CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210583Orig1s000

SUMMARY REVIEW

Combined Medical Review and Summary Review for Regulatory Action

Date	See stamp on electronic signature page
From	Robert Shibuya, MD, Medical Officer Pamela Horn, MD, Clinical Team Leader Naomi Lowy, MD, Acting Deputy Division Director
Subject	Combined Medical Review and Summary Review
NDA/BLA # and Supplement#	NDA 210583 (sequence 035)
Applicant	Baudax Bio
Date of Original Submission	July 26, 2017 Complete Response letter issued May 23, 2018
Date of First Complete Response Submission	September 24, 2018 Complete Response letter issued March 22, 2019
Date of Second Complete Response Submission	December 20, 2019
PDUFA Goal Date	February 20, 2020
Proprietary Name	ANJESO
Established or Proper Name	Meloxicam injection
Dosage Form(s)	Injection for intravenous injection
Applicant Proposed Indication(s)/Population(s)	Management of moderate to severe pain, alone or in combination with other analgesics
Applicant Proposed Dosing Regimen(s)	30 mg Q24 hours
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Management of moderate to severe post-surgical pain alone or in combination with other non-NSAID analgesics

1. Benefit-Risk Assessment

This is a resubmission of a 505(b)(2) NDA that was the subject of two prior Complete Response (CR) Actions. The Applicant appealed the second CR via the Formal Dispute Resolution (FDR) process and, at the Office level, the NDA was found to provide sufficient evidence of effectiveness and safety to support approval. Efficacy was established in two adequate and well-controlled studies in post-operative pain and safety was evaluated in more than 1100 patients and healthy volunteers.

In the FDR memo, the Acting Office Director delegated final labeling to the Division. We have negotiated labeling that we believe appropriately informs prescribers of the limitations of the product's performance as an analgesic. In particular, the agreed-upon labeling includes 1) a

Limitation of Use statement informing prescribers that Anjeso should not be used alone when rapid onset of analgesia is required and 2) information to alert prescribers to end-of-dose failure. (b) (4)

2. Background

Anjeso is a reformulation of meloxicam, a nonsteroidal anti-inflammatory drug (NSAID). Some published data support the position that meloxicam has COX-2 selectivity. However, in approved labeling of other meloxicam products, meloxicam is described as a non-selective NSAID. Anjeso is an injection for IV administration; the approved formulations of meloxicam are all oral dosage forms. The oral meloxicam-containing products are approved for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and Juvenile Rheumatoid Arthritis Pauciarticular and Polyarticular course, all of which are chronic indications.

Following is a brief review of the regulatory history and rationale for the two prior CR actions. Further details can be found in Dr. Lloyd's Cross-Discipline Team Leader Review for the original NDA dated May 23, 2018, Dr. Shibuya's Cycle 2 review dated March 22, 2019, and Dr. Thanh-Hai's "APPEAL GRANTED" letter dated October 28, 2019.

Deficiencies relate to the product's delayed onset failing to meet prescriber expectations for an intravenous drug as well as waning of the analgesic effect at approximately 18 hours after dosing even though the drug is dosed every 24 hours.

The development program included two Phase 3 studies, which were randomized, double-blind, placebo-controlled trials in patients following abdominoplasty (Study REC-15-015 [Study 015]) or bunionectomy (Study REC-15-016 [Study 016]. The studies were similar in design. Patients underwent surgery using a standardized anesthetic protocol (general endotracheal for Study 015; regional for Study 016). In order to be randomized, among other criteria, patients had to report at least 4/10 pain on a 0-10 point numerical pain rating scale (NPRS). In Study 016, the popliteal block was stopped prior to determining randomization eligibility. Eligible patients were randomized to Anjeso, 30 mg Q24 hours or placebo. They were followed for efficacy with NPRS assessments and they performed the two-stopwatch procedure. Two stopwatches are started at the time of dosing; patients are told to stop the first stopwatch at the onset of perceptible pain relief and the second at meaningful pain relief. The primary endpoint for Study 015 was the summed pain intensity difference (SPID) over 24 hours (SPID24) and SPID48 for Study 016. Both studies met their protocol-specified primary efficacy endpoint (SPID24 and SPID48) with p-values of 0.0145 and 0.0034 for Studies 015 and 016, respectively.

Data presentations and discussion pertaining to time to meaningful pain relief (from prior review)

Tables 1 and 2 summarize the time to pain relief analyses for Studies 15 and 16.

Table 1: Summary of Time to Pain Relief Analysis – Study 015

Parameter / Statistic	N1539 30 mg (N=110)	Placebo (N=109)
Time to First Perceptible PR (hr)		
Subjects Achieved Endpoint, n (%)	63 (57.3)	45 (41.3)
25% (95% CI)	0.26 (0.23, 0.41)	0.37 (0.22, 0.88)
50% (95% CI)	0.76 (0.5, 0.89)	1.28 (0.96, NA)
75% (95% CI)	1.69 (1.03, 2.24)	NA (3.94, NA)
Log-Rank Test	0.0050	
Time to Meaningful PR (hr)		
Subjects Achieved Endpoint, n (%)	32 (29.1)	27 (24.8)
25% (95% CI)	1.04 (0.69, 2.01)	1.23 (0.96, 2.27)
50% (95% CI)	3.02 (2.01, 4.43)	2.92 (1.71, NA)
75% (95% CI)	4.43 (3.18, NA)	NA (3.94, NA)
Log-Rank Test	0.5096	

Source: Medical Officer's review of original NDA

Table 2: Summary of Time to Pain Relief Analysis – Study 016

Parameter / Statistic	N1539 30 mg (N=100)	Placebo (N=101)
Time to First Perceptible PR (hr)		
Subjects Achieved Endpoint, n (%)	66 (66.0)	59 (58.4)
25% tile (95% CI)	0.18 (0.14, 0.27)	0.25 (0.16, 0.35)
50% tile (95% CI)	0.52 (0.35, 0.74)	1.59 (0.48, 2.00)
75% tile (95% CI)	4.45 (1.03, 8.06)	4.00 (2.00, 8.75)
Log-Rank Test	0.1228	-
Time to Meaningful PR (hr)		
Subjects Achieved Endpoint, n (%)	46 (46.0)	40 (39.6)
25% tile (95% CI)	0.56 (0.44, 0.95)	2.03 (0.62, 2.38)
50% tile (95% CI)	2.16 (1.00, 12.01)	3.19 (2.39, 4.82)
75% tile (95% CI)	12.01 (2.62, 12.01)	8.75 (4.35, 11.79)
Log-Rank Test	0.1048	-

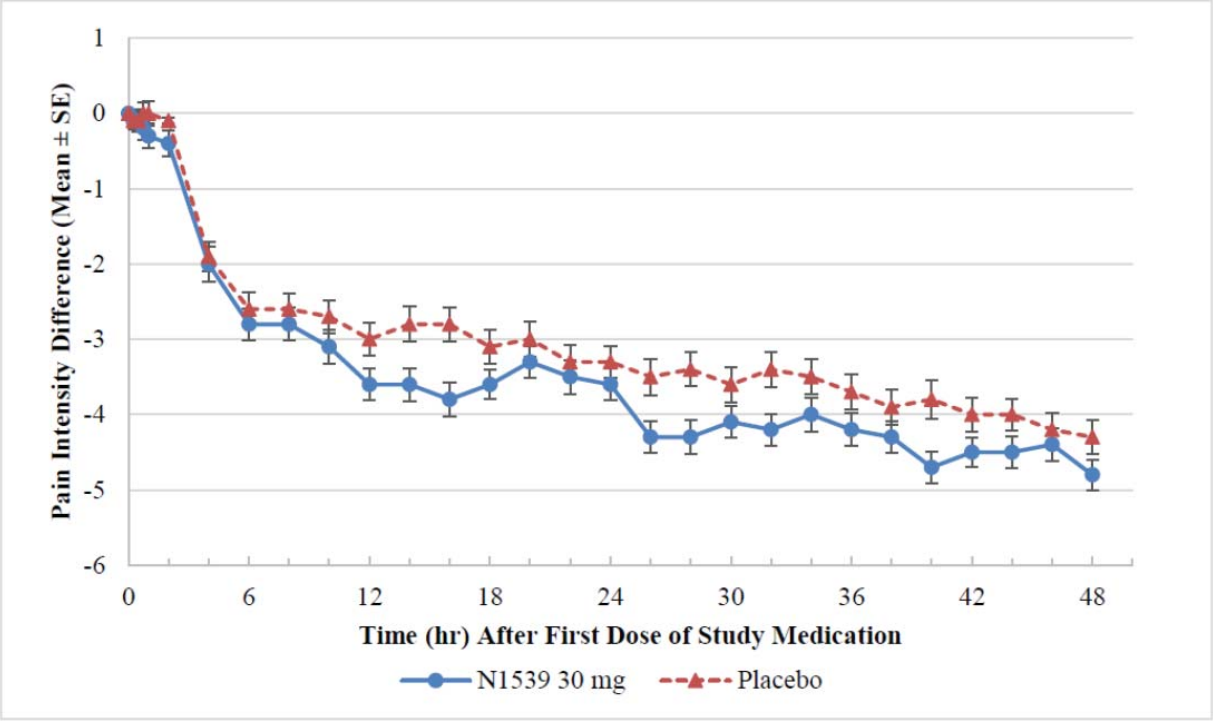
Source: Medical Officer's review of original NDA

For drugs for acute pain, a rapid onset of action is desirable both for patient comfort and to prevent unnecessary redosing with the same or dosing with a different analgesic. This risk is likely greater in the outpatient setting where a healthcare professional cannot monitor analgesic ingestion. To assess onset of pain relief, the Division has recommended and accepted the two-stopwatch method, with the primary metric being median time to meaningful pain relief. In other product reviews, analgesia by 1 hour post-dose has been used as a landmark for adequate time to onset. As Tables 1 and 2 show, the median times to meaningful pain relief in patients treated with Anjeso were 3 and 2 hours for Studies 015 and 016, respectively. Furthermore, most patients had already been dosed with the rescue analgesic (oral oxycodone) prior to the 3 and 2 hours, so the relative contribution of Anjeso and oxycodone to the observed onset of pain relief was unclear.

Data presentations and discussion pertaining to end-of-dose failure (from prior review)

Figure 1 and 2 and Tables 3 and 4 summarize the data related to end-of-dose failure for Studies 15 and 16.

Figure 1. Pain intensity vs. time – Study 015 (abdominoplasty)



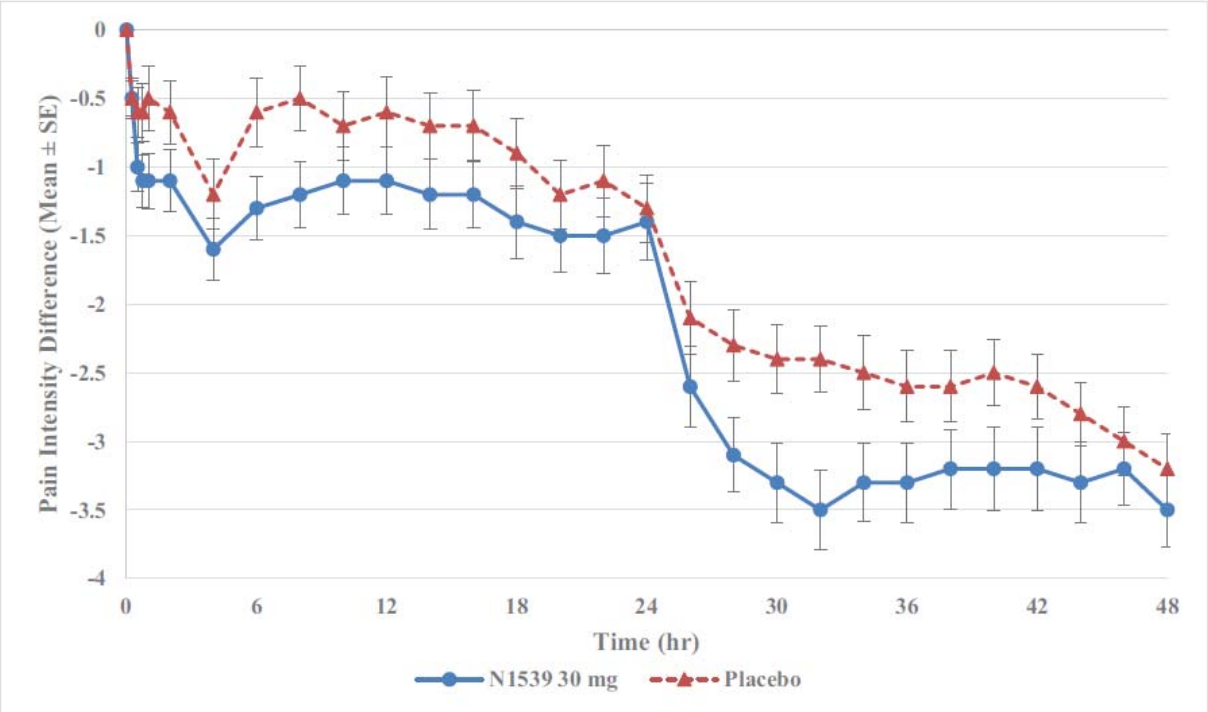
Source: Medical Officer's review of original NDA

Table 3: Summary of LS Mean SPID at End of Dosing Interval – Study 015

Parameter	N1539 30 mg (N=110)	Placebo (N=109)	P-Value
$SPID_{12-24}$	-2498.3 (123.63)	-2064.7 (124.12)	0.0115
$SPID_{18-24}$	-1204.7 (64.28)	-1078.7 (64.54)	0.1556
$SPID_{36-48}$	-3276.2 (128.54)	-2827.6 (129.05)	0.0119
$SPID_{42-48}$	-1631.9 (65.50)	-1442.8 (65.76)	0.0370

Source: Medical Officer's review of original NDA

Figure 2. Pain intensity vs. time – Study 016 (bunionectomy)



Source: Clinical Study Report, Figure 2

Table 4: Summary of LS Mean SPID at End of Dosing Interval – Study 016

Parameter	N1539 30 mg (N=100)	Placebo (N=101)	p-value
$SPID_{6}$	-510.78 (66.22)	-288.33 (65.95)	0.0153
$SPID_{12}$	-957.83 (123.30)	-480.15 (122.80)	0.0053
$SPID_{24}$	-2071.0 (247.01)	-1167.9 (246.00)	0.0084
$SPID_{24-48}$	-4885.1 (313.60)	-3661.4 (312.32)	0.0050

Source: Medical Officer's review of original NDA

The Division interpreted the shape of the pain curves and SPIDs at the end-of-dosing interval to be indicative that Anjeso is not likely to be effective for the 24-hour dosing interval

proposed. This issue was discussed prior to NDA submission, during the review, and at End-of-Review meetings. The Applicant proposed that Anjeso is to be used as part of multimodal analgesia; thus end-of-dose failure can be covered with other analgesics. Recro (now Baudax) also argued that other approved analgesics have evidence of similar end-of-dose failure.

(b) (4)

After review of the FDR, Dr. Thanh-Hai (Acting Office Director), found that "accurate labeling can convey the limitations of Anjeso as an intravenous analgesic used in combination with other modalities of analgesia" to address the concerns raised by the Division. The key reasons for her decision follow.

a. Onset of action:
    i. Dr. Thanh-Hai took greater account of the shape of the early portion of the pain curves in assessing the onset of analgesia. She noted that separation between Anjeso and placebo occurred sooner in the bunionectomy study than abdominoplasty and inferred that procedure may influence the treatment effect.
    ii. Dr. Thanh-Hai acknowledged precedents of other IV drugs and noted that some other drugs do not produce a rapid effect when administered IV.
    iii. Even if the onset of action is delayed, Dr. Thanh-Hai found that would not preclude the use of Anjeso as an IV analgesic. She suggested that labeling can be developed to informer prescribers who could then formulate a regimen that would provide adequate analgesic coverage.
b. End-of-dose failure
    i. Dr. Thanh-Hai noted that end-of-dose failure is not a unique observation to Anjeso. She also noted that the SPIDs at end-of-dosing interval were post hoc analyses, not corrected for multiple comparisons.
    ii. Dr. Thanh-Hai also noted that, while the later pain scores show a decreased effect size compared to placebo, patients treated with active used less rescue analgesic (oral oxycodone).
    iii. Dr. Thanh-Hai encouraged the Division to explore whether q18 hour dosing is an appropriate solution to the diminished efficacy near the end of the dosing interval.

(b) (4)

In the Applicant's latest submission, they have proposed the 24-hour doing interval with language to appropriately convey the potential for end-of-dose failures.

3. Product Quality

No new chemistry/manufacturing/controls data were submitted. Per the CDTL memo, the Office of Product Quality recommended approval at the time of the first CR Action.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted. Our Pharmacology/Toxicology team recommended approval at the time of the last Action.

5. Clinical Pharmacology

No new clinical pharmacology data were submitted. Our Clinical Pharmacology team recommended approval at the time of the last Action.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The safety update (Section 8, following) indicated that two new efficacy studies have been completed since the last resubmission. Both studies were randomized, double-blind, placebo-controlled multicenter studies. REC-17-024 (Study 024) studied safety and "treatment impact…on the overall postoperative recovery course" in patients following colorectal surgery. REC-17-025 studied drug effects on opioid consumption, pain, safety, and healthcare utilization costs in patients following total knee arthroplasty. In both studies, study drug was administered prior to surgery.

The efficacy results were not included with the resubmission of December 20, 2019. The summary of Study 024 in the Safety Update makes the following statement, "Following review of the data from the 51 subjects randomized to Cohort 1 it was decided not to enroll additional study cohorts." Summaries of the efficacy results were requested and subsequently provided.

The response to information request (IR) indicates that the studies were conducted for medical affairs/health economic purposes and did not capture typical Phase 3 efficacy outcome measures. Outcomes in the IR response are summarized by study below.

Study 024 (colorectal surgery)

Table 5: Total Opioid Consumption Study RAC-17-024

Time Interval	ANJESO N=27	Placebo N=28
End of surgery (H0) through Discharge		
LS mean (SE)	29.22 (5.237)	45.17 (5.188)
Difference (95% CI)	-16.0 (-30.7, -1.26)	
p-value[a]	0.0339	

Source: IR response, January 7, 2019

Table 6: Time to first opioid rescue medication use Study REC-17-024

Parameter	ANJESO N=27	Placebo N=28
Time from end of surgery to first rescue (IV or oral, hrs):		
Number (%) Subjects with Event	27 (100)	28 (100)
KM 25th percentile (95% CI)	0.43 (0.22, 0.55)	0.39 (0.28, 0.70)
KM 50th percentile (95% CI)	0.72 (0.50, 1.07)	0.79 (0.52, 1.03)
KM 75th percentile (95% CI)	1.18 (0.73, 2.90)	1.35 (0.90, 3.82)
KM Mean (SE)	2.01 (0.99)	2.17 (1.07)
Hazard Ratio (95% CI)	1.129 (0.660, 1.931)	
p-value[a]	0.6586	

Source: IR response, January 7, 2019

Study 025 (total knee arthroplasty)

Table 7: Total use of opioid analgesia from end of surgery through Hour 24 Study REC-17-025

Time Interval	ANJESO N=93	Placebo N=88
End of surgery through Hour 24 (PSD 1)		
LS mean (SE), mg	18.94 (1.320)	27.73 (1.371)
Difference (95% CI)	-8.79 (-12.2, -5.37)	
p-value[a]	< 0.0001	

Source: IR response, January 7, 2019

Table 8: Summary of SPI from first study dose to 24 hours following dose Study REC-17-025

Parameter	ANJESO N=93	Placebo N=88
SPI_{24}		
LS mean (SE)	5328 (238.1)	6854 (248.6)
Difference (95% CI)	-1525 (-2148, -903)	
p-value	<0.0001	

Source: IR response, January 7, 2019

Table 9: Opioid-free patents from end-of-surgery through Hour 24 Study REC-17-025

Parameter	ANJESO N=93	Placebo N=88
Opioid free subjects; end of surgery through H24 (PSD 1)		
n (%)	1 (1.1%)	0
Difference (95% CI)	1.08 (-1.02, 3.17)	
p-value[a]	0.2482	

Source: IR response, January 7, 2019

Table 10: Time to first opioid rescue medication use Study REC-17-025

Parameter	ANJESO N=93	Placebo N=88
Time (hr) from end of surgery (H0) to first rescue (IV or oral):		
Subjects (%) censored	1 (1.1)	0
KM 25th percentile (95% CI)	2.20 (1.13, 2.65)	1.06 (0.57, 1.80)
KM 50th percentile (95% CI)	3.38 (3.10, 3.97)	2.78 (2.23, 3.28)
KM 75th percentile (95% CI)	5.30 (4.17, 6.77)	4.08 (3.57, 4.97)
KM Mean (SE)	4.94 (0.54)[b]	3.09 (0.28)
Hazard ratio (95% CI)	0.559 (0.409, 0.763)	
p-value[a]	0.0003	

Source: IR response, January 7, 2019

The IR response indicates that other endpoints were supportive of findings from prior clinical studies.

The summaries submitted for Studies 024 and 025 appear to show that Anjeso has an analgesic effect in post-surgical pain. As was found previously, we note that, even when dosed prior to surgery (presumably at least two hours prior to anesthetic emergence), as evidenced by the time to opioid rescue, the drug had no effect (Study 024) or an effect (3.4 vs 2.8 hours [Study 025]) with questionable clinical significance. We only have the summary data at this time which is not sufficient to support specific labeling for these two studies. However, the data inform the importance of labeling that will clearly communicate that patients will likely require concomitant opioid analgesia upon anesthetic emergence.

8. Safety

The safety database size was adequate in the original submission (a total of 1099 patients having received at least 30 mg and 526 patients having received at least 3 doses). Risks of bleeding, wound healing, and anemia were thoroughly interrogated by the initial review team. The review team for the initial submission concluded that "the overall safety profile of [Anjeso] is consistent with what has been observed in patients treated with NSAIDs as a class, particularly one that is administered IV over a short duration." Safety data submitted subsequently have not revealed any new safety signals.

The Applicant has provided a Safety Update in this resubmission with a data cutoff of October 31, 2019. As noted in Section 7 (Efficacy) above, two Phase "3b" studies were completed. In addition, one Phase 1 study was completed and added to the safety update. Study REC-17-021 was planned to be a 2-part Phase 1 study to assess CNS penetration of meloxicam administered IV vs. oral. While the safety update did not include the pharmacokinetic results, Part 2 of the study (oral meloxicam) did not proceed, implying that CSF meloxicam levels following IV administration were low or undetectable.

Major Safety Findings (all three studies)

Major safety metrics per study are summarized in Table 11, below.

Table 11: Major safety findings, Studies 021, 024, 025

Study	Deaths	Serious Adverse Events	Adverse Events leading to discontinuation
021	0	0	0
024	0	3 active; 4 placebo	0
025	0	3 active; 9 placebo	0

Source: Derived from summaries from Safety Update dated 19 November 2019

The SAEs occurring in patients treated with Anjeso in the colorectal surgery study were: Wound dehiscence, Incision site cellulitis and Ileus/Urinary Retention. The SAEs occurring in patients treated with Anjeso in the knee replacement study were: Rectal hemorrhage, Anemia, and Syncope. I reviewed all narratives for patients on Anjeso.

- Study 024: The case of wound dehiscence occurred in the context of vomiting.
- Study 025: The case of rectal hemorrhage occurred in a 73-year old woman with a relevant medical history of diverticulosis and hiatal hernia. She was dosed with Anjeso from March 5 to March 7, 2019. On (b) (6), she experienced dyspnea, dizziness, and bloody, maroon stools. Her hemoglobin/hematocrit were 9.4 g/dL and 30.1%, respectively. She was admitted and received 2 units of pRBC, pantoprazole IV, and normal saline IV. Endoscopy showed active gastic ulcers with no active bleeding. A colonoscopy performed the next day notably showed diverticulosis and internal hemorrhoids. The event was considered resolved and the patient was discharged on pantoprazole.
- Study 025: The case of anemia occurred in a 56-year old woman with a medical history of hypertension, hypothyroidism, bipolar disorder, depression, GERD, obesity with gastric bypass, and bilateral knee osteoarthritis. She received Anjeso on December 26 and 27, 2018. On (b) (6), her labs were remarkable for a hemoglobin of 7.7 g/dL. The next day, the hemoglobin was 6.8 mL and the patient was transfused 2 units of pRBC. The hemoglobin stabilized and the patient was discharged on (b) (6).
- Study 025: This 77-year old man experienced defecation syncope following his second dose of Anjeso.

Summary tables for the non-serious adverse events follow.

Table 12: Treatment Emergent Adverse Events – Study 024 (colorectal surgery)

TEAE Preferred Term (MedDRA 20.1)	Placebo N=28		N1539 30 mg N=27	
	n (%)	Events	n (%)	Events
Nausea	14 (50.0)	17	9 (33.3)	11
Vomiting	5 (17.9)	5	5 (18.5)	5
Hypokalaemia	7 (25.0)	7	2 (7.4)	2
Hypophosphataemia	6 (21.4)	6	2 (7.4)	2
Ileus	5 (17.9)	5	1 (3.7)	1
Hypertension	3 (10.7)	3	2 (7.4)	2
Anxiety	3 (10.7)	3	1 (3.7)	1
Insomnia	3 (10.7)	3	1 (3.7)	1
Oliguria	3 (10.7)	3	1 (3.7)	1
Pyrexia	2 (7.1)	2	2 (7.4)	2
Constipation	2 (7.1)	2	1 (3.7)	1
Hypomagnesaemia	2 (7.1)	2	1 (3.7)	1
Hypotension	2 (7.1)	2	1 (3.7)	1
Musculoskeletal pain	2 (7.1)	2	1 (3.7)	1
Gastrooesophageal reflux disease	2 (7.1)	2	0	0
Paranasal sinus hypersecretion	0	0	2 (7.4)	2
Urinary retention	0	0	2 (7.4)	2
Wound dehiscence	0	0	2 (7.4)	2
Wound infection	0	0	2 (7.4)	2

Source: Safety Update dated 19 November 2019

Table 13: Treatment Emergent Adverse Events – Study 025 (knee arthroplasty)

	Placebo N=88		N1539 30 mg N=93	
Preferred Term (MedDRA 20.1)	**n (%)**	**Events**	**n (%)**	**Events**
Nausea	52 (59.1)	55	37 (39.8)	42
Vomiting	19 (21.6)	19	15 (16.1)	16
Hypotension	13 (14.8)	13	13 (14.0)	14
Pruritus	10 (11.4)	10	14 (15.1)	14
Constipation	11 (12.5)	11	10 (10.8)	10
Dizziness	5 (5.7)	5	6 (6.5)	8
Pyrexia	5 (5.7)	5	7 (7.5)	7
Hypokalaemia	6 (6.8)	6	2 (2.2)	2
Hypertension	7 (8.0)	7	0	0
Headache	5 (5.7)	5	1 (1.1)	1
Insomnia	3 (3.4)	3	3 (3.2)	3
Anaemia	2 (2.3)	2	3 (3.2)	3
Bradycardia	2 (2.3)	3	1 (1.1)	1
Gamma-glutamyltransferase increased	2 (2.3)	2	2 (2.2)	2
Tachycardia	1 (1.1)	1	3 (3.2)	3
Urinary retention	1 (1.1)	1	3 (3.2)	3
Cellulitis	3 (3.4)	3	0	0
Rash	3 (3.4)	3	0	0
Anxiety	0	0	2 (2.2)	2
Diarrhoea	0	0	2 (2.2)	2
Gastrooesophageal reflux disease	0	0	2 (2.2)	2
Hyponatraemia	2 (2.3)	2	0	0
Muscle spasms	2 (2.3)	2	0	0
Pain	2 (2.3)	2	0	0
Pulmonary embolism	2 (2.3)	2	0	0

Source: Safety Update dated 19 November 2019

In Study 021, all subjects received a single dose of Anjeso. There were 6 events reported in 4 subjects (6 subjects were dosed). All events were of mild intensity and resolved without intervention with the exception of a caffeinated beverage for a headache. These included typical Phase 1 adverse events such as headache, nausea, vasovagal symptoms, etc.

Collectively, the updated clinical safety data on patients treated with Anjeso do not substantively change the risk assessment for this product. It is a high-dose NSAID with the attendant risks.

The Safety Update also contained a review of the pertinent clinical literature. There were four citations that described clinical findings related to meloxicam but were not publications of data already submitted by the Applicant. I reviewed the abstracts. The literature do not change my assessment of the risks of Anjeso.

9. Advisory Committee Meeting

This NDA was never a subject of an Advisory Committee meeting.

10. Pediatrics

This product is the subject of an approved Pediatric Study Plan (PSP). Given that the landmark dates were negotiated prior to the last CR action, the Applicant has updated the PSP with new deadlines. The revised PSP changed the deadlines by 14 to 15 months. The rationale for the extension length is that 11 months elapsed between the second CR action and the planned action on this resubmission. The Applicant also indicates that they had assumed that the last cycle would be a 2-month Class 1 resubmission but it was classified to be on a 6-month clock, justifying another 4 months. The revised timelines are acceptable.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

As discussed in Section 2 (Background), Dr. Thanh-Hai provided clear direction to the Division to address the concerns articulated in the prior actions. The Applicant has proposed revisions to pertinent sections of the package insert. Key disagreements between what the Applicant proposed and labeling discussions and negotiations are summarized following by pertinent section. This memo does not enumerate all changes negotiated and several minor changes were made to the final package insert although not described here. Final labeling will be included in the Approval Letter.

Section 1: Indications and Usage:

The issue of the indication implying use as monotherapy was raised in both Complete Response Letters (CRL). CRL1 stated, "the frequent use of rescue medication suggests that ANJESO does not provide analgesia suitable to manage postoperative pain." CRL2 stated, "Meloxicam Injection is unfit for use as an IV drug for acute pain as monotherapy."

One could argue that the word "alone" should be deleted from the indication because a high proportion of patients on Anjeso required opioid rescue (88% and 83% in the first 24 hours). This can be compared to Dyloject (diclofenac injection) where a similar metric (over 48 hours) was only 63% (vs. 92% in placebo). The other approved non-opioid IV analgesics (ketorolac, ibuprofen, and acetaminophen) used a study design (add-on) such that the proportion of patients needing rescue is not estimable or the data are no longer available (Toradol was approved in 1989). However, editing the indication to "moderate to severe pain in combination with other analgesics" appears to require concomitant use of another analgesic. Since rescue analgesic use was not consistent in every patient, the implication that all patients must receive concomitant analgesics while on Anjeso is not accurate. Thus, the "alone and in combination with" phrasing is acceptable.

In order to accurately convey the unexpected delayed onset of this intravenous analgesic, a Limitation of Use (LOU) has been added*: "Because of delayed onset of analgesia, ANJESO*

alone is not recommended when rapid onset of analgesia is required." The Applicant proposed to add "potential for" to the LOU although, given the strength of the clinical study data, the Division insisted in deleting that phrase.

Section 2: Dosage and Administration

Consistent with Dr. Thanh-Hai's comments, we added a section to inform prescribers about the long onset of action and potential for end-of-dose failure and to be prepared to use adjunctive non-NSAID analgesics. The negotiated language follows in *blue/italic.*

When initiating ANJESO, monitor patient analgesic response. Because the median time to meaningful pain relief was 2 and 3 hours after ANJESO administration in two clinical studies, a non-NSAID analgesic with a rapid onset of effect may be needed, for example, upon anesthetic emergence or resolution of local or regional anesthetic blocks [see Clinical Studies (14)].

Some patients may not experience adequate analgesia for the 24-hour dosing interval and may require administration of a short-acting, non-NSAID, immediate-release analgesic [see Clinical Studies (14)].

Section 6: Adverse Reactions:

During the second cycle review, a labeling review of Section 6 was not conducted because of the Complete Response Action. For this review, I reviewed Section 6 of the current, proposed, annotated package insert which largely referenced an Integrated Summary of Safety to support the tabular and numerical data. In an Information Request (IR), I confirmed that the data used for the current package insert consist of pooled data from the completed and reviewed randomized, controlled trials (RCT) summarized at the time of the initial NDA submission.

While there are additional RCT data (Studies 024 and 025), we have not reviewed those studies nor do the safety findings from the individual study reports convey a different impression of the adverse event profile from that understood following the first review cycle. Thus, the safety data, as represented in the proposed labeling, is acceptable.

Section 12.1

The proposed PI reads, [redacted (b) (6)] " The Mobic PI does not have this statement and Recro/Baudax has not submitted sufficient data to support a regulatory finding, specifically they have not shown any clinical benefit from the in-vitro studies. Thus, this statement must be deleted.

Section 14: Clinical Studies

In the clinical studies section, we added language to emphasize the waning efficacy at end-of-dose after the descriptions of both Studies 1 and 2. The final agreed-upon language, following the p-value appear in *blue/italics* below.

Study 1: …The average pain intensity over time is depicted for the treatment groups in Figure 2. A generally consistent separation in pain scores between the ANJESO and placebo groups was observed from time of onset through most of the dosing interval with a narrowing at the end of the first 24-hour dosing interval.

Study 2…The average pain intensity over time is depicted for the treatment groups in Figure 3. A generally consistent separation in pain scores between the ANJESO and placebo group was observed from time of onset through most of the dosing interval with a narrowing at the end of the first 24-hour dosing interval.

The other major label modification in Section 14 was the addition of a paragraph that describes the onset of action and use of rescue analgesics. We considered adding data presentations to convey the use of rescue. This included review of the Kaplan-Meier curves and required an information request to the Applicant to provide a figure plotting percent of patients in each treatment group that received a dose of rescue during hours 0-2, 2-4, 4-6, 6-8 and so on by time for the entire 48 hour treatment period. Baudax provided the new analyses in a January 29 response. Neither the Kaplan-Meier curves nor the new figures provided information useful to the prescriber. Final language for this paragraph appears below.

Onset of Meaningful Pain Relief and Use of Rescue Analgesic Medication

The median time to first rescue analgesic use in patients treated with ANJESO (2 hours in Study 1 and 1 hour in Study 2) came before the median time to patient-reported meaningful pain relief in both studies (2 hours in Study 1 and 3 hours in Study 2). Fifty percent of patients treated with ANJESO and 49% of patients treated with placebo in Study 1 received rescue analgesia medication in the first 2 hours after the start of dosing. Seventy-eight percent of patients treated with ANJESO and 78% of patients treated with placebo in Study 2 received rescue in the first 3 hours after the start of dosing.

13. Postmarketing Recommendations

No REMS was required at the time of approval and neither postmarketing data nor data submitted support the need for a REMS.

14. Recommended Comments to the Applicant

I have no further comments.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROBERT B SHIBUYA
02/20/2020 12:33:47 PM

PAMELA J HORN
02/20/2020 12:34:42 PM

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