CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207233Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ellen Fields, MD, MPH
Subject	Deputy Division Director Summary Review
NDA #	207233
Applicant Name	Iroko Properties, Inc.
Date of Submission	December 23, 2014
PDUFA Goal Date	October 23, 2015
Proprietary Name / Established (USAN) Name	VIVLODEX/meloxicam capsules
Dosage Forms / Strength	Capsules/ 5 mg and 10 mg
Proposed Indication(s)	Management of osteoarthritis pain
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Amelia Luckett, MD
CDTL	Ellen Fields, MD, MPH
Statistical Review	Kate Meaker, MS, Freda Cooner, PhD
Pharmacology Toxicology Review	Armaghan Emami, PhD, Jay Chang, PhD, R. Daniel Mellon, PhD
CMC Review	Ciby Abraham, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Deep Kwatra, PhD, Yun Xu, PhD
OPDP	L. Shenee Toombs
OSI	John Lee, Janice Pohlman
OSE/DMEPA	Millie Shah, Pharm D, Vicky Borders-Hemphill, Pharm D
OSE/DRISK	N/A
Other	N/A

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
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

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1. Introduction

Iroko Properties, Inc. (the Applicant) submitted this 505(b)(2) new drug application to obtain approval to market VIVLODEX Capsules, a new immediate-release capsule formulation of meloxicam, for the proposed indication of management of osteoarthritis pain. This NDA was submitted via the 505(b)(2) regulatory pathway and has relied in part on the Agency's prior findings of efficacy and safety for Mobic Tablets 7.5 and 15 mg (NDA 20938, Boehringer Ingelheim).

The key issues that will be discussed in this review are the Applicant's theory about the effect of a smaller particle size of meloxicam in this formulation, and efficacy findings for the 10 mg compared to the 5 mg dosage strengths. This memo serves as both the CDTL and Summary memos for this NDA.

2. Background

The Applicant conducted the clinical development program under IND 114045, and proposes to market VIVLODEX in two capsule strengths, 5 mg and 10 mg to be dosed once daily. The application is supported by a relative bioavailability, dose proportionality, and food-effect study, an adequate and well-controlled Phase 3 efficacy and safety study, and an open-label Phase 3 safety study. A single efficacy study was deemed sufficient because the Applicant is relying in part on prior findings of efficacy and safety for Mobic, which is also approved for management of osteoarthritis pain. The Division advised the Applicant during development that they need to address the risk of possible medication errors and confusion with other meloxicam products. For additional details regarding the development program for VIVLODEX see the review by Dr. Amelia Luckett.

VIVLODEX capsules are a reformulation of meloxicam with reduced particle size. The 5 and 10 mg capsules contain 33% less meloxicam that the approved Mobic 7.5 and 15 mg tablets. The Applicant's rationale for the reduced particle size is to increase the surface area-to-mass ratio and thereby facilitate the rapid absorption in the gastrointestinal tract. Mobic reaches a peak concentration (Cmax) of meloxicam at 5 hours (Tmax) and the bioavailability of meloxicam after oral administration is almost 89%. Therefore, there appears to be little room for a new formulation to improve on the extent of absorption in terms of bioavailability of the drug, but there is potential to improve the rate of absorption to reduce the Tmax.

The final area of concern discussed in this memo is the result of the efficacy study that showed similar efficacy of the 5 mg and 10 mg doses of VIVLODEX. Although both doses were shown to be superior to placebo on the primary endpoint, there did not appear to be additional efficacy conferred by the 10 mg compared to the 5 mg dose.

3. CMC/Device

Ciby Abraham, PhD was the CMC lead reviewer for this application. Additional reviewers contributed to the review and those names are listed in Dr. Abraham's review. Based on recommendations from the following disciplines, drug substance, process, microbiology,

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biopharmaceutics, facilities, and drug product, CMC recommends the approval of Vivlodex 5 mg and 10 mg capsules.

As stated in Dr. Abraham's review:

> The drug substance, Meloxicam is manufactured by [redacted] (b) (4) and is referenced in DMF# [redacted] (b) (4) (adequate, last reviewed 6/2/2015). Meloxicam is a pale yellow [redacted] (b) (4) with no chiral centers. The drug substance has a [redacted] (b) (4) retest period.
>
> The drug product Vivlodex is manufactured by [redacted] (b) (4) Vivlodex immediate release 5 mg and 10 mg capsules are manufactured from [redacted] (b) (4) Vivlodex capsules are stored in 100 cc round HDPE bottles with a 38 mm [redacted] (b) (4), in 90-count bottles and 30-count bottles. Physician samples of Vivlodex capsules 5 mg and 10 mg will be provided in [redacted] (b) (4) count blister [redacted] (b) (4) in clear [redacted] (b) (4) film with push through foil. Based on the stability data provided, an expiry of 24-months will be granted for the 5 mg and 10 mg capsules when stored in the 90-count and 30-count 100 cc HDPE bottles with the storage statement "Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F)." For the [redacted] (b) (4) count blister [redacted] (b) (4) 24-month expiry will be granted for the 5 mg and 10 mg capsules using the storage statement "Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F) protected from moisture."
>
> The sponsor has provided adequate information to support the manufacturing and control of the drug substance, process, microbiology, biopharmaceutics, facilities, and drug product. The application is therefore recommended for approval.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable.

4. Nonclinical Pharmacology/Toxicology

No nonclinical studies with VIVLODEX were conducted for this NDA, as the Applicant is relying in part on previous findings for Mobic as well as nonclinical pharmacologic, pharmacokinetic, and toxicology literature from 1990 to 2014. There were no novel excipients in the Vivlodex formulation.

As noted by Dr. Emami, an in silico computational genotoxicity evaluation of three meloxicam-related impurities was performed by the Applicant. Two of the impurities showed no evidence of genetic toxicity to humans. However, one impurity, [redacted] (b) (4) showed evidence of potential genotoxicity. This will be mitigated by the Applicant controlling levels of this impurity below 1.5 mcg/day in accordance with ICH M7.

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

5. Clinical Pharmacology/Biopharmaceutics

One study, MELl-12-04 was conducted with the to-be marketed formulation of VIVLODEX and assessed relative bioavailability (BA), dose-proportionality (5 and 10 mg VIVLODEX), and food effect. The relative BA of VIVLODEX was compared to Mobic 15 mg tablets under fasting conditions. As stated by Dr. Kwatra in his review:

- VIVLODEX 10 mg dose not result in similar systemic exposure as reference meloxicam 15 mg tablets and are not bioequivalent.

- When taken under fasted conditions, 33% lower dose of VIVLODEX capsules (10 mg) compared to meloxicam tablets (15 mg) results in equivalent (geometric mean) peak concentrations (Cmax), and 18 and 33 % lower (geometric mean) AUC_{0-t} and $AUC_{0-\infty}$, respectively. Since the 33% lower dose of VIVLODEX results in 33% lower $AUC_{0-\infty}$ compared to Mobic, the new formulation does not improve the bioavailability of meloxicam. The median time to reach peak concentrations (Tmax) for VIVLODEX capsules is two hours earlier compared to meloxicam tablets (VIVLODEX 2 hours versus Mobic 4 hours). There were no significant differences in elimination half-life ($t_{1/2}$) between VIVLODEX capsules and Mobic tablets (VIVLODEX 22.04 hours vs. Mobic tablets 23.64 hours).

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The figure and table below from Dr. Kwatra's review show the relative BA for 5 and 10 mg VIVLODEX compared to Mobic 15 mg tablets.

Figure 2.4.1a: Mean meloxicam plasma concentration-time profiles after administration of VIVLODEX capsules (5mg & 10 mg) and mobic tablet (15mg) under fasted conditions.

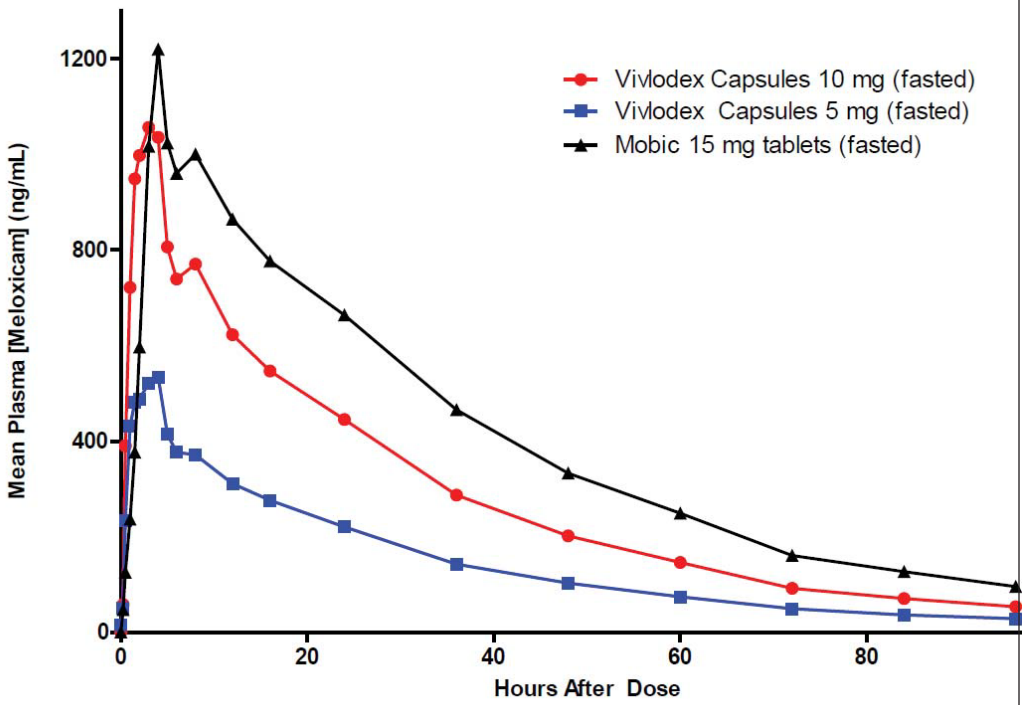

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Table 2.4.1a. Pharmacokinetic parameters comparing VIVLODEX capsules and Mobic tablets under fasted conditions.

Parameter Arithmetic mean ± SD (n)	**VIVLODEX capsules Fasted**		**Mobic tablets (15 mg) Fasted (27)**
	5 mg (26)	**10 mg (27)**	
Cmax (ng/mL)	642.4± 138.5	1252.8±254.2	1288.8± 424.4
AUC_{0-t} (hr*ng/mL)	14206.5 ±5415.3	28190.5±9264.7	39093.8 ±16500.2
$AUC_{0-\infty}$ (hr*ng/mL)	13610.5 ±3342.7	29173.0±11042.1	40875.6 ±11733.5
Tmax (hr)*	2.00 (0.50, 4.07)	2.00 (1.00, 5.00)	4.00 (2.02, 8.00)
$T_{1/2}$ (hr)	22.32± 10.91	22.04 ±10.08	23.64±10.04

*Median (min, max);

The two strengths VIVLODEX 5 and 10 mg capsules are compositionally proportional. The 5 and 10 mg strengths show dose proportional pharmacokinetics for Cmax and AUC under fasted conditions.

Food effect was assessed for VIVLODEX 10 mg capsules

- When taken under fed conditions, VIVLODEX capsules results in decreasing rate (Cmax and Tmax) but not the overall extent of meloxicam absorption (AUC0-∞). Under fed conditions, VIVLODEX 10 mg capsules results in 22% lower Cmax, 6% lower AUC_{0-t} and 8% lower $AUC_{0-\infty}$ respectively compared to the fasted conditions. Taking VIVLODEX with food delayed the Tmax by 3 hours (2 hours fasted vs. 5.00 hours fed).
- Under fed conditions, the reference Mobic tablet results in 22% higher Cmax and no change in AUC compared to fasted conditions. Taking Mobic tablets with food resulted in Tmax achieved between 5 and 6 hours. The source of reference food effect data is from the label of the reference drug.
- The Mobic label states that it can be administered without regard to timing of meals. The observed food effect for VIVLODEX capsules though not comparable to the reference meloxicam tablets, significant changes were not observed in the overall exposure and hence it can be labeled to be taken without regard to timing of meal.

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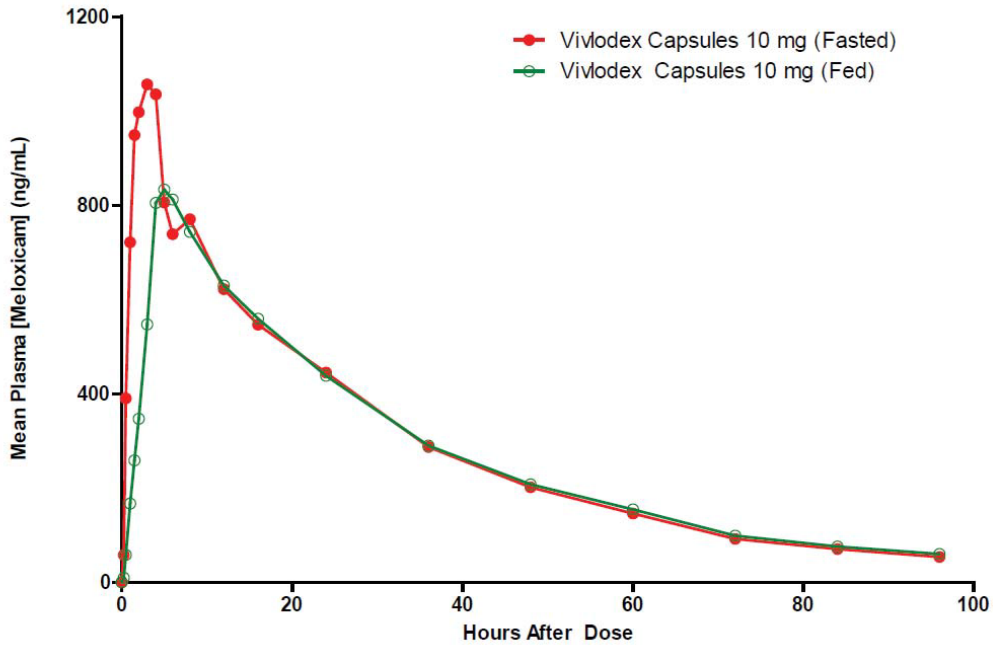
This figure from Dr. Kwatra's review illustrates the above information:

Figure 2.4.2a: Mean meloxicam plasma conc.-time profiles for 10 mg VIVLODEX capsules under fasted and fed conditions (Study MEL1-12-04)



Dr. Kwatra states that overall, adequate information has been provided characterizing the clinical pharmacology aspects of VIVLODEX capsules

The Applicant developed VIVLODEX to have a greater extent of absorption than Mobic, and has failed to demonstrate this to be the case. The relative BA study demonstrated that 10 mg VIVLODEX is a dose that is 33% lower than 15 mg of Mobic, and the exposure to meloxicam for VIVLODEX based on $AUC_{0-\infty}$ is 33% lower as well. The median time to reach peak concentrations (Tmax) for VIVLODEX capsules is two hours earlier compared to meloxicam tablets (VIVLODEX 2 hours versus Mobic 4 hours). For a product intended to be used chronically, this clinical relevance of this difference is questionable. I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

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7. Clinical/Statistical-Efficacy

A single adequate and well-controlled efficacy study conducted to support the efficacy of VIVLODEX for the management of the pain of OA was deemed sufficient by the Division as the Applicant is relying in part on the Agency's prior findings of efficacy and safety for Mobic. The Applicant conducted Study MEL3-12-02, a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled, fixed-dose, parallel-group, efficacy and safety trial of meloxicam capsules in patients with pain due to OA of the knee or hip. The trial was conducted in the US, and 402 subjects with OA pain of the knee or hip were randomized in a 1:1:1 ratio to receive VIVLODEX 10 mg, VIVLODEX 5 mg, or placebo once daily for 12-weeks. Subjects included in the trial were those who were 40 years of age or older with a primary diagnosis of OA of the hip or knee based on the American College of Rheumatology diagnostic criteria. They were prior chronic users (at least 20 of the prior 30 days) of NSAID or acetaminophen treatment for their OA pain and were expected to benefit from continuous treatment with therapeutic doses of NSAIDs. Subjects discontinued use of NSAIDs or other pain medication prior to the baseline visit. They were allowed to take acetaminophen as rescue medication during the treatment period. Additional details of the study design can be found in Dr. Luckett's review.

As stated in Ms. Meaker's statistical review:

> The single primary efficacy endpoint was the change in WOMAC pain from baseline to Week 12. Other assessments of OA pain, such as WOMAC function subscale, total WOMAC score, and Patient Global Impression of Change (PGIC) were collected in the study as secondary endpoints, not intended to support an efficacy labeling claim. The protocol specified that no adjustment for multiple endpoints would be made.
>
> The planned analysis model was a mixed model for repeated measurements (MMRM) model which included observed data at baseline, Week 2, Week 6, and Week 12 on blinded study treatment. This methodology does not impute data for missing values. The concern with the approach, discussed at the End of Phase 2 (EOP2) and pre-NDA meetings with the applicant, is that the model assumes missing at random (MAR). The applicant planned few sensitivity analyses intended to address this concern regarding discontinuation reasons which could be attributed to treatment received, i.e., not at random.
>
> The results of the efficacy analyses showed that both doses of VIVLODEX capsules (5 mg or 10 mg) were statistically significantly different from placebo in the reduction of pain due to OA after a flare during screening. Additional analyses, using alternate models or methods for handling missing data, provided supportive evidence. Both VIVLODEX dose groups showed consistently better reduction in pain on the WOMAC pain subscale comparing to placebo.
>
> My conclusion is that the results of Study MEL3-12-02 show sufficient evidence of efficacy to support an indication of treatment of pain due to OA of the knee or hip for VIVLODEX 5 mg and 10 mg dose strengths.

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The following table showing the efficacy analysis is from the Applicant's clinical study report for Study MEL3-12-02. The results indicate that both Meloxicam dose groups are statistically superior to placebo group for reduction in OA pain (p-values < 0.01)

Table 12 Primary Efficacy Analysis (MMRM Analysis) change from Baseline to Week 12 in WOMAC Pain Subscale Scores—(ITT population)

Visit Statistics	Placebo N=133	Meloxicam SoluMatrix Capsules	
		5 mg N=139	10 mg N=130
Baseline, n	133	139	130
Mean (SD)	73.20 (15.472)	72.51 (15.360)	72.19 (13.938)
Median	75.20	73.20	72.10
Week 12, n	127	131	119
Mean (SD)	44.64 (27.917)	32.91 (26.212)	34.74 (26.709)
Median	44.60	25.00	32.20
Change from Baseline to Week 12, n	127	131	119
LS mean (SE)[a]	-25.68 (2.636)	-36.52 (2.485)	-34.41 (2.678)
95% CI[a]	(-30.86, -20.50)	(-41.40, -31.63)	(-39.68, -29.15)
Comparison vs placebo[a]			
Difference in LS mean (SE)	--	-10.84 (3.097)	-8.74 (3.154)
95% CI for difference	--	(-16.93, -4.75)	(-14.94, -2.53)
P value for difference	--	0.0005	0.0059

Source: Section 14.2. Table 14.2.1.1

A cumulative responder analysis was performed as a secondary analysis. The proportion of patients in each group who demonstrated reduction in their pain intensity score from baseline to Week 12 is shown in the Applicant's figure (proposed for labeling) below. The figure is cumulative, so patients whose change from baseline is, for example, 30%, are also included in every level of pain reduction below 30%. Patients who discontinued study treatment were classified as non-responders.

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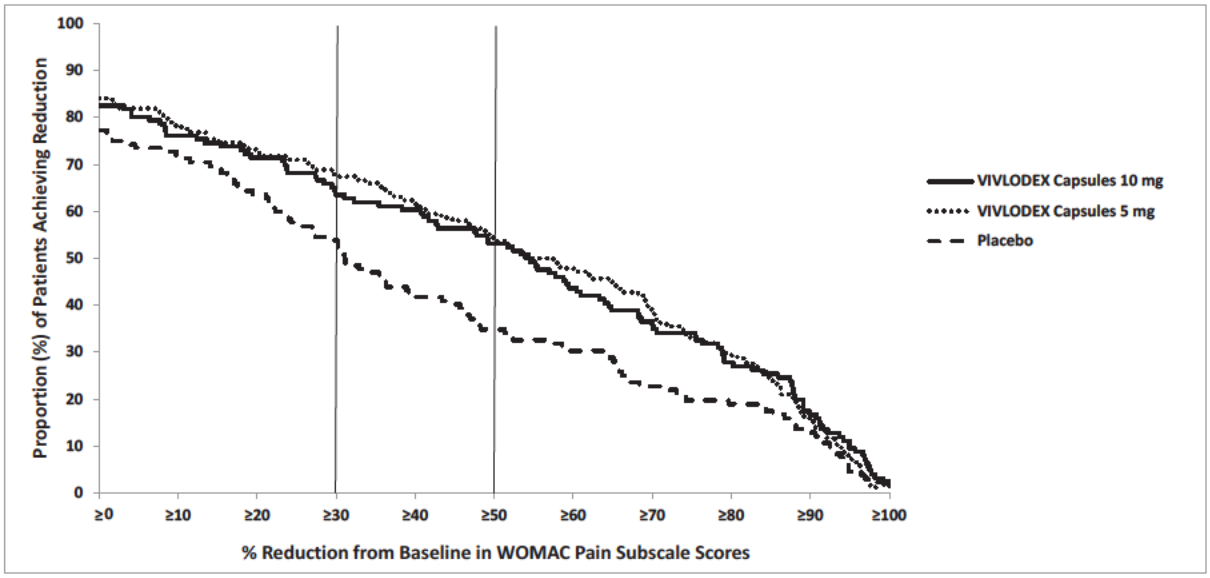
Proportion (%) of Patients Achieving Various Percentage Reductions in Pain Intensity from Baseline to Week 12



It is noteworthy that although both VIVLODEX doses were superior to placebo in terms of efficacy, there was an absence of a dose response, that is, the observed treatment effect for VIVLODEX 10 mg is slightly smaller than that for VIVLODEX 5 mg in this study. This is evident both in the analysis of the primary endpoint as well as in the cumulative responder analysis shown above. Formal statistical testing between VIVLODEX doses was not planned or performed. The Applicant was queried regarding this finding, and they pointed to dose-related differences in certain secondary endpoints that were more favorable for the 10 mg dose than the 5 mg dose. These include, for the 10 mg vs the 5 mg doses respectively, less rescue medication usage as measured by proportion of subjects requiring rescue (80% vs 84%), mean cumulative number of rescue doses (40 vs 46), mean daily rescue medication dosage (281 mg vs 306 mg), and average number of days of rescue use (20 vs 22). Subjects receiving VIVLODEX Capsules 10 mg in this study also reported more positive results overall as measured by the Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) assessments. Both doses of VIVLODEX Capsules resulted in more positive overall PGIC responses compared to placebo; the odds ratio for subjects rating their condition as "much improved" or "very much improved" compared to "much worse" or "very much worse" was greater for VIVLODEX 10 mg compared to 5 mg. A higher percentage of responders were noted in the VIVLODEX 10 mg group compared with the 5 mg and placebo groups in a modified Outcome Measures in Rheumatology-Osteoarthritis Research Society (OMERACT/OARSI) analysis (79% vs 76%). Fewer subjects in the VIVLODEX 10 mg treatment group withdrew from the study due to lack of efficacy (2% vs 5%). Overall differences for these secondary endpoints in favor of the 10 mg dose were small.

Based on the results of the primary endpoint analysis, both the 5 mg and 10 mg doses of VIVLODEX have demonstrated efficacy compared to placebo in subjects with OA of the hip or knee. The finding of similar efficacy for both doses based on the primary endpoint, and

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important secondary endpoints that favored the 10 mg dose will be discussed in the context of safety, pharmacokinetic results, and reliance on prior findings of efficacy for Mobic in the risk-benefit analysis section of this memo.

Although an active comparator arm of Mobic would have enabled the Applicant to evaluate whether their initial hypothesis of greater absorption leading to greater efficacy with a lower dose had merit, as well as providing early evidence of any differences in safety due to the different doses, the Applicant chose not to include a head to head comparison with Mobic. Therefore there is no basis at this time for comparisons to Mobic to be made in labeling or promotional materials.

8. Safety

Dr. Luckett conducted a thorough review of the safety database for this application. No new or unexpected safety issues were identified in her review. VIVLODEX appears to have a similar safety profile to Mobic and to the NSAID class in general.

In support of this NDA, the Applicant provided safety data for VIVLODEX from two Phase 3 trials (MEL3-12-02 and MEL3-12-03). MEL3-12-12 was described above, and MEL 2-12-03 was an open-label, 12-month, Phase 3 trial in patients with OA of the hip or knee conducted for the purpose of obtaining additional safety data for VIVLODEX 10 mg for up to one year. Exposure to at least one dose of VIVLODEX in the two Phase 3 studies consists of 868 subjects.

There were two reported deaths in patients from the open-label study. One was a 69 year old male with a history of hypertension and hyperlipidemia who received VIVLODEX 10 mg for approximately 142 days when he had a ruptured infrarenal abdominal aortic aneurysm. He died of postoperative complications. There was no mention of worsening hypertension in the patient's narrative, however it is possible that Vivlodex may have worsened the hypertension and may have been a contributing factor among many others. The second death was a 62 year old man who received VIVLODEX 10 mg for 282 days when he was noted to have pneumonia, bilateral pulmonary emboli, and heart failure. Of note, he had an additional risk factor for venous thrombosis: heterozygous for the G20210A mutation in the prothrombin/factor II gene. He was taken off the study drug at that time. He expired approximately 2 months later and at which time it was conveyed that he had metastatic mucinous adenocarcinoma. It is unlikely that VIVLODEX contributed to this death.

Of the 600 subjects in study MEL3-12-03, 35 (5.8%) experienced at least one serious adverse event (SAE), and no SAEs were reported in other studies. Dr. Luckett determined that 12 of the 35 events may be related to VIVLODEX. These included cardiovascular (angina, cardiac failure, coronary artery stenosis, chest pain, hypertension), gastrointestinal (GI bleeding, abdominal pain, ulcer), and embolic events (pulmonary emboli) that are labeled for Mobic and other NSAIDs. There was one case of drug induced hepatitis (also labeled for NSAIDs) possibly related to VIVLODEX administration. For details of these events see Dr. Luckett's review.

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Dr. Luckett performed an extensive analysis of the development of hypertension during treatment with VIVLODEX. In the double-blind study, hypertension was reported as an adverse event in 2 subjects (1.5%) who received 10 mg, no subjects who received 5 mg, and 1 subject (0.7%) who received placebo. Shifts from normal blood pressure at baseline to high during the 12-week double-blind study was similar for both the 5 mg and 10 mg Vivlodex groups, both were approximately 4% for diastolic BP and 7% for systolic.

In the open-label safety study (n=600), hypertension was reported in 25 (4.2%) subjects who received 10 mg of Vivlodex (no comparator groups in this study). Shifts from normal to high BP over the one year study were 4% for diastolic and 13% for systolic. The Applicant was asked to address the higher rate of high systolic BP in the open-label study. They stated that because there was no comparator in the open-label study, it is difficult to interpret these findings. Also, the study was one year long, and in the study population with a mean age of 61, there is increased risk of developing hypertension over 12 months compared to 12 weeks. Additionally, some changes in the shift table from normal to high could represent relatively small changes in values that may not be clinically significant. That is the reason, according to the Applicant, that all shifts to high were not reported as adverse events, as the reporting of adverse events depends in part on the investigator's determination of whether the events are clinically significant. Dr. Luckett was in general agreement with the Applicant's reasoning, as am I. In addition, because the systemic exposure to meloxicam in Vivlodex 10 mg is less than the exposure in Mobic 15 mg, it is unlikely there would be a different or worse safety profile for Vivlodex.

Dr. Luckett performed a complete review of laboratory and ECG abnormalities and noted no new or unexpected safety findings for Vivlodex.

Common adverse events that occurred at a greater rate in subjects receiving VIVLODEX compared to placebo include diarrhea, headache, nausea, and abdominal discomfort, all of which are expected in patients being treated with NSAIDS.

VIVLODEX will have the NSAID class language in the package insert including all of the same warnings as Mobic, and will have the NSAID class medication guide.

9. Advisory Committee Meeting

No advisory committee was convened for this application.

10. Pediatrics

The Applicant received a waiver for all pediatric studies under PREA based on the indication (treatment of osteoarthritis), as this condition does not occur in pediatric patients and studies would be infeasible.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations inspected two study sites, one that participated in both the double-blind and open-label studies (Dr. David Bouda), and one that participated in only

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the double-blind study (Dr. Enrico Jones). The data for both sites were noted to appear reliable. Both sites were designated NAI by OSI.

The Applicant provided adequate financial disclosure information and no financial incentives that might adversely affect data integrity were identified.

There are no other unresolved relevant regulatory issues.

12. Labeling

The proprietary name VIVLODEX was found acceptable. Reviews of the package insert, medication guide, and carton and container labels were conducted as appropriate by OSE's Division of Medication Error Prevention and Analysis, and OPDP's Division of Consumer Drug Promotion, and comments were conveyed to the Applicant for inclusion in labeling.

VIVLODEX will have the NSAID class language in the package insert including all of the same warnings as Mobic, and will have the NSAID class medication guide.

The Dosage and Administration Section of the label will include instructions to start treatment with the lowest dose (5 mg) of VIVLODEX and increase to 10 mg for patients who require additional analgesia.

The package insert will also include language stating that VIVLODEX capsules have not shown equivalent systemic exposure to other formulations of oral meloxicam. Therefore, VIVLODEX capsules are not interchangeable with other formulations of oral meloxicam, and are not substitutable.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

VIVLODEX is a novel formulation of meloxicam intended for the management of pain of osteoarthritis. There is evidence of efficacy from one adequate and well-controlled clinical trial for both the 5 mg and 10 mg doses, and from the Agency's prior findings of efficacy for Mobic. There is evidence of safety from the 12-week double blind study for both doses, the 1-year open label study for the 10 mg dose, and the Agency's prior findings of safety for Mobic. There do not appear to be any unexpected or new safety issues for VIVLODEX.

While there was no formal statistical testing for this comparison, there was no apparent dose-response based on the primary endpoint analysis for the 10 mg compared to the 5 mg dose. However, several important secondary endpoints favor the 10 mg dose over the 5 mg dose. In the statistical review for the Mobic (NDA 20938), there was a small dose response for efficacy (between the two approved doses, 7.5 mg and 15 mg) for the pain endpoint in a 12-week double-blind study of patients with osteoarthritis, which is evidence

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that higher doses of meloxicam may provide additional efficacy. Given that the safety profiles of the two doses of VIVLODEX appear comparable, both doses were superior to placebo in the efficacy study, the systemic exposure for 10 mg VIVLODEX is proportionally higher than 5 mg, and the findings for Mobic of increased efficacy of 15 mg compared to 7.5 mg, it is reasonable to approve both the 5 mg and 10 mg doses of VIVLODEX. There may be patients who will benefit from the higher dose, and the package insert will state that treatment should be initiated with the 5 mg dose, and those who need additional analgesia could be increased to 10 mg.

The Applicant did not demonstrate that their formulation using smaller particle sizes enhanced the absorption of meloxicam in a clinically significant manner compared to Mobic, and did not demonstrate evidence of improved efficacy or safety. There is no basis at this time for comparative claims versus Mobic.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

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/s/

ELLEN W FIELDS
10/22/2015