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APPLICATION NUMBER:

204760Orig1s000

SUMMARY REVIEW

Division Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, M.D., M.P.H. Deputy Director Division of Gastroenterology and Inborn Errors Products (DGIEP)
Subject	Division Director Summary Review
NDA #	204760
Applicant Name	AstraZeneca Pharmaceuticals LLP
Date of Submission	September 16, 2013
PDUFA Goal Date	September 16, 2014
Proprietary Name / Established (USAN) Name	Movantik (naloxegol)
Dosage Forms / Strength	Tablets (12.5 mg and 25 mg)
Proposed Indication	to treat opioid-induced constipation (OIC) in adults with chronic non-cancer pain.
Recommended Action for NME:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Aisha Johnson
Statistical Review	Wen Jen Chen
Pharmacology Toxicology Review	Yuk-Chow Ng / David Joseph
CMC Review	Bogdan Kurtyka
Microbiology Review	
Clinical Pharmacology Review	Sandhya Apparaju Elizabeth Shang Justin Earp
Biopharmaceutics	Kareen Riviere
OC/OSI-Clinical Inspection	Susan Leibenhaut
CDTL Review	Anil Rajpal
OSE/DMEPA – label review and trade name review	Lisa Khosla
OSE/DRISK	Nyedra Booker
OSE/DPV – Pharmacovigilance	Christian Cao
OSE/DEPI	Carolyn McCloskey
DB7	Clara Kim, Jessica Kim
OMP/Patient Labeling Team	Karen Dowdy
OMP/OPDP	Meeta Patel
Neurology consultant	Heather Fitter
Controlled Substance Staff	Katherine Bonson
DCaRP	Preston Dunnmon

DAAAP	Liz Kilgore
DRISK	Shelly Harris
Facilities Inspection	Christina Capacci-Daniel

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DAAAP=Division of Analgesia, Anesthesia and Addiction Products
DCRP= Division of Cardiovascular and Renal Products

Division Summary Review

1. Recommendation:

I recommend approval of Movantik (naloxegol) 25 mg and 12.5 mg for the treatment of opioid induced constipation (OIC) in adult patients with chronic non-cancer pain. This recommendation is based upon my review of the memoranda and recommendations of the review team members, including consultant reviewers. I am in concurrence with their recommendations for approval. There are no outstanding issues that preclude approval.

2. Introduction

Movantik (naloxegol), an opioid antagonist, contains naloxegol oxalate as the active ingredient. (Naloxegol is a PEGylated derivative of naloxol.) Naloxegol is considered a new molecular entity (NME).

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 mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids.

Naloxegol is a PEGylated derivative of naloxol, and is a substrate for the P-glycoprotein transporter (P-gp). Also, the presence of the PEG moiety in naloxegol reduces its passive permeability as compared with naloxone. Due to the reduced permeability and increased efflux of naloxegol across the blood-brain barrier, related to P-gp substrate properties, the CNS penetration of naloxegol is expected to be negligible at the recommended dose levels limiting the potential for interference with centrally mediated opioid analgesia.

3. Background

Opioid induced constipation (OIC) is a frequent complication of chronic opioid use. Laxatives are the primary medication used for the treatment of OIC. Currently, only two medications are specifically indicated for the treatment of OIC: Amitiza (lubiprostone) and Relistor (methylnaltrexone bromide). Relistor is approved for use only in patients undergoing palliative care while Amitiza is indicated for all adult patients with OIC or chronic idiopathic constipation (CIC).

Two safety issues of special interest were considered during the review of this application; the potential for cardiovascular adverse reactions and potential of opioid withdrawal. Entereg (alvimopan), another opioid receptor antagonist approved to accelerate the time to upper and lower gastrointestinal recovery following surgeries that include partial bowel resection with primary anastomosis, was associated with a possible cardiovascular safety signal in one long-term trial in the original NDA. As a result, a Risk Evaluation and Mitigation Strategy (REMS) was instituted limiting its use to the labeled indication, in a hospital setting, for a maximum of 15 doses. Because Movantik is a member of this drug class, the potential for cardiovascular risk was closely examined in this review. Both of these safety issues will be addressed in my review.

The final recommendations for dosing were based upon the results of the efficacy studies (004 and 005), clinical pharmacology study results and physiologically based pharmacokinetic modeling (PBPK).

Regulatory History:

- IND 078781 was opened on October 22, 2007 by Nektar Therapeutics and on January 12, 2010 the IND was transferred to AstraZeneca Pharmaceuticals LLP.
- The End-of-Phase 2 meeting was held on January 26, 2010.
- On October 8, 2012, DGIEP provided written comments regarding the Division’s concerns of the potential for opioid withdrawal and related adverse cardiovascular outcomes that may be associated with peripherally acting mu-opioid receptor antagonists, including naloxegol. Specific advice regarding the analyses of these events, which were to be included as part of the NDA filing, was discussed. The applicant agreed.
- On April 23, 2013 during the meeting and in the final minutes (May 22, 2013), the Division further clarified that the results from a cardiovascular outcomes trial would not be required prior to NDA filing as long as there was “equipoise after you have reviewed your safety data”.
- AstraZeneca submitted NDA 204760 on September 16, 2013. The applicant was granted a standard review and reviewed under the Program.
- On June 11-12, 2014, a meeting of the Anesthesia and Analgesia Drug Products Advisory Committee (AADAC) was held to discuss the assessment of cardiovascular safety for five peripherally acting mu-opioid receptor antagonists in various stages of development for the treatment of OIC in patients with chronic non-cancer pain, including Cubist’s Entereg (alvimppan), Salix’s Relistor (methylnaltrexone bromide), and AstraZeneca’s Movantik (naloxegol).

4. CMC

The Quality Reviewer concluded that the applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. In addition, review of the final professional labeling, carton and container was found to be acceptable.

On 25-Aug-2014, Method Validation was documented for the following methods:

1. (b) (4) test by LC
2. Assay by UHPLC
3. Assay by HPLC
4. (b) (4) by LC

The report found all methods acceptable for the quality control and regulatory purposes.

On 23-Jun-2014 the Office of Compliance issued an overall recommendation of “Acceptable” for the facilities involved in this application.

The sponsor provided the results of up to 12 months long-term stability studies, and proposed a 24-month expiration dating period for all packaging presentations under the controlled room

temperature conditions. According to the quality review the requested expiration dating periods are granted for all the packaging configurations (6/12/14).

Environmental Assessment

The applicant claimed categorical exclusion from the Environmental Assessment based on 21CFR 25.31(a) or (b). The review of the Environmental Assessment was documented on 18-Jul-2014, with the determination that the application qualifies for the categorical exclusion claimed by the sponsor.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

5. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewer discussed naloxegol's potential for CNS effects, carcinogenicity study results and the potential for formulation of ethylene glycol (EG), diethylene glycol (DEG) and other metabolites.

Based on the studies submitted in the NDA, the reviewer concluded the results suggested that naloxegol at high doses in animals has considerable CNS effects. These exposures were in excess of what can be expected in humans at the labeled recommended doses.

The nonclinical reviewer also concluded that the results of the 2-year carcinogenicity study in rats support the proposal that the observed drug-related increase in the incidence of benign Leydig cell adenoma and hyperplasia in rats was likely due to naloxegol-induced centrally mediated hormonal changes (i.e. elevated LH levels). The reviewer further noted that such a mechanism in tumor formation is common in rats. Given that the drug-induced increase in Leydig cell adenoma increase was statistically significant only at 400mg.kg.day (818 times the human AUC at the MHRD), the nonclinical reviewer concluded that this effect is unlikely to be relevant to humans. These data are represented in section 13.1 [Carcinogenesis, Mutagenesis, and Impairment of Fertility] of the approved professional labeling.

The proposed metabolism of naloxegol, a PEGylated product, is described as formation of partially shortened PEG chain products. DGIEP was interest in in the potential for EG or DEG exposure. This issue was addressed by the applicant using both a theoretical worst case scenario and estimates modeled on the measurement of the shortened products. Based on these explorations and relying on EPA Reference Doses (RfD) as well as Permitted Daily Exposure (PDE) stated in the International Conference on Harmonization (ICH) guidance Q3C, the nonclinical reviewer was assured that this information provides reasonable assurance of safety for the potential exposure to EG and DEG as metabolites of naloxegol. Review of the clinical safety data base supported this assertion.

The nonclinical reviewer recommended approval of this application and final version of the professional labeling.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

6. Clinical Pharmacology/Biopharmaceutics

The applicant conducted an *in vivo* BE study in order to demonstrate the bioequivalence between two formulations: the commercial to be marketed film-coated tablet 25 mg (naloxegol oxalate) and the naloxegol film-coated tablet 25 mg (as free base) which was used in the phase 3 studies. Based on the data, the biopharmaceutics reviewer concluded that the commercial formulation is bioequivalent to the phase 3 formulation.

Data regarding pharmacokinetics, specific populations and drug-drug interactions were reviewed by the clinical pharmacology and biopharmaceutics reviewers. They noted an exposure-response relationship for the primary efficacy endpoint stating that the “shallow exposure-response analysis also indicates that lower exposures compared to that observed with 25 mg may not result in a meaningful loss of efficacy”. In addition, they also found “a dose and exposure-response based on an evaluation of gastrointestinal adverse events. In particular abdominal pain was evaluated by severity, and relationships for moderate and severe and severe events were considered to be shallow. Dose-response was also apparent for discontinuations due to opioid withdrawal events. Discontinuations were 2-fold higher for the 25 mg compared to 12.5 mg dose group, due to adverse events. However, the drug was fairly well tolerated overall with less than 20% of patients discontinuing the study in the 25 mg group due to adverse events.” Based on the efficacy results in study 004 and 005 with a shallow exposure-response relationship and apparent dose-response in both studies, the clinical pharmacology review recommended that patients who cannot tolerate the drug due to abdominal pain reduce the dose to 12.5 mg prior to discontinuing the drug.

Based on *in vitro* studies, CYP 3A4/5 appear to be the major isoforms for the metabolism of naloxegol. This resulted in several recommendations for the Drug-Drug Interaction section of the label (section 7). Concomitant use of a strong CYP 3A4/P-gp inhibitor was contraindicated due to the potential to increase the C_{max} and AUC of naloxegol by 11- fold and ~13-fold. Moderate CYP3A4/P-gp inhibitors resulted in a 3 fold increase in C_{max} and AUC. A recommendation was made to avoid use of Movantik with moderate CYP3A4 inhibitors; if unavoidable, decrease the dosage of Movantik to 12.5 mg once daily and monitor for adverse reactions. No dosage adjustments are necessary for weak CYP3A4 inhibitors. Strong CYP3A4 inducers significantly decrease plasma naloxegol concentrations and may decrease the efficacy of Movantik. Use with strong CYP3A4 inducers is not recommended. (Refer to approved professional labeling for more information).

In patients with mild to moderate hepatic impairment no adjustment in dose is recommended. Studies with severe hepatic impairment have not been performed.

Some subjects with creatinine clearance (CL_{cr}) values < 60 mL/minute (i.e., moderate, severe or end-stage renal disease) were shown to exhibit markedly higher systemic exposure of naloxegol compared to subjects with normal renal function. The reason for these high exposures is not understood. However, as the risk of adverse reactions increases with systemic

exposure, a lower starting dosage of 12.5 mg once daily is recommended. No dosage adjustment is needed in patients with mild renal impairment.

Information regarding the effect of hepatic CYP2C8 enzyme on naloxegol provided by the sponsor was not sufficient. A post-marketing commitment to conduct an *in vitro* study to evaluate the time-dependent/mechanism-based inhibition potential of naloxegol on the hepatic CYP2C8 enzyme was agreed upon.

The cardiovascular reviewer's recommendation to add wording from the naloxone label was rejected by the review team (see CDTL memo). We concluded that the available data did not demonstrate significant amounts of naloxone or naloxol present in the drug product or drug metabolites.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

7. Clinical Microbiology

Clinical Microbiology does not apply to this application because naloxegol is not an antimicrobial agent.

8. Clinical/Statistical-Efficacy

The evaluation of efficacy was based on two randomized, double-blind, placebo-controlled controlled trials (Study 004 and Study 005) in patients with opioid-induced-constipation (OIC) and non-cancer related pain.

Patients receiving an opioid morphine equivalent daily dose of between 30 and 1,000 mg for at least four weeks before enrollment and self-reported OIC were eligible to participate. OIC was confirmed through a two-week run in period and was defined as <3 spontaneous bowel movements (SBMs) per week on average with at least 25% of the SBMs associated with one or more of the following conditions: (1) straining, (2) hard or lumpy stools; and (3) having a sensation of incomplete evacuation. An SBM was defined as a bowel movement (BM) without rescue laxative taken within the past 24 hours. Patients with 0 BMs over the two-week run-in period or patients with an uneven distribution of SBMs across the two-week run-in period (0 SBMs in one week with ≥ 4 SBMs in the other week) were excluded. Throughout the studies (including the two-week run-in period), patients were prohibited from using laxatives other than bisacodyl rescue laxative (if they had not had a BM for 72 hours) and one-time use of an enema (if after 3 doses of bisacodyl, they still did not have a BM).

Patients suspected of having clinically important disruptions to the blood-brain barrier were not enrolled in these studies.

A total of 652 patients in Study 004 and 700 patients in Study 005 were randomized in a 1:1:1 ratio to receive 12.5 mg or 25 mg of MOVANTIK or placebo once daily for 12 weeks.

The mean age of the subjects in these two studies was 52 years, 10% and 13% were 65 years of age or older, 61% and 63% were women, and 78% and 80% were white in Studies 1 and 2, respectively.

Back pain was the most common reason for pain (56% and 57%); arthritis (10% and 10%) and joint pain (3% and 5%) were other prominent reasons in Studies 004 and 005, respectively. Prior to enrollment, patients had been using their current opioid for an average of 3.6 and 3.7 years. The patients who participated in Studies 004 and 005 were taking a wide range of opioids. The mean baseline opioid morphine equivalent daily dosage was 140 and 136 mg per day.

Use of one or more laxatives on at least one occasion within the two weeks prior to enrollment was reported by 71% of patients in both Studies 004 and 005. The primary endpoint was response defined as: ≥ 3 SBMs per week and a change from baseline of ≥ 1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks.

There was a statistically significant difference for the 25 mg Movantik treatment group versus placebo for the primary endpoint in Study 004 and Study 005 (see Table 1). Statistical significance for the 12.5 mg treatment group versus placebo was observed in Study 004 but not in Study 005.

TABLE 1. Primary Endpoint: Response[#]

	Study 004			Study 005		
	Placebo (N = 214)	Naloxegol 12.5 mg (N = 213)	Naloxegol 25 mg (N = 214)	Placebo (N = 214)	Naloxegol 12.5 mg (N = 232)	Naloxegol 25 mg (N = 232)
Patients responding, n (%)	63 (29%)	87 (41%)	95 (44%)	8 (29%)	81 (35%)	92 (40%)
Treatment Difference [†] (95% CI)	----	11.4% (2.4%, 20.4%)	15.0% (5.9%, 24.0%)	---	5.6% (-2.9%, 4.1%)	10.3% (1.7%, 18.9%)
p-value	----	0.015*	0.001*	---	0.202	0.021*

[#]Response defined as: ≥ 3 SBMs per week and a change from baseline of ≥ 1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks.

*Statistically significant: p-values based on the Cochran-Mantel-Haenszel test.

The results from these two studies support the approval of the naloxegol 25mg daily dose. Another drug, lubiprostone, approved for the treatment of OIC utilized this primary endpoint analysis for the determination of efficacy. This primary efficacy endpoint analysis was recommended by DGIEP and is acceptable.

Discussion regarding the lack of statistical significance for the 12.5 mg naloxegol treatment arm, the data from Study 004 and the PKPB analysis supports the approval of the 12.5 mg dose for patients who have significant abdominal pain while taking the 25mg naloxegol dose. In addition, the 12.5 mg dose is recommended in patients who require a dose reduction. (see clinical pharmacology/biopharmaceutics section).

The applicant designated three analyses as prespecified key secondary endpoint analysis:

- Response in a sub-group of laxative users with OIC symptoms at entry during study weeks 1 to 12. (Response is identical to the primary analysis endpoint),
- Time to first post-dose SBM without use of rescue laxatives within 24 hours,
- Mean number of days per week with at least 1 SBM during Weeks 1 to 12 (only days with no more than 3 SBM's in one day are included).
 - (Differences between treatment groups will be analyzed using the mixed model repeated measures (MMRM) approach; the MMRM will include the treatment group, the baseline value of the response variable, time (as a class variable for weeks 1 to 12 as applicable) and treatment-time interaction and baseline laxative response as fixed effects, and center as a random effect (Source: Statistical Analysis Plan of each study). See the Statistics Review for additional details.

These endpoints were analyzed in order, following the testing of the primary efficacy variable in each group. The secondary endpoints were part of the statistical Multiple Testing Procedure. These secondary analyses do not include the results for Movantik 12.5 mg versus placebo in study 005 because the primary endpoint was not statistically significant.

Although there was much discussion during development and review of this product regarding the potential recall bias of the screening questionnaire, a subgroup was defined based upon the information collected by this questionnaire and this subgroup was used as a stratification variable for the randomization procedure. The statistical procedures were appropriate and were validated by the statistical reviewer. Because each was statistically significant the applicant requested these results be placed into the label. A decision was made that it would be useful to describe the characteristics of this population in the label so that clinicians would have a more complete understanding of the types and approximate frequency of laxative use in the 2 weeks prior to screening for this study. Finally, the results in this subgroup were similar to the overall study population results for the primary endpoint. The results of this analysis are described in the approved label as follows:

“This subgroup comprised 55% and 53% of total patients in these two studies respectively. These patients (identified using an investigator-administered questionnaire), prior to enrollment, had reported using laxative(s) at least 4 out of the past 14 days with 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. In this subgroup, in Studies 1 and 2, 42% and 50% reported using laxatives on a daily basis. The most frequently reported laxatives used on a daily basis were stool softeners (18% and 24%), stimulants (16% and 18%), and polyethylene glycol (6% and 5%). Use of two laxative classes was reported in 31% and 27% anytime during the 14 days prior to enrollment. The most commonly reported combination was stimulants and stool softeners (10% and 8%). In Study 1, a statistically significantly higher percentage of patients in this subgroup responded with MOVANTIK 12.5 mg compared to placebo (43% vs. 29%; $p=0.03$) and with MOVANTIK 25 mg compared to placebo (49% vs. 29%; $p=0.002$). In Study

2, a statistically significantly higher percentage of patients in this subgroup responded with MOVANTIK 25 mg compared to placebo (47% vs. 31%; $p=0.01$)”.

The next secondary endpoint was an analysis of time to first SBM (laxation without the use of rescue laxatives in the previous 24 hours). Estimates of the median times to first post-dose SBM for the three treatment arms were calculated using the Kaplan-Meier technique. A log-rank test was also used to derive the p-value for the comparisons between the treatment groups and placebo. The estimates represented in the label are based on this analysis. It should be noted that the study protocol restricted rescue medication in the first 72 hours after the initial dose with Movantik. Internal discussion regarding the clinical meaningfulness of the data to the individual patient was questioned. During labeling discussions the clinical review team felt it was important to represent the data somewhat differently agreeing with the applicant to describe the time in hours for the first SBM as well. “In the two studies, 61-70% and 58% of patients receiving Movantik 25 mg and Movantik 12.5 mg, respectively, had an SBM within 24 hours of the first dose”. P-values are not associated with these results as they were not prespecified; however, they resulted from the statistically significant, prespecified analysis. Finally, the lubiprostone label includes an analysis of response (laxation) and timing which is somewhat different from this analysis. At this time the division does not have a specific preference.

The label states the results of this secondary analysis as follows:

“Another secondary endpoint was time to first post-dose SBM. The time to first post-dose SBM was significantly shorter with Movantik 25 mg compared to placebo in both Study 1 ($p < 0.001$) and Study 2 ($p < 0.001$), and for Movantik 12.5 mg as compared to placebo in Study 1 ($p < 0.001$). For Study 1, the median times to first post-dose SBM were 6, 20, and 36 hours with Movantik 25 mg, Movantik 12.5 mg, and placebo, respectively. For Study 2, the median times to first post-dose SBM were 12 and 37 hours with Movantik 25 mg and placebo, respectively. These analyses do not include the results for Movantik 12.5 mg versus placebo in Study 2 because the primary endpoint was not statistically significant. In the two studies, 61-70% and 58% of patients receiving Movantik 25 mg and Movantik 12.5 mg, respectively, had an SBM within 24 hours of the first dose”.

The last prespecified secondary endpoint was an evaluation of change from baseline between the treatment groups for mean number of days per week with at least 1 SBM but no more than 3 SBM's. This analysis was supportive of the primary endpoint, was prespecified and statistically significant. However, the clinical meaningfulness and interpretation of this analysis by clinicians was questioned by DGIEP. There were patients who had more than 3 SBMs per day in all groups. This analysis may be viewed as a subgroup of patients who may have an “optimal” quality of response (no diarrhea). In addition, the results are a summary of responses averaged by week over 12 weeks of the study treatment. This group mean may have little meaning for the individual patient. However, a compromise was reached to describe the results in the label as follows:

“There was a significant difference in number of days per week with 1 to 3 SBM’s per day on average over 12 weeks between MOVANTIK 25 mg (Study 1 and Study 2) and MOVANTIK 12.5 mg (Study 1) and placebo”.

Movantik is used to treat the constipating side effects of opioid therapy; as such there are several points of information in section 2.1 (Administration) of the professional labeling which are important for the clinician to consider. These points were based upon the entry criteria and are listed in the label as follows:

- “Discontinue all maintenance laxative therapy prior to initiation of MOVANTIK. Laxative(s) can be used as needed if there is a suboptimal response to MOVANTIK after three days”.
- “Alteration in analgesic dosing regimen prior to initiating MOVANTIK is not required”.
- “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 “.
- “Discontinue MOVANTIK if treatment with the opioid pain medication is also discontinued.”

The recommended adult dosage of Movantik is 25 mg once daily in the morning on an empty stomach 1 hour prior to the first meal or 2 hours after the meal. If patients are not able to tolerate Movantik, reduce the dosage to 12.5 mg once daily. Alterations depending on drug-drug interaction and special populations are discussed in the clinical pharmacology section of this review.

9. Safety

The overall safety database was reviewed and the common adverse reactions are listed in the approved labeling. The database was adequate for the evaluation of these reactions. As mentioned above, concern regarding the cardiac safety based results of safety from another member of this class (Entereg), required additional analyses by the clinical team and consults from the Division of Cardiovascular and Renal Products. In addition, while the applicant claimed that there was no central withdrawal with concomitant use of Movantik and opioids, the results of efficacy and other symptoms may be viewed as “peripheral” withdrawal. A consult to the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) division was also reviewed. Finally, since several opioid antagonist receptor products are in development a general matters Advisory Committee (AC) was held to discuss these safety issues of interest specific interest across this class of drug seeking the OIC indication. Additional descriptions of the AC members recommendations can be found later in this review.

Through QT Study:

A randomized, blinded, four-period crossover study, 51 healthy subjects received a single dose 25mg (therapeutic dose) and 150 mg (supratherapeutic dose) of naloxegol, placebo, and a single oral dose of moxifloxacin 400 mg. The TQT team reviewer concluded that “no

significant QTc prolongation effect of NKTR-118 [naloxegol] was detected in this TQT study. The largest upper bound of the 2-sided 90% CI's for the mean differences between NKTR-118 and placebo is below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines". They further state that "the suprathereapeutic dose (150 mg) produces mean Cmax values 7.7-fold the mean Cmax for the therapeutic dose (25 mg). These concentrations are not above those for the predicted worst case scenario (drug interaction with ketoconazole). It is expected from drug interaction studies that co-administration of NKTR-118 with ketoconazole can elevate naloxegol's mean Cmax as much as 9.6-fold". The Sponsor states that they plan to contraindicate co-administration of strong CYP3A4 and Pgp inhibitors.

The clinical pharmacology reviewer agrees with the recommendation to contraindicate the use of concomitant strong CYP3A4 and Pgp inhibitors. Co-administration of moderate CYP3A4 and Pgp inhibitors are predicted to result in less than a 5- fold increase in AUC of naloxegol. Therefore, the resultant naloxegol exposure is less than that produced by the supra-therapeutic dose used in this study.

Changes in heart rate, RR, PR, and QRS ECG intervals were also monitored in this study and were similar between placebo and naloxegol 25 or 150 mg.

Section 6 ADVERSE REACTIONS of the professional label describes the overall safety and the results of the potential for opioid withdrawal symptoms as follows:

"The data described below reflect exposure to MOVANTIK in 1497 patients in clinical trials, including 537 patients exposed for greater than six months, and 320 patients exposed for 12 months".

"The safety data described in Table 1 are derived from two double-blinded, placebo-controlled trials (Studies 1 and 2) in patients with OIC and non-cancer related pain".

"Study 3 (n=302) was a safety extension study that allowed patients from Study 1 to continue the same blinded treatment for an additional 12 weeks. Safety data for patients in Study 3 are similar to those listed in Table 1".

"Study 4 (n=844) was a Phase 3, 52-week, multi-center, open-label, randomized, parallel group, safety and tolerability study of naloxegol versus usual care treatment for OIC (as determined by the investigator and excluding peripheral opioid antagonists) in patients with non-cancer related pain. The population enrolled in Study 4 was similar to that of the other studies. Eligible patients were randomized in a 2:1 ratio to receive either naloxegol 25 mg once daily or usual care treatment for OIC. The most commonly used laxatives in the usual care group were rectal stimulants (e.g., bisacodyl), oral stimulants (e.g., senna), and oral osmotics (e.g., macrogol, magnesium). Safety data for patients in Study 4 are similar to those listed in Table 1".

"Table 1 lists adverse reactions in pooled Studies 1 and 2 occurring in $\geq 3\%$ of patients receiving MOVANTIK 12.5 mg or 25 mg and at an incidence greater than placebo".

Table 1. Adverse Reactions* in Patients with OIC and Non-Cancer Pain (Studies 1 and 2)

Adverse Reaction	MOVANTIK 25 mg (n=446)	MOVANTIK 12.5 mg (n=441)	Placebo (n=444)
Abdominal Pain	21%	12%	7%
Diarrhea	9%	6%	5%
Nausea	8%	7%	5%
Flatulence	6%	3%	3%
Vomiting	5%	3%	4%
Headache	4%	4%	3%
Hyperhidrosis	3%	<1%	<1%

Opioid Withdrawal

“Possible opioid withdrawal, defined as at least three adverse reactions potentially related to opioid withdrawal that occurred on the same day and were not all related to the gastrointestinal system, occurred in less than 1% (1/444) of placebo subjects, 1% (5/441) receiving Movantik 12.5 mg, and 3% (14/446) receiving MOVANTIK 25 mg in Studies 1 and 2 regardless of maintenance opioid treatment. Symptoms included but were not limited to hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning. Patients receiving methadone as therapy for their pain condition were observed in Studies 1 and 2 to have a higher frequency of gastrointestinal adverse reactions than patients receiving other opioids [39% (7/18) vs. 26% (110/423) in the 12.5 mg group; 75% (24/32) vs. 34% (142/414) in the 25 mg group]”.

The cluster of symptoms reported above as possible opioid withdrawal, are related to the action of naloxegol as a peripheral mu-opioid receptor antagonist. The clinical consult from DAAAP and discussions with the review team during labeling negotiations concurs with the wording in the previous paragraph. It further concludes that “naloxegol does not appear to have an effect on analgesia, based on analyses of opioid dose and pain scores during the trials. However, these analyses were descriptive in nature as the studies were not designed to assess these endpoints in a statistical manner”. These results influenced the wording of the approved labeling.

Although patients suspected of having clinically important disruptions to the blood-brain barrier were not enrolled in clinical trials of naloxegol, these patients may be at increased risk

for opioid withdrawal or reduced analgesia. This appears in section 5.2 Warnings and Precautions of the labeling.

The potential for cardiovascular risk was evaluated in the 52 week multi-center, open-label, randomized, parallel group, safety study described above. The naloxegol trial was similar in size to the Entereg study, had better follow-up and predefined cardiovascular assessments. While the sample size of this study cannot rule out a rare cardiovascular signal, it is reassuring that one was not seen. As a result of the clinical and consultant reviews, and AC comments, this safety database is acceptable for approval of Movantik. (see FDA's and Astra Zeneca's backgrounder for additional details:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm390304.htm>). A post-market observational study will be required (see below).

No association was seen between symptoms potentially related to opioid withdrawal was and adverse cardiovascular events. No patients experiencing opioid withdrawal symptoms had a report of major adverse cardiovascular event (MACE).

Cases of gastrointestinal perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using MOVANTIK in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent or worsening abdominal pain; discontinue MOVANTIK in patients who develop this symptom. This information was included in the Warnings and Precautions section of the labeling.

10. Advisory Committee Meeting

The Anesthesia and Analgesia Drug Products Advisory committee (AADAC) met on June 11-12, 2014, to discuss the cardiovascular safety for five peripherally acting mu-opioid receptor antagonists in various stages of development for the treatment of OIC in patients with chronic non-cancer pain, including Movantik (naloxegol). (For additional detail, the reader is referred to the background materials and minutes from the meeting available on the FDA website noted above)

The committee discussed the strength of the potential cardiovascular signal which was seen in one long term study with Entereg. Many members felt that it was a weak signal, but further study with Entereg would be required to rule out a signal for Entereg. The advisors were also asked to discuss what studies might be required to assess the cardiac safety of drugs in this class of drugs. The majority of committee members (17 of 24) voted against the need for pre-approval cardiovascular outcome trials for members of this drug class intended to treat OIC in patients with non-cancer pain. There was general consensus that a 12-month controlled trial of modest size would be a useful addition to the safety database of new members of this class of

drugs. Thus, the FDA is requiring a postmarketing observational study to further evaluate the potential risk of cardiovascular adverse events in patients taking Movantik.

11. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Based on the limited available literature, few pediatric patients in all age groups receive round the clock opioids for > 4 weeks. There is also a lack of consensus on the use of opioids for treatment of chronic non-cancer pain in pediatric patients.

12. Other Relevant Regulatory Issues

- Abuse potential: Controlled substance staff (CSS) was consulted to evaluate the abuse-related preclinical and clinical data submitted to this NDA. 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. The CSS consult concluded that “it [*naloxegol*] 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”. This recommendation for decontrol under the Controlled Substance Act has been sent to the DEA and any changes in classification will be made in the future. The approved labeling will have to contain the Schedule II designation until that time. Wording in section 9.0 (Drug Abuse and Dependence) was found acceptable to the CSS reviewer at this time.
- DSI Audits: findings did not preclude an approval recommendation.
- Financial Disclosure: was reported by applicant and found to be acceptable.
- Other consults: no outstanding issues

There are no other unresolved relevant regulatory issues.

13. Labeling

- Proprietary name: The proprietary name, Movantik, was found acceptable.
- Physician labeling: major issues were discussed and resolved.
- Medication Guide (approval letter attachment).
- Carton and immediate container labels: The final carton and container labels have been agreed upon and are acceptable.

- A Medication Guide is included in this label and is approved under 21 CFR 208.

14. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** Approval of Movantik (naloxegol) 25 mg and 12.5 mg tablets for the treatment of opioid-induced constipation (OI) in adult patients with chronic non-cancer pain.

- **Risk Benefit Assessment:**

The benefit of naloxegol for the treatment of OIC in adult patients with chronic non-cancer pain has been demonstrated. Although there is concern regarding a potential signal of cardiovascular safety with this class of drugs, the long-term comparative safety study, TQT study, and nonclinical data do not demonstrate such a signal for naloxegol. The potential for peripheral withdrawal symptoms are both part of the action of naloxegol (inhibition of mu-opioid receptor antagonists in the gastrointestinal tract) and a side effect (abdominal pain). The safety of naloxegol has been demonstrated in phase 3 clinical trials and one long term comparative study. The risks can be mitigated through professional labeling and a required postmarketing observational study.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS):**

Based upon the Risk Benefit Assessment a REMS is not necessary for the safe use of Movantik.

- **Recommendations for other Postmarketing Requirements (PMRs) and Commitments (PMCs):**

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that Astra Zeneca is required to conduct the following:

PMR 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 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.

A Postmarketing Commitment (PMC) was also established.

PMC 2779-2

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

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/s/

JOYCE A KORVICK
09/16/2014