at any dose. However, during administration of the 150 mg/kg dose, there was excessive salivation and/or emesis. Administration of the 500 mg/kg dose also produced excessive salivation, retching and/or emesis, and a slight reduction in body weight gain. Despite these behavioral changes during drug administration, there were no behavioral observations during the recovery period following discontinuation of any dose of naloxegol, compared to vehicle.

b. Irwin Screen with Naloxegol (Study #SP-D3820-SPG-2707)

Male Wistar rats received a single oral dose of naloxegol at 100, 300 or 1000 mg/kg prior to observation using the Irwin screen. The Sponsor states that drug doses were selected to cover "the expected therapeutic range in humans and multiples thereof". The oral route was selected because that is the proposed therapeutic route.

The animals were observed using a standard Irwin screen protocol at 15 and 30 minutes, and 1, 2, 6 and 24 hours after dosing. Observations included: occurrence of vocalization, stereotypies, aggressiveness, abnormal gait, Straub tail, tremor, twitches, convulsions, body posture, sedation, catalepsy, ptosis, exophthalmos, salivation, lacrimation, piloerection, abnormal respiration, defecation, urination and death; increase or decrease of spontaneous activity, touch response, body tonus and pupil size; increase of sniffing, grooming, scratching and rearing; decreased pinna reflex, traction response and grip strength and any additional observed behaviors. Behaviors were rated on a scale of 0 (none) to 3 (high). None of the doses of naloxegol altered observed behaviors over a 24 hour period, as would be expected from an opioid antagonist. However, there was a decrease in body weight following the 1000 mg/kg dose.

c. Evaluation of Ability of Naloxegol to Induce Analgesia (Study # SP-D3820-SPG-2959, SP-D3820-SPG-2995, SP-SPG-2958 and RD00001766.00)

Rodents were tested in two models of analgesia to determine if naloxegol had analgesic activity or the ability to block the analgesic effects of morphine.

Using the grid stimulation analgesia model in mice, subcutaneous morphine (0.96, 3.2, 9.6 and 32.1 mg/kg) caused a dose dependent reduction of vocalization, ranging from 5% at the lowest dose to 86% at the highest dose. In contrast, oral naloxegol (30, 100, 300 and 1000 mg/kg) induced a small increase (11-15%) in latency to vocalization from a 60 and 120 minute

pretreatment time (respectively). This result was not statistically different from vehicle, suggesting that naloxegol does not have analgesic activity.

Using a hotplate model of analgesia in rats, morphine (5 mg/kg, i.v.) increased the latency of withdrawal from the heat source, demonstrating analgesia. Animals where then given oral doses of naloxegol (10, 30, and 90 mg/kg), naloxone (1, 3, 10, and 30 mg/kg), or saline and tested again 30 minutes later. As expected, the opioid antagonist, naloxone, produced a complete reversal of analgesia at 10 and 30 mg/kg, and partial reversal of analgesia at 1 mg/kg. In contrast, naloxegol at doses of 10 and 30 mg/kg did not produce any significant reversal of analgesia, while the 90 mg/kg dose produced only partial reversal of analgesia.

d. Drug Discrimination Studies

The drug discrimination study in rats is a pivotal animal behavioral study for abuse potential assessment and is reviewed in detail. The Sponsor conducted four drug discrimination studies in which naloxegol was tested either for its ability to generalize to morphine (one study) or for its ability to block the morphine cue in rats trained to discriminate morphine from saline (three studies).

Drug Discrimination Study in Rats -- Naloxegol Generalization to Morphine Cue (Study # SP-D3820-SPG-2736)

Study Design

Rats (n = 6) were trained to discriminate the mu opioid agonist, morphine (3.22 mg/kg, s.c., 30 min pretreatment) from no drug (no injection given). The schedule of reinforcement was started at a fixed ratio (FR) of 1 for food reinforcement and increased to FR10. Morphine training sessions and no-drug training sessions were conducted on average three times in a 14 day period during the test phase. When animals achieved FR10 performance, they were switched to a double alternation schedule in which pairs of two consecutive drug sessions (D) and two consecutive no drug (N) sessions alternate (e.g., D, D, N, N, D, D, N, N, etc.).

Once animals responded with 90% accuracy on the appropriate morphine or no drug lever, challenge sessions began. Rats received challenge doses of naloxegol (30, 100, 300 and 1000 mg/kg, by oral gavage, 30 minutes pretreatment time) approximately four times in a 14 day period during the test phase. All rats were tested at all doses once, with two days washout inbetween drug sessions. (PK for Tmax and human plasma)

During testing, animals were run according to a single alternation schedule and test sessions (T) interspersed between the training sessions (D, N) (e.g., D, T, N, D, T, N, T, D, N, T, etc.). Unlike most drug discrimination studies, lever-pressing produced food reward during test sessions. If training day performance fell below criteria for any rat on a single training day, the upcoming test was postponed for that rat and it was tested again only after completing two consecutive training sessions during which criteria were met.

The doses and route of administration of naloxegol were justified on the basis of their ability to "cover the expected therapeutic range in humans and multiples thereof". The oral route of administration was chosen because it is the proposed therapeutic route of administration.

Results

Naloxegol (30 to 1000 mg/kg) produced a mean maximum percentage of 15.67 morphine appropriate responding. Further, naloxegol reduced the rate of responding in a dose dependent fashion from a mean of 1.79 responses per second after vehicle alone to a mean of 1.0 response per second after 1000 mg/kg, corresponding to a decrease to 56% of vehicle alone rates.

Conclusions

Naloxegol produced less than 20% morphine appropriate responding at any dose, which meets criteria for a no-drug like interoceptive cue. Thus, naloxegol did not produce morphine-like discriminative effects.

Drug Discrimination Studies in Rats -- Naloxegol Antagonism of Morphine Cue (Study # SP-D3820-SPG-2966, SP-D3820-SPG-2924 and SP-D3820-SPG-2819)

Study Designs

Three drug discrimination studies were conducted that tested the ability of a range of naloxegol doses to block the discriminative cue produced by morphine in rats trained to discriminate morphine from vehicle.

In all studies, rats were trained to discriminate morphine (3.2 mg/kg, s.c., 30 min pretreatment) from vehicle on a fixed ratio 10 (FR10) schedule of reinforcement for food. After discrimination was stable, rats were challenged with morphine (0.32, 0.96, 1.8, 3.2, 5.6 or 9.6 mg/kg, s.c.) in combination with an oral dose of naloxegol (3, 30 or 300 mg/kg).

The doses of naloxegol were selected based on previous studies suggesting these doses can enter the CNS. The oral route is the proposed therapeutic route of administration.

Results

When 3 mg/kg oral naloxegol was given as a pretreatment prior to administration of morphine, it prevented the generalization of morphine to the morphine cue at 0.96 mg/kg morphine (11%), partial generalization at 0.32 and 1.8 mg/kg morphine (25 and 40%, respectively) and full generalization at 3.2 and 5.6 mg/kg morphine (100% and 99%, respectively).

When 30 mg/kg oral naloxegol was given as a pretreatment prior to administration of morphine, it prevented the generalization of morphine to the morphine cue at 0.32 and 0.96 mg/kg morphine (12% and 13%, respectively), partial generalization at 3.2, 5.6 and 9.6 mg/kg morphine (37, 62 and 75%, respectively)

When 300 mg/kg oral naloxegol was given as a pretreatment prior to administration of morphine, it prevented the generalization of morphine to the morphine cue at 0.96, 3.2, 5.6 mg/kg morphine (21%, 26% and 28%, respectively) and no generalization at 9.6 mg/kg morphine (9%).

Conclusion

Naloxegol caused a reversal of the discriminative effects of morphine, demonstrating the ability of naloxegol to penetrate the CNS and act as an antagonist at central μ-opioid receptors.

e. Self-Administration Studies

The self-administration study in rats is a pivotal animal behavioral study for abuse potential assessment and is reviewed in detail. The Sponsor conducted two self-administration drug studies in which naloxegol and morphine were tested in separate studies for their ability to induce self-administration as a measure of the rewarding property of the drug.

Naloxegol Self-Administration Study in Rats (Study #SP- D3820-SPG-2817)

Study Design

Male rats (n = 8) were trained to self-administer cocaine (0.5 mg/kg/infusion, i.v.), using a schedule of reinforcement that increased from fixed ratio 1 (FR1) to FR5 over time. Stable self-administration behavior was defined as 3 consecutive sessions with <15% intersession variability in delivered infusions and >10 delivered infusions in each session. After stable cocaine self-administration was established, rats underwent an extinction procedure by substituting vehicle for cocaine. When extinction criteria were met (3 consecutive sessions of ≤10 delivered infusions), challenge sessions with naloxegol were initiated, at doses of 1, 3, 10 and 30 mg/kg/infusion. These doses are justified on the basis of "earlier results in other test models."

Results

The number of naloxegol infusions that were self-administered was statistically similar to those produced by vehicle alone at all doses tested.

Conclusion

Naloxegol was not self-administered and does not have rewarding or reinforcing properties.

Morphine Self-Administration Study in Rats (Study # SP-MethDev-SPG-2607)

Study Design

This study does not utilize naloxegol and appears to have been conducted to demonstrate that the Sponsor was capable of producing self-administration with known drugs of abuse (cocaine and morphine).

Male rats (n = 8) were trained to self-administer cocaine (0.5 mg/kg/infusion, i.v.), using a schedule of reinforcement that increased from fixed ratio 1 (FR1) to FR5 over time. Stable self-administration behavior was defined as 3 consecutive sessions with <15% intersession variability in delivered infusions and >10 delivered infusions in each session. After stable cocaine self-administration was established, rats underwent an extinction procedure by substituting vehicle for cocaine. When extinction criteria were met (3 consecutive sessions of ≤10 delivered infusions), challenge sessions with morphine were initiated, at doses of 0.03, 0.1, 0.3 and 1 mg/kg/infusion. These doses are justified on the basis of "previously published studies." The morphine challenge sessions were conducted using an FR5 schedule of reinforcement as well as a progressive ratio schedule of reinforcement.

Results

Morphine produced an inverted U-shape dose-response pattern of self-administration. The peak number of morphine infusions per hour occurred with the 0.1 mg/kg/infusion (~10 infusions) and the 0.3 mg/kg/infusion dose (~7 infusion), both of which were statistically significantly greater than the ~2 infusions produced by vehicle.

Using progressive ratio, the mean breakpoint from the highest dose of morphine, 1.0 mg/kg/infusion, was ~9 infusions, with the other three doses (0.03, 0.01, 0.30 mg/kg/infusion) producing breakpoints of ~7 infusions. All morphine responses on progressive ration were statistically significantly greater than the mean breakpoint for vehicle alone (~4 infusions). The Sponsor adds a historical note that the "overall breakpoints for morphine were low compared to cocaine (~16 infusions)."

Conclusion

Both cocaine and morphine produce self-administration compared to vehicle.

3. Physical Dependence Studies in Animals

The Sponsor conducted two physical dependence studies, one with naloxegol, and the other with morphine. The data support the conclusions from the toxicological studies (see above) in which chronic naloxegol did not produce physical dependence.

a. Naloxegol Physical Dependence Study (#SP-D3820-SPG-2746)

Study Design

Male Wistar rats (n = 8/group) received vehicle or naloxegol at 50, 150 or 500 mg/kg (p.o.) for 15 days. The dose selections for naloxegol were not justified, nor was the oral route of administration.

On Day 1, 5, 8 and 11 rats were observed at 1 hour after treatment. On Day 16, animals underwent drug discontinuation and were observed in the morning and in the afternoon on Day 15, 16 and 17, and in the morning on Day 18, 19, 22 and 26. Using the Irwin test as a model, the following behaviors were monitored during drug administration (Days 1-15) and drug discontinuation (Days 16-30):

- Occurrence of vocalization, stereotypies, aggressiveness, abnormal gait, Straub tail, tremor, twitches, convulsions, body posture, sedation, catalepsy, ptosis, exophthalmos, salivation, lacrimation, piloerection, abnormal respiration, defecation, urination and death.

- Increase or decrease of spontaneous activity, touch response, body tonus and pupil size.

- Increase of sniffing, grooming, scratching and rearing.

- Decreased pinna reflex, traction response and grip strength.

- Acoustic startle response was measured on Day 16, 17, 18, 19, 22 and 26 (with a baseline measure prior to the initiation of naloxegol administration).

- Body temperature

- Body weights (daily on Day 1 to 19, and on Day 22 and 26.

- Any additional symptoms observed were also noted.

Animal behavior was recorded in terms of frequency and a score of 0 to 3 (not present to highest score).

Blood samples were taken 60 min after the first and last dose (Day 1 and 15) and 1, 2, 3, 4, 7 and 11 days after the last dose (Day 16, 17, 18, 19, 22 and 26) for analysis of naloxegol content in plasma.

Results

Naloxegol produced no significant finding in behavioral scoring either during the treatment phase or during the withdrawal phase. There was a reduction in food intake during the treatment period after 500 mg/kg. The food intake was normalized during the withdrawal period. During

the treatment there was a reduction in body weight after 150 and 500 mg/kg. The body weight was normalized towards the end of the withdrawal period. The mean plasma concentrations of naloxegol at 60 min post-dose on Day 15 were: 2.23, 5.86 and 32.7 µmol/L after 50, 150 and 500 mg/kg naloxegol, respectively.

Conclusion

During the treatment phase, there were acute effects such as reduced bodyweight after 150 and 500 mg/kg and reduced food intake after 500 mg/kg. Naloxegol produced no significant finding on any parameter measured during the withdrawal phase, suggesting the drug does not induce physical dependence.

b. Morphine Physical Dependence Study (#SP-SPG-2747)

The naloxegol physical dependence study (above) did not have a positive control (a drug that is known to produce withdrawal signs) as part of the study design. Thus, this separate study with morphine serves to demonstrate that the Sponsor's laboratory can conduct an investigation in which a drug is able to produce a withdrawal syndrome. (Note that this study with morphine does not involve administration of naloxegol, and that the withdrawal syndrome described was precipitated by discontinuation of morphine alone.)

Study Design

Male Wistar rats received once daily oral doses of morphine at 0 (vehicle), 10 or 30 mg/kg for 15 days. Thereafter, the animals were subjected to a withdrawal period for 14 days during which the occurrence of discontinuation symptoms was monitored. On Day 1, 5, 8 and 11 rats were observed at 1 hour after treatment. On Day 16, animals underwent drug discontinuation and were observed in the morning and in the afternoon on Day 15, 16 and 17, and in the morning on Day 18, 19, 22 and 26. Using the Irwin test as a model, the following behaviors were monitored during drug administration (Days 1-15) and drug discontinuation (Days 16-30):

- Occurrence of vocalization, stereotypies, aggressiveness, abnormal gait, Straub tail, tremor, twitches, convulsions, body posture, sedation, catalepsy, ptosis, exophthalmos, salivation, lacrimation, piloerection, abnormal respiration, defecation, urination and death.

- Increase or decrease of spontaneous activity, touch response, body tonus and pupil size.

- Increase of sniffing, grooming, scratching and rearing.

- Decreased pinna reflex, traction response and grip strength.

- Acoustic startle response was measured on Day 16, 17, 18, 19, 22 and 26 (with a baseline measure prior to the initiation of naloxegol administration).

- Body temperature
- Body weights (daily on Day 1 to 19, and on Day 22 and 26.
- Any additional symptoms observed were also noted.

Animal behavior was recorded in terms of frequency and a score of 0 to 3 (not present to highest score).

Blood samples were taken 60 min after the first and last dose (Day 1 and 15) and 1, 2, 3, 4, 7 and 11 days after the last dose (Day 16, 17, 18, 19, 22 and 26) for analysis of morphine content in plasma.

Results

During treatment, morphine produced effects in behavioral scoring including increased body tonus, spontaneous activity, rearing and sniffing after 10 and 30 mg/kg. During withdrawal, piloerection and increased body tonus were evident after 10 and 30 mg/kg. The body temperature was increased during treatment after 10 and 30 mg/kg. During withdrawal, the body temperature was decreased after 30 mg/kg. During treatment there was an initial reduction in food intake after 10 and 30 mg/kg. The reduction persisted throughout the treatment period after 30 mg/kg. During withdrawal, food intake was increased, particularly after 30 mg/kg. During treatment, there was an initial decrease in body weight between consecutive days. During withdrawal there was an initial decrease in body weight followed by an increase in body weight after 10 and 30 mg/kg. During withdrawal, there was a reduction in startle response after 30 mg/kg. The mean plasma concentrations of morphine at 60 min post-dose on Day 1 and 15 were: 220 and 181 nmol/L after 10 mg/kg and 332 and 951 nmol/L after 30 mg/kg.

Morphine produced significant findings during treatment and withdrawal. The acute effects included increased spontaneous activity, rearing, sniffing, increased body tonus and body temperature and reduced food intake and body weight. The discontinuation symptoms were piloerection, increased body tonus, decreased body temperature and startle response. Furthermore, the body weight was initially decreased during withdrawal followed by an increase and increased food intake. As both tested doses (10 and 30 mg/kg daily for 15 days) produced effects in some respect, the NOED for physical dependence could not be determined.

Conclusion

During morphine administration, the acute effects included increased spontaneous activity, rearing, sniffing, increased body tonus and body temperature and reduced food intake and body weight.

During the drug discontinuation phase, withdrawal symptoms included piloerection, increased body tonus, decreased body temperature and startle response. Furthermore, the body weight was initially decreased during withdrawal followed by an increase and increased food intake. These data show that morphine produces physical dependence.

C. Human Pharmacokinetics

1. Absorption

In humans, the highest proposed therapeutic dose of 25 mg oral naloxegol is absorbed rapidly (Tmax = 1.5-2.0 hours). The plasma half-life of naloxegol is approximately 7-9 hours, with a Cmax of 45 ng/ml and an AUC of 230 ng*hr/ml.

2. Metabolism and Elimination

The predominant peak in human urine is intact naloxegol (81%), with comparable presence in plasma samples. This profile is similar to that in rats and mice. There are no major metabolites in humans (e.g., ones that exceed 10% of the parent drug).

D. Clinical Studies

1. Phase 1 Studies (# 08-PNL-04, D3820C00025, D3820C00018, 05-IN-OX001, 07-IN-NX002, D3820C00001, D3820C00020, D3820C00009, D3820C00010, D3820C00011, D3820C00012, D3820C00015, D3820C00032, D3820C00014)

Fourteen Phase 1 studies were conducted with 474 healthy individuals to assess pharmacokinetics, safety and tolerability of naloxegol at doses ranging from 8 to 1000 mg. In two of the studies (#05-IN-OX001 and D3820C00011), participants (n = 19-48) received morphine in combination with naloxegol to evaluate orocecal transit time and miosis response. These studies were not included in the evaluation of abuse-related AEs since the effects of naloxegol cannot be distinguished from the psychoactive effects of morphine.

Across all 14 Phase 1 studies, there were no adverse events representative of any euphoria-related signs or symptoms. Few individuals in these studies experienced any nervous system or psychiatric disorders, which were generally limited to dizziness (0-25%), headache (0-25%), and paresthesia (0-13%).

2. Phase 2/3 Studies *(*Study #04 and 05)

Phase 2/3 studies were conducted with patients who were receiving opioids for pain management and were then given varying doses of naloxegol to determine if naloxegol could prevent opioid-induced constipation. With the design of these studies, it is not possible to attribute any euphoria-related or abuse-related adverse event observed during these studies to naloxegol administration. Thus, an AE profile from these studies is not included in this review of the abuse potential of naloxegol.

Given that the Sponsor asserts that naloxegol is a peripherally-acting opioid antagonist, DGIEP consulted Dr. Elizabeth Kilgore, a Medical Officer in the Division of Analgesia, Anesthesia and Addiction Products to evaluate whether there was any evidence of classic opioid withdrawal

signs or symptoms that would indicated naloxegol had central nervous system activity. Her evaluation examined withdrawal- related AEs that occurred in the controlled 12-week Study #04 and 05. Dr. Kilgore concludes (in a review placed in DARRTS on January 30, 2014) that:

• "While the overall incidence was generally low, possible opioid withdrawal symptoms occurred with a higher frequency in patients taking naloxegol (2%) compared to placebo (<1%) and occurred with a greater incidence in the naloxegol 25 mg group (14/446=3%) than the naloxegol 12.5 mg group (5/441=1%).

• "Analyzing the data using expanded terms from DSM-IV, COWS, SOWS, OOWS and other relevant terms including GI terms resulted in the identification of a higher number of cases with potential opioid withdrawal terms but not all cases met the criteria of clinically meaningful possible OWS.

• "When analyzing preferred terms potentially related to opioid withdrawal, the most frequently occurring AE term was hyperhidrosis, which occurred more frequently in naloxegol-treated patients than placebo. This term, however, may also be associated with mechanical straining from bowel movements. Making a determination of opioid withdrawal is challenging since opioid withdrawal syndrome may mimic other clinical presentations. We do not have adequate data to make definitive determinations of causality of the clinical manifestations reported."

In a personal communication on May 16, 2014, Dr. Kilgore noted that an FDA Advisory Committee will be convened on June 11-12, 2014, to discuss whether withdrawal signs associated with "peripherally-acting opioid antagonists" (such a naloxegol and methyl-naltrexone) are completely attributable to peripheral activity. Thus, it is not possible at this time to reject the possibility that the limited withdrawal signs associated with naloxegol is not the result of centrally-mediated activity.

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/s/

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06/02/2014

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Pediatric and Maternal Health Staff Review

Date: May 14, 2014

From: Carrie Ceresa, Pharm D, MPH
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Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Movantik (naloxegol oxalate) tablets

NDA: 204760

Subject: Labeling recommendations for subsections 8.1 and 8.3

Applicant: AstraZeneca

Materials Reviewed:

- September 16, 2013, NDA submission, draft labeling
- DGIEP Pharmacology/Toxicology labeling recommendations
- March 26 and April 10, 2014, Applicants response to Mid-Cycle Communication requests

Consult Question: "Review pregnancy and nursing mothers labeling."

INTRODUCTION

On September 16, 2013, AstraZeneca submitted NDA 204760, for Movantik (naloxegol oxalate) tablets, for oral use, for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain. Naloxegol oxalate is a new molecular entity and is being reviewed under "The Program", PDUFA V review timelines, with a PDUFA date of September 16, 2014.

DGIEP consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the Movantik labeling. In addition, PMHS-MHT participated in a review team teleconference on March 13, 2014, to update the applicant regarding the status of the NDA review. During this teleconference, PMHS-MHT requested the applicant to: 1) submit case reports on all pregnancies that occurred during the naloxegol Phase 3 clinical trials, as only one pregnancy report was submitted and the Summary of Clinical Safety mentioned three pregnancies; and, 2) provide references and a summary of published data of fetal effects (human and animal) with maternal use of opioid antagonists to substantiate the applicant's safety concern regarding the potential for fetal opioid withdrawal with maternal use of naloxegol.[1]

This review provides a summary of available relevant published data and recommended revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Naloxegol is a peripherally acting μ-opioid receptor antagonist that has been developed for the treatment of once daily opioid-induced constipation.[2] Naloxegol is a PEGylated derivative of the opioid antagonist naloxone. Opioid use slows the motility of the gastrointestinal tract. Naloxegol, *in vitro*, acts as an opioid antagonist with highest binding at the μ-opioid receptor. The applicant reports that naloxegol works in the gastrointestinal tract by decreasing constipation caused by opioids without impacting the analgesic effects. The PEGylation of naloxegol reduces the drug's ability to cross the blood-brain barrier and enter into the central nervous system (CNS).[3] However, there were case reports of opioid withdrawal reported in the Phase 3 clinical trials and patients with disruptions in the blood-brain barrier were excluded from the naloxegol clinical trials as these patients may have a higher risk of opioid withdrawal with naloxegol use.

Three pregnancies were reported during the naloxegol Phase 3 clinical trials. Two pregnancies were reported with use of naloxegol and one pregnancy was reported in the placebo group. No adverse outcomes were reported in these three pregnancies.

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[1] See DGIEP Mid-Cycle Communication Letter, March 31, 2014

[2] Webster, L., Dhar, S., Eldon, M., Masuoka, L., Lappalainen, J., Sostek, M. (2013). A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety and tolerability of naloxegol in patients with opioid-induced constipation. *Pain*, 154(9), 1542-1550. http://dx.doi.org/10.1016/j.pain.2013.04.024

[3] Gottfridsson, C., Carlson, G., Lappalainen, J., Sostek, M. (2013). Evaluation of the Effect of Naloxegol on Cardiac Repolarization: A Randomized, Placebo- and Positive-Controlled Crossover Thorough QT/QTc Study in Health Volunteers. *Clinical Therpeutics*, 35(12), 1876-1883. http://dx.doi.org/10.1016/j.clinthera.2013.09.019 0149-2918/$-seefrontmatter

Adverse developmental findings were observed in animal embryo-fetal development studies in rabbits at a dose 409 times the human AUC at the maximum recommended human dose. No adverse developmental findings were observed in animal embryo-fetal development studies in rats (see DGIEP Nonclinical review). The applicant [redacted] recommends against the use of Movantik during pregnancy because of the potential for fetal opioid withdrawal due to the immature fetal blood brain barrier.

REVIEW OF DATA

Pregnancy

A search of published literature was performed and no publications were found evaluating the use of Movantik (naloxegol) in pregnant women. The applicant provided information on naloxegol-exposed pregnancies in the Phase 3 clinical trials and available published literature regarding the use of opioid antagonists during pregnancy.

Reports of Two Naloxegol-Exposed Pregnancies in the Phase 3 Clinical Trials

On March 26, 2014, the applicant provided the two pregnancy case reports (summarized below) requested by PMHS-MHT.

- A 34 year-old female patient with history of opioid-treated fibromyalgia, headache, insomnia and low back pain, became pregnant while using naloxegol. The patient was concomitantly taking armodafinil, alprazolam, eszopicolone, topiramate, tizanidine, zolpidem, hydrocodone, and oxycodone/acetaminophen. The patient was discontinued from the study [redacted] after diagnosis of pregnancy. The patient's last menstrual cycle was [redacted] The patient had an uncomplicated birth at approximately 39 weeks gestation and delivered a healthy baby. No adverse outcomes were reported. It is unknown if or for how long the infant was followed after birth.

- A 21 year-old female patient with history of opioid-treated chronic lumbar sacral pain became pregnant while using naloxegol. The patient was concomitantly taking hydrocodone bitartrate/acetaminophen. The patient's last reported menstrual period was [redacted] The patient had a negative urine test for pregnancy [redacted] however a positive pregnancy test was reported [redacted] The patient discontinued study drug at that time. The patient delivered a full-term, healthy newborn. No adverse outcomes were reported. It is unknown if or for how long the infant was followed after birth.

[redacted]

Literature References and Summary Submitted by the Applicant

On April 10, 2014, the sponsor submitted a summary of published animal and human literature regarding fetal effects with maternal use of opioid antagonists as requested at the mid-cycle communications meeting. Although many of the references were included in the submission, several were on order at the time awaiting copyright permissions. At the time of this review, the remaining references had not yet been submitted by the applicant.

The applicant conducted a literature search using Embase and PubMed for publications evaluating fetal effects of opioid antagonists in animals and humans. The search resulted in a total of 742 articles; however, the applicant only summarized the articles which focused on naloxone and naltrexone because both are opioid antagonists similar to naloxegol. The majority of articles found in the initial literature search focused on methadone and buprenorphine which are both partial agonists generally used in detoxification programs; therefore, those references were excluded from the applicant's summary. In regard to the human literature, the applicant concluded that limited data are available on the effect of naloxone and naltrexone on a fetus. An important clinical adverse reaction observed in the literature postnatal was Neonatal Abstinence Syndrome (NAS).[5] NAS is generally diagnosed in newborns of women using opioid agonists and can appear anywhere from day 1 to day 10 after birth. Symptoms of NAS are consistent with withdrawal from exposure to opioids and include excessive crying, blotchy skin color, diarrhea, hyperactive muscles, irritability, poor feeding, hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnea, respiratory depression and bradycardia.[6]

The seven articles found with respect to naltrexone were found not relevant for this review. Two of the articles discussed the use of naltrexone for hypothalamic or hyper androgenic ovarian failure.[7,8] Five of the articles focused on fetal outcomes with the use of implantable and oral naltrexone used in detoxification program in Australia, Portugal, and the United Kingdom.[9,10,11,12,13]

[5] Hudak, M., Tan, R., The Committee on Drug and the Committee on Fetus and Newborn. (2012). Neonatal Drug Withdrawal. Pediatrics, 129, e540. DOI: 10.1542/peds.2011-3212

[6] National Center for Biotechnology Information, U.S. National Library of Medicine. (2012). Neonatal abstinence syndrome. Retrieved April 16, 2014, from www ncbi nlm nih.gov/pubmedhealth/PMH0004566/

[7] Wildt, L., Leyendecker, G., Sir-Petermann, T., Waibel-Treber, S. (1993). Treatment with naltrexone in hypothalamic ovarian failure: induction of ovulation and pregnancy. *Human Reproduction*, 8(3), 350-358.

[8] Wildt, L., Sir-Petermann, T., Leyendecker, G., Waibel-Treber, S., Rabenbauer, B. (1993). Opiate antagonist treatment of ovarian failure. *Human Reproduction*, 8(2), 168-174.

[9] Hulse, GK., O'Neill, G., Pereira, C., Brewer, C. (2001). Obstetric and neonatal outcomes associated with maternal naltrexone exposure. *Aust N Z J Obstet Gynaecol*, 41(4), 424-428.

[10] Hulse, GK., O'Neill. (2002). A possible role for implantable naltrexone in the management of the high-risk pregnant heroin user. *Aust N Z J Obstet Gynaecol*, 42(1), 104-105.

[11] Hulse, GK., O'Neill. (2002). Using naltrexone implants in the management of the pregnant heroin user. *Aust N Z J Obstet Gynaecol*, 42, 569-573.

[12] Hulse, GK, Arnold-Reed, D.E., O'Neill, G., Hansoon, RC., Naltrexone implant and blood naltrexone levels over pregnancy. *Aust N Z J Obstet Gynaecol*, 43, 386-388.

[13] Hulse, GK., O'Neill, Arnold-Reed, DE. (2004). Methadone maintenance vs. implantable naltrexone treatment in the pregnant heroin user. *Int J Gynaecol Obstet*, 85, 170-171.

The most relevant articles found for review for this consult are summarized below:

Arduini, D., Rizzo, G., Dell-Acqua, S., Mancuso, S., Romanini, C. (1987). Effect of naloxone on fetal behavior near term. *American Journal of Obstetrics & Gynecology*, 156, 474-8.
Fetal behavior was studied in 54 pregnant, healthy women that were given 0.4 mg of naloxone or an equal amount of saline. Each of the women were between 37 week and 39 weeks gestation. The patients underwent cardiotocographic and echographic examinations at the same time of day while in the same positions. Gross fetal body movement, fetal eye movements and fetal breathing were evaluated as well as fetal heart rate. In the naloxone group, the number of fetal body movements and fetal breathing movement increased over time but especially during the first hour. Additionally, increases were seen in the naloxone group in the number, duration and amplitude of fetal heart rate accelerations and in the active sleep and active awake states. The authors concluded these differences to be because of the reversal of the effects of fetal endorphins.

Debelak, K., Morrone, W., O'Grady, K., Jones, H. (2013). Buprenorphine + Naloxone in the Treatment of Opioid Dependence during Pregnancy – Initial Patient Care and Outcome Data. *The American Journal on Addictions*, 22, 252-254.
In a retrospective chart review, the authors identified 10 opioid dependent pregnant women who were treated with buprenorphine and naloxone. The following outcomes were measured in the 10 women: weight gain, fetal presentation at delivery, Cesarean delivery, analgesia during delivery, urine drug screening results at delivery, number of days of maternal hospital stay, and began breastfeeding following delivery. Eleven neonatal outcome measures were also measured: gestational age at delivery, 1 and 5 minute Apgar score, head circumference, length, and weight at birth, treated for neonatal abstinence syndrome (NAS), total amount of morphine sulfate needed to treat NAS, length of hospital stay for NAS treatment, and length of hospital stay. Although the sample size reviewed was small and there was no comparison group, an important clinical adverse reaction present at birth was neonatal abstinence syndrome in four of the infants. The criteria used for diagnosing NAS in these infants was not listed in the article.

Lactation
The Drugs and Lactation Database (LactMed)[14] was searched for available lactation data on with the use of naloxegol, and no information was located. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Naltrexone and naloxone, other approved opioid antagonists, are both present in human milk. In addition, animal studies showed the presence of naloxegol in the milk of lactating rats.

[14] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

Pregnancy

There were no adequate and well-controlled studies conducted with Movantik in pregnant women and no there is no published data on the maternal use of naloxegol during pregnancy. No adverse maternal or fetal outcomes were reported with two naloxegol-exposed pregnancies during the Phase 3 clinical trials. Adverse developmental findings were observed in animal reproduction studies in one species (rabbit) at doses 409 times higher than the relevant human exposure. The applicant (b) (4) recommended against use of the product during pregnancy because of the potential for fetal opioid withdrawal due to the immature fetal blood brain barrier. (b) (4) The pregnancy data from the Phase 3 clinical trials are insufficient to draw any conclusions regarding the use of the product during pregnancy. PMHS-MHT reviewed the literature references and summary of the literature submitted by the applicant regarding fetal effects with maternal opioid antagonist use. Neonatal abstinence syndrome (NAS) in the newborn was a serious adverse reaction reported in the literature with maternal use of opioid antagonists. However, NAS is also associated with *in utero* exposure to opioids and other centrally-acting drugs including, heroin, methadone, codeine and amphetamines, barbiturates, benzodiazepines and cocaine.[5,6] NAS has been documented in 55 to 94% of neonates that have been exposed to opioids *in utero*.[5] The symptoms, duration and severity of NAS differ between the different opioids.[5] All patients receiving Movantik will also be taking opioids.

Reviewer comment: PMHS-MHT discussed the cases of NAS with DGIEP and it was decided that not enough information is available at this time (b) (4)

Lactation
The applicant recommends against breastfeeding due to the potential for opioid withdrawal in an infant with an immature blood brain barrier. Although it is not known if Movantik is present in human milk, it is present in animal milk and absorbed by a nursing pup. Other opioid products have been demonstrated to be present in human milk. Therefore, based on the available information that naloxegol has the potential to be present in breast milk, and that there is the potential for opioid withdrawal in an infant if a nursing mother is taking naloxegol, PMHS-MHT concurs with the applicant's recommendation against breastfeeding with the use of Movantik.

CONCLUSIONS
Based on the adverse developmental findings seen in rabbits in animal reproduction studies, as well as the potential for fetal opioid withdrawal with maternal use of Movantik, PMHS-MHT recommends a Pregnancy Category C classification for this drug.[15] Labeling should state that Movantik should be used during pregnancy only if the potential maternal benefits outweigh the potential fetal risks. PMHS-MHT concurs with the applicant's recommendation against breastfeeding with maternal use of Movantik due to the potential for opioid withdrawal in a breastfed infant if Movantik is present in breast milk.

The pregnancy subsection of the labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of labeling was revised to comply with current labeling recommendations.

LABELING RECOMMENDATIONS
See Appendix A for the sponsor initial labeling recommendations

PMHS-MHT discussed our labeling recommendations with DGIEP at a labeling meeting on April 30, 2014. PMHS-MHT and the DGIEP Pharmacology/Toxicology team recommendations are below and reflect the discussions with the Division at that meeting. PMHS-MHT refers to the NDA action for final labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS-------
- Pregnancy: may precipitate opioid withdrawal in a fetus. (8.1)
- Nursing Mothers: discontinue drug or nursing taking into consideration importance of drug to mother (8.3)

[15] Pregnancy Category C Definition: Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well controlled studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no adequate and well controlled studies in humans.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy category C

Risk Summary

There are no adequate and well-controlled studies with Movantik in pregnant women. The use of Movantik during pregnancy may precipitate opioid withdrawal in a fetus due to the undeveloped fetal blood brain barrier. (b) (4) no effects on embryo-fetal development were observed following administration of naloxegol in pregnant rats during the period of organogenesis at doses up to 1452 times the human AUC at the maximum recommended human dose. (b) (4) following administration of naloxegol in pregnant rabbits during the period of organogenesis (b) (4) 409 times the human AUC at the maximum recommended human dose. Movantik should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Oral administration of up to 750 mg/kg/day naloxegol in rats (1452 times the human AUC at the maximum recommended human dose) during the period of organogenesis produced no adverse effects on embryo-fetal development. (b) (4) Oral administration of up to 500 mg/kg/day in rats (195 times the maximum recommended human dose based on body surface area) during the period of organogenesis through lactation produced no adverse effects on parturition or the offspring.

8.3 Nursing Mothers

It is unknown whether Movantik is present in human milk. However, naloxegol is present in rat milk and is absorbed in nursing rat pups. Because of the potential for serious adverse reactions, including opioid withdrawal, in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

17 PATIENT COUNSELING INFORMATION

(b) (4) **Pregnancy**

Females of reproductive potential, who become pregnant or are planning to become pregnant (b) (4) that the use of Movantik during pregnancy may precipitate opioid withdrawal in a fetus due to the undeveloped blood brain barrier.

(b) (4) **Nursing** (b) (4) (b) (4)

Appendix A
Initial labeling recommendations from the sponsor

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS-------

(b) (4)

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

(b) (4)

8.3. Nursing Mothers

It is unknown whether (b) (4) is excreted in human breast milk. (b) (4)

(b) (4)

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/s/

CARRIE M CERESA
05/14/2014

JEANINE A BEST
05/14/2014

LYNNE P YAO
05/14/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 5, 2014

TO: Maureen Dewey, M.P.H., Regulatory Project Manager
Aisha Peterson Johnson, M.D., Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204760

APPLICANT: AstraZeneca Pharmaceuticals LP

DRUG: Movantik® (naloxegol oxalate)
NME: Yes
THERAPEUTIC CLASSIFICATION: Standard

INDICATION: treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

CONSULTATION REQUEST DATE: November 5, 2014
INSPECTION SUMMARY GOAL DATE: May 9, 2014
DIVISION ACTION GOAL DATE: September 16, 2014
PDUFA DATE: September 16, 2014

I. BACKGROUND:

AstraZeneca Pharmaceuticals LP submitted an NDA for the new molecular entity naloxegol (NKTR-118, NKT-10018, PEG-Naloxol) for the indication of treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. Naloxegol is a PEGylated derivative of naloxone and functions as a peripherally-acting mu-opioid receptor antagonist (PAMORA) in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system. In 2010, the Drug Enforcement Administration (DEA) classified naloxegol as a Schedule II substance, as defined by the Controlled Substances Act (CSA), based on naloxegol's chemical structure. During the clinical development program FDA requested that AstraZeneca perform a comprehensive program of nonclinical studies to define the pharmacology of naloxegol and evaluate its potential for abuse and for inducing physical or psychological dependence. AstraZeneca executed this program (b) (4) Additional issues concerning cardiovascular safety and bowel perforation are a concern with this class of drugs.

The clinical development plan included two identical protocols, D3820C00004 and D3820C00005, both entitled "A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NKTR-118 in Patients with Non-Cancer-Related Pain and Opioid-Induced Constipation (OIC)."

The consult request noted that four clinical sites were chosen because of high enrollment for the clinical trial and because of ranking on the risk-based site selection model. The review division request included inspection for verification of clinical data. Because the product is a new molecular entity, a focused sponsor inspection was also conducted.

II. RESULTS (by Site):

Type and Name and Address of Inspected Entity	**Protocol # Site # and # of Subjects**	**Inspection Date**	**Final Classification** *Pending
CI: Corey Jacobs, MD 1506 N. McKenzie Street, Suite 104 Foley AL 36535	D3820C00005/ Site #5235/ 30 Subjects	January 30 to February 25, 2014	VAI
CI: Mahendra Sanapati, MD 1101 Professional Blvd Evansville, IN 47714	D3820C00004/ Site #4056/ 30 Subjects	January 22 to February 6, 2014	VAI
CI: Egilius Spierings, MD 72 Mount Auburn Street Watertown, MA 02472	D3820C00005/ Site #5267/ 26 Subjects	January 13 to 28, 2014	NAI
CI: Rafaelito Victoria, MD 1020 South Anaheim Boulevard, Suite 316 Anaheim, CA 92805	D3820C00004/ Site 4068 / 44 Subjects	January 21 to 30, 2014	NAI
Sponsor: AstraZeneca Pharmaceuticals LP 1800 Concord Pike Wilmington, Delaware 19803-8355	D3820C00004 and D3820C00005	March 31 to April 7, 2014	Pending (Preliminary NAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Corey Jacobs, MD, Foley AL 36535

a. **What was inspected:** At this site, for Protocol D3820C00005, a total of 82 subjects were screened, 30 subjects were randomized and 20 subjects completed the study. An audit of 14 subjects' records was conducted. The review included consent form documents, study correspondence, source records, and test article handling and accountability.

b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events and the efficacy data could be verified. A Form FDA 483 was issued because the investigation was not conducted in accordance with the investigational plan and because of inadequate and inaccurate records. Below are selected citations from the Form FDA 483:

1. The investigation was not conducted in accordance with the investigational plan. Specifically:
   a. The protocol provided that patients on medications that may prolong the QT interval be excluded from the study and metoclopramide was on this list of medications. Subject 5235028 was enrolled in spite of the fact that the patient was taking this medication.
   b. The protocol excluded patients who had ECG QTcF > 450 msec at screening. Subject 5235039 was enrolled even though an ECG QTcF of 454 was obtained at screening.
   c. The protocol required that subjects have colon cancer screening appropriate to risk. Subjects 5235012, 5235028, 5235039, 5235041, 5235046, 5235050, 5235060, and 5235077 were enrolled without documentation of the screening.

Reviewer Note: This was cited as a protocol violation on the Form FDA 483 but is considered by this reviewer to be an instance of inadequate record keeping, because subjects had actually had previous colonoscopies.

   d. The site randomized Subject 5235067 even though the subject failed to meet the inclusion criterion of stable maintenance opioid regimen.

2. The clinical investigator did not maintain adequate and accurate records. This occurred for some start and stop dates for medications. Specifically:
   a. Subject 5235002 maintenance medication SD (Opioid Concomitant Medication Worksheet) documented Opana ER 20 mg BID from 2010 to 08/01/11 and Opana ER 30 mg from 08/01/11 to ongoing. The eCRF only documented Opana ER 30 mg BID from 2010 to ongoing.
   b. Subject 5235046 maintenance medication SD (Opioid Concomitant Medication Worksheet) documented Morphine 15 mg TID from 2011 to 06/11/11; Morphine 30 mg TID 2009 to ongoing; and Lortab 10 mg TID 07/07/11 to ongoing. The eCRF only documented Morphine 30 mg TID from 2009 to ongoing and Lortab 10mg TID from 2011 to ongoing.
   c. Subject 5235077 maintenance medication SD (Opioid Concomitant Medication Worksheet) documented Percocet 10/325 mg 1-2 tabs/every 6 hours from 06/25/11 to ongoing. The eCRF documented Percocet 10/325 mg 1-2 tabs/every 6 hours from 07/25/11 to ongoing.

The clinical investigator responded in a letter received by FDA on March 18, 2914, promising corrective action.

c. **Assessment of data integrity:** The violations noted above are not considered significant. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Mahendra Sanapati, MD, Evansville, IN 47714

a. **What was inspected:** At this site, for Protocol D3820C00004, a total of 54 subjects were screened, 30 subjects were randomized and 18 subjects completed

the study. An audit of all 54 subjects' records was conducted. The review included consent form documents, study correspondence, source records, and test article handling and accountability.

b. **General observations/commentary:** A Form FDA 483 was issued because the investigation was not conducted in accordance with the investigational plan. Specifically, the protocol required that potential subjects on medications that may prolong the QT interval be excluded from the study. A list of such medications was provided in Appendix J of the protocol. Subject E4056007 on amitriptyline and Subject E4056009 on nortriptyline were enrolled in violation of this exclusion criterion. Dr. Sanapati responded adequately in a letter dated February 19, 2014 and stated that he had instituted corrective action. These violations do not significantly impact data integrity.

c. **Assessment of data integrity:** The violations are isolated. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

3. Egilius Spierings, MD, Watertown, MA 02472

a. **What was inspected:** At this site, for Protocol D3820C00005, a total of 53 subjects were screened, 26 subjects were randomized, and 3 subjects discontinued the study prior to completion. A total of 23 subjects completed the study. An audit of all 53 subjects' records was conducted. The review included informed consent form documents, study correspondence, source records, and test article handling and accountability. Three subjects were adjudicated for a cardiovascular event, and three subjects experienced opioid withdrawal.

b. **General observations/commentary:** Data listings specific to primary efficacy were verifiable through the PHT e-diary data contained on the CD provided to the site for archive. There was no evidence of under-reporting of AEs. No significant regulatory violations were noted, and no Form FDA 483 was issued.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

4. Rafaelito Victoria, MD, Anaheim, CA 92805

a. **What was inspected:** At this site, for Protocol D3820C00004, a total of 80 subjects were screened, 36 subjects were screen failures, and 44 subjects were randomized. Ten subjects discontinued the study prior to completion, and 34 subjects completed the study. An audit of all 44 subjects' records was conducted. The review included consent form documents, study

correspondence, source records, and test article handling and accountability.

b. **General observations/commentary:** There was no evidence of under-reporting of AEs. Data listings specific to primary efficacy were verifiable. No significant regulatory violations were noted, and no Form FDA 483 was issued.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

5. AstraZeneca Pharmaceuticals LP, Wilmington, Delaware 19803-8355

Note: Observations below for this site are based on e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

a. **What was inspected:** The current inspection covered Protocols D3820C00004 and D3820C00005. Records from three clinical sites for D3820C00004 and two sites for D3820C00005 were inspected. These included the sites noted above and also Dr. James Shoemaker, site 4061 for study D3820C00004 who enrolled only 18 subjects. Study records including contracting for the development of the eDiary, CRO for monitoring, adverse event reporting, data collection and handling, financial disclosure, electronic records and handling, and other study administrative records were reviewed.

b. **General observations/commentary:** Monitoring and other sponsor responsibilities were conducted adequately by the sponsor. The sponsor performed numerous vendor audits and clinical site audits prior to launch of the clinical studies. Study records were very well organized. There were two clinical investigator sites in Florida that were discontinued and these site terminations were reported to FDA. Primary efficacy endpoint data was able to verified by comparing the spontaneous bowel movement data located in the e-diary records with the line listing data for 12 randomly selected subjects and no discrepancies were found. No regulatory violations were noted and no Form FDA 483 was issued.

c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by the sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigator sites and the sponsor were inspected for this NDA. As noted above, the classifications were NAI for two clinical sites and VAI for two clinical sites.

The sponsor inspection is classified as NAI based on a preliminary report. The data generated by these clinical sites and the sponsor are considered reliable for the respective indication.

An inspection summary addendum will be written if conclusions change upon receipt and review of the final EIR from the sponsor inspection.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
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CONCURRENCE:

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/s/

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05/07/2014

SUSAN D THOMPSON
05/07/2014

KASSA AYALEW
05/07/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
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MEMORANDUM TO FILE

From:	Ethan D. Hausman, MD, Medical Officer Pediatric and Maternal Health Staff (PMHS), OND
Through:	Hari Cheryl Sachs, MD, Medical Team Leader PMHS, OND Lynne P. Yao, MD, OND Associate Director PMHS
NDA [IND]:	204,760 [78,781]
Sponsor:	AstraZeneca
Drug:	Naloxegol [pegylated-(PEG)-naloxol]
Dosage form and route of administration:	25 and 12.5 mg tablets for oral administration
Adult Dose regimen:	25 mg once daily - taken in the morning on an empty stomach; 12.5 mg/day for patient on moderate CYP3A4 Inhibitors
Proposed Pediatric dose regimen:	To be determined
Adult Indication:	Opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain
[redacted] (b) (4)	
Date of internal meeting:	TBD
Date of applicant meeting:	TBD
Division Consult Request:	The Division of Gastroenterology and Inborn Error Products (DGIEP) requests PMHS "assistance with preparation for PeRC (partial waiver (b) (4) [redacted] (b) (4) [redacted]).

Introduction

Naloxegol (PEG-naloxol; NDA 204760; IND 78781) is a polyethylene glycolated form of naloxone under development for treatment of 'opioid-induced constipation (OIC) in adults with chronic non-cancer pain'.

The applicant states that the pegylation assures 'markedly reduced capacity to cross the blood brain barrier (BBB), with preservation of peripheral' mu-opioid receptor antagonism in gut receptors. This gut-targeted mu-opioid antagonism is intended to counteract mu-opioid receptor induced OIC.

On September 16, 2013, the applicant (AstraZeneca) submitted the original NDA for marketing review under The Program. The application seeks approval for treatment of adults only. (b) (4)

The PMHS consult request is to focus on the waiver (b) (4)

- The sponsor requests a waiver for studies in children (b) (4) based on perceived increased risk of acute opioid withdrawal due to the drug being able to cross the BBB, which is underdeveloped in these children compared to older patients. As detailed below, PMHS recommends waiver of studies for all pediatric age groups.

(b) (4)

Reviewer comment: The plan for waiver in patients (b) (4) *is appropriate. As detailed later in this document, the relatively underdeveloped BBB in these patients compared to older patients may be associated with increased risk of CNS drug penetration with commensurate increased risk of acute opioid withdrawal. Labeling will need to reflect this safety concern.*

(b) (4)

Materials Reviewed

PMHS consult request form from DGIEP (M. Scherer; December 16, 2013)

(b) (4) Draft Labeling (contained in the NDA submission)

(b) (4)

Prior FDA communications including consults and sponsor letters:

Naloxegol (IND 78781)

PMHS Consult: J. Best; March 26, 2013

Relistor (methylnaltrexone bromide; NDA 21964)

PMHS Consult: J. Best; March 11, 2010; J. Best; March 27, 2012

Pediatric Inadequate PPSR Inadequate Letter: D. Griebel, April 8, 2010

Pediatric Ethics Consult: R. Nelson, August 26, 2010

PubMed literature search to identify incidence or prevalence of OIC in children—none identified.

Disease Background

Constipation is common in patients with chronic opioid exposure, such as debilitated patients with cancer-related pain and patients with chronic non-cancer pain. OIC is believed to arise from activation of local mu-opioid receptors in the gut. Factors contributing to constipation in this population, in addition to opioid exposure, include interruption of enteral feeding and possible concomitant exposure to drugs with anti-cholinergic activity (e.g., hydroxyzine, ANDA 85551). A variety of laxatives and stool softeners are available for treatment of constipation from any etiology and may be used to treat OIC. However, no uniform practice guidelines exist for treatment of OIC in children, and not all products approved in adults for treatment of constipation have pediatric dosing information (e.g., EZ2GO PEG 3350, ANDA 91077).

Non-tissue-specific opioid receptor blockers such as naloxone may reverse OIC,[1] but cross into the central nervous system (CNS) and cause acute opioid withdrawal.[2] Drugs with restricted distribution outside the BBB such as methylnaltrexone bromide may provide laxative effect with lower risk acute opioid withdrawal, particularly in patients with chronic opioid exposure.

Recent evidence-based guidelines support use of some form of laxative in patients with chronic opioid exposure for chronic non-cancer pain.[3,4] The authors concluded,

[1] Lie M, Wittbrodt E. Low-dose oral naloxone reverses opioid-induced constipation and analgesia. J Pain Symptom Manage 2002 Jan; 23(1):48-53.
[2] Label, naloxone, ANDA 72,076
[3] Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) Guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 1- Evidence Assessment. Pain Physician 2012; 15:S1-S66.
[4] Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) Guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2 - Guidance. Pain Physician 2012; 15:S67-S116.

however, that there was insufficient evidence to recommend use of opioid antagonists for the prevention of constipation in patients chronically exposed to mu-opioids.

Product Background

PEG-naloxol is a systemically absorbed orally administered compound. The sponsor's preclinical data suggest that PEG-naloxol has reduced capacity to cross the BBB compared to naloxone and that this characteristic allows peripheral mu-opioid receptor blockade in the gut with reduced risk of acute opioid withdrawal compared to non-pegylated naloxone

From the integrated summary of safety (ISS), the adult preclinical program showed potential reversible increase in liver size and hepatocyte size in rats (6-month exposure) and dogs (9-month exposure). Conversion of the no-observable-adverse-event-level (NOAEL) in both species to human equivalent dose suggested a >120-fold safety margin over the maximum dose used in human adult studies (25 mg/day).

Reviewer comment: If pediatric studies are pursued, DGIEP and Pharmacotoxicology should determine the need for any additional animal studies or if currently available data suggest any pediatric safety concerns that preclude pediatric drug development.

Summary of Adult Phase 3 Program

The five Phase 3 studies in the adult program are:

- Study D3820C00004: This was a 12-week, randomized, double-blind, placebo-controlled (RDBPC) study of 652 adults patients with chronic non-cancer-related pain, randomized 1:1:1 to 12.5 mg, 25 mg, or placebo, as once daily dose (qD).
- Study D3820C00005: This was a 12-week, RDBPC study of 700 adult patients with chronic non-cancer-related, randomized 1:1:1 to 12.5 mg, 25 mg, or placebo qD.
- Study D3820C00007: This was a 12-week, DB, safety extension study of Study D3820C000004, wherein 297 adult patients with chronic non-cancer-related pain continued to receive the same blinded treatment as in the prior study.
- Study D3820C00008: This was a 52-week, open-label (OL) parallel group safety study of 884 patients with chronic non-cancer-related pain, treated 2:1 with either 25 mg qD or OIC 'standard of care'.
- Study D3820C00006: This was a 2-part study in patients with cancer-related pain and OIC. Of 336 patients planned for enrollment, 14 patients were enrolled over 10 months, and enrollment was discontinued due to slow patient accrual.
    - Part 1 was a 4-week, randomized double-blind, placebo-controlled study. 14 patients were randomized 1:1:1 to 12.5 mg, 25 mg, or placebo qD.
    - Part 2 was a treatment extension of the same dose given in part 1; however patients given placebo in part 1 were given 25 mg qD in part 2.

Patients had to be on between 30 to 1000 mg morphine-equivalent-units/day (meu/d) for non-cancer related pain for at least four weeks prior to screening. Patients receiving intrathecal opioids were eligible for participation if they were also taking oral opioids at a dose ≥30 meu/d. Constipation was required for entry and was defined as fewer than three spontaneous bowel movements (SBMs)/week with symptoms of constipation for at least four weeks.

For randomization to the double blind period, patients had to have less than three SBMs/week on average and report at least one of the following symptoms with at least 25% of the BMs: Bristol Stool Scale (BSS) type 1 or 2; moderate, severe, or very severe straining; or feeling of incomplete BM ("consistent with the Rome III criteria for functional constipation"). An SBM was defined as a BM which occurred without taking a rescue laxative or enema within the previous 24 hours.

Reviewer comment: (b) (4) *DGIEP should agree that available data exist*

(b) (4)

(b) (4)

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(b) (4)

[redacted]

Conclusion/Recommendations: Pediatric studies for OIC associated with chronic opioid exposure for chronic cancer-related pain and chronic non-cancer-related pain are unlikely to be feasible. Therefore, PMHS recommends that a full waiver of studies in pediatric patients 0 through 17 years be granted.

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/s/

ETHAN D HAUSMAN
04/03/2014

LYNNE P YAO
04/04/2014

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RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204760 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Movantik Established/Proper Name: naloxegol oxalate Dosage Form: Tablet Strengths: 12.5 mg, 25 mg		
Applicant: AstraZeneca Pharmaceuticals LP Agent for Applicant (if applicable):		
Date of Application: 9-16-13 Date of Receipt: 9-16-13 Date clock started after UN:		
PDUFA Goal Date: 9-16-14	Action Goal Date (if different):	
Filing Date: 11-15-13	Date of Filing Meeting: 10-30-13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): NA

List referenced IND Number(s): 078781

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☒	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff: 10-30-13* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☒	☐	☐	(b) (4) [redacted]
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☒	☐	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☒	☐	☐	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	☒	☐	Requested waiver (b) (4) [redacted] FDA has previously determined that pediatric studies for this indication are not feasible and therefore plans to fully waive PREA studies. Therefore, certification may not necessary (will confirm with PMHS)
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Coded correctly
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☒	☐	Consult request pending
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☒	☐	Consult request pending
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	Via tradename review process
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☒	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☒	
Other Consults	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☐	DAAAP consult pending and other consults to be determined
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 1-26-10 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 9-12-10 (CMC - cancelled), 10-10-12 (content/format – cancelled), 3-13-13 (content/format – cancelled), 4-23-14 (CV safety) ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10-30-13

BLA/NDA/Supp #: NDA 204760

PROPRIETARY NAME: Proposed tradename is Movantik

ESTABLISHED/PROPER NAME: naloxegol oxalate

DOSAGE FORM/STRENGTH: Tablets, 25 mg, 12.5 mg

APPLICANT: AstraZeneca Pharmaceuticals LP

PROPOSED INDICATION: for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

BACKGROUND: Naloxegol oxalate (historically referred to as NKTR-118, PEG-naloxol, PEGylated naloxone derivative) is a NME mu-opioid receptor antagonist developed to treat opioid-induced constipation (see above for the specific wording of the proposed indication). The phase 3 program consists of 2 12-week, placebo-controlled, double-blind efficacy trials (04, 05), a 12-week extension of 04 (07) and an open-label long-term extension safety study of patients from studies 05 and 07 for up to 52 weeks of total exposure (08).

This NDA will be reviewed under the PDUFA V Program.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matthew Scherer	y
	CPMS/TL:	Wes Ishihara	y
Cross-Discipline Team Leader (CDTL)	Anil Rajpal		y
Clinical	Reviewer:	Aisha Peterson Johnson	y
	TL:	Anil Rajpal	y
Clinical Pharmacology	Reviewer:	Elizabeth Shang Sandhya Apparaju	y y
	TL:	Sue Chih Lee	y
Biostatistics	Reviewer:	Wen Jen Chen	y

	TL:	Freda Cooner	y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Eddie Ng	y
	TL:	David Joseph	y
Product Quality (CMC)	Reviewer:	Bogdan Kurtyka	y
	TL:	Marie Kowblansky	y
Quality Microbiology *(for sterile products)*	Reviewer:	Stephen Langille	n
	TL:		
CMC Labeling Review	Reviewer:	Bogdan Kurtyka	y
	TL:	Marie Kowblansky	y
Facility Review/Inspection	Reviewer:	TBD	n
	TL:	TBD	n
OSE/DMEPA (proprietary name)	Reviewer:	Lisa Khosla	y
	TL:	Lubna Merchant	n
OSE/DRISK (REMS, Medguide)	Reviewer:	Nyedra Booker	y
	TL:	Kendra Worthy	n
Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	y
	TL:	Jean Mulinde	n
Controlled Substance Staff (CSS)	Reviewer:	Katherine Bonson	n
	TL:		
Other reviewers	Ping Zhao, Pharmacometrics/PBPK Yuzhou Pan, Pharmacometrics/PBPK Kareen Riviere, Biopharmaceutics Elizabeth Kilgore, DAAAP Ellen Fields, DAAAP Justin Earp, Pharmacometrics Christian Cao, DPV		
Other attendees	Julie Beitz, Director, ODE III Donna Griebel, Director, DGIEP Joyce Korvick, Deputy Safety Director, DGIEP Phong (Pete) Do, OSE-RPM		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: Acceptable	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO OSI site inspection request issued
• Advisory Committee Meeting needed? **Comments**: AC will be convened to discuss the safety data requirements and timing (e.g., preapproval) for naloxegol and other opioid antagonists. ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public***	☒ YES Date if known: March 10-11, 2014 ☐ NO ☐ To be determined Reason:

health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease	
• Abuse Liability/Potential **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: issues for 74-day letter are detailed in the 10-30-13 Clinical Pharmacology filing review	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed? Bioequivalence site inspection consult request issued	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	☒ Not Applicable ☐ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☐ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☒ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz, Director, ODE III **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): target February 16, 2014 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional):	

Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): See 10-30-13 Clinical Pharmacology filing review. Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]

☒	Other: Issue all necessary consults

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MATTHEW C SCHERER
11/15/2013

RICHARD W ISHIHARA
11/15/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	November 7, 2013
Reviewer(s):	Monica M Calderon, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, MS, PharmD Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	Movantik (Naloxegol) Tablets 12.5 mg and 25 mg
Application Type/Number:	NDA 204760
Applicant/sponsor:	AstraZeneca Pharmaceuticals LP
OSE RCM #:	2013-2139

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

As part of the approval for Movantik (Naloxegol) Tablets, NDA 204760, the Division of Gastroenterology and Inborn Error Products (DGEIP) requested we review the proposed container label, carton and full prescribing information for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the September 27, 2013 proprietary name submission.

- Active Ingredient: Naloxegol
- Indication of Use: Opioid-induced constipation
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 12.5 mg and 25 mg
- Dose and Frequency: One tablet once daily
- How Supplied: Bottles of 30 tablets and 90 tablets; blister sample packs and blisters for distribution
- Storage: Room Temperature
- Container and Closure System: N/A

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted September 27, 2013 (Appendix B)
- Carton Labeling submitted September 27, 2013 (Appendix C)
- Blister Labels submitted September 27, 2013 (Appendix D)
- Prescribing Information submitted September 27, 2013

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 MEDICATION ERROR RISK ASSESSMENT

DMEPA performed a risk assessment of the proposed full prescribing information to identify any deficiencies that may lead to medication errors. We also reviewed the proposed container label, blister labels and carton labeling to identify areas of improvement and noted (b) (4) on the labels (b) (4) Additionally, the blister pack labels are not well differentiated (b) (4) We provide recommendations in Section 5 to address these deficiencies.

4 CONCLUSIONS

DMEPA concludes that the full prescribing information is acceptable from a medication error perspective. However, the proposed carton labeling, container labels, and blister labels can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

5.1 COMMENTS TO THE APPLICANT

A. All Labels and Labeling

(b) (4)

B. Container Labels

1. Remove the net quantity statement (b) (4) and relocate it (b) (4) . As currently presented, the net quantity statement is (b) (4)
2. Add the dosage form, "Tablets", next to or below the established name (naloxegol).

C. Carton Labeling

1. See comments B1 and B2.
2. Delete (b) (4) .

D. Blister Labels

The blister labels (b) (4); remove (b) (4)

If you have further questions or need clarifications, please contact Phong Do, project manager, at 301-796-4795.

Appendices

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

Appendix B: Container Label

Appendix C: Carton Labeling

Appendix D: Professional Sample Blistercards

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

/s/

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11/07/2013

LUBNA A MERCHANT
11/07/2013