CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022569Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	June 30, 2011
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA #	022569
Applicant Name	Archimedes Development Limited
Date of Submission	August 30, 2009
PDUFA Goal Date	June 30, 2011 (second cycle, clock extension)
Proprietary Name / Established (USAN) Name	Lazanda/ Fentanyl nasal spray
Dosage Forms / Strength	Nasal spray 100 mcg/spray and 400 mcg/spray
Proposed Indication	For the relief of breakthrough pain in opioid-tolerant cancer patients
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Clinical Review	Luke Yip, M.D. (efficacy; safety 2nd cycle) Nick Olmos-Lau, M.D. (safety 1st cycle)
Statistical Review	David Petullo, M.S.; Dionne Price, Ph.D.
Pharmacology Toxicology Review	Elizabeth A. Bolan, Ph.D.; R. Daniel Mellon, Ph.D.
CMC Review	Sheldon Markofsky, Ph.D.; Julia Pinto, Ph.D.; Prasad Peri, Ph.D.
Microbiology Review	Steven Fong, Ph.D.; David Hussong, Ph.D.
Clinical Pharmacology Review	Sheetal Agarwal, Ph.D.; Suresh Doddapaneni, Ph.D.
DSI	Roy Blay, Ph.D.; Tejashri Purohit-Sheth, M.D.
CDTL Review	Robert B. Shibuya, M.D.
OSE/DMEPA	Loretta Holmes, B.S.N., Pharm.D.; Irene Z. Chan, Pharm.D., B.C.P.S.; Kristina Arnwine, Pharm.D.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.
OSE/DRISK	LaShawn Griffiths, R.N., M.S.H.S.-P.H., B.S.N.; Sharon R. Mills, B.S.N., R.N., C.C.R.P.; Doris Auth, Pharm.D.; Kate Heinrich, M.A.;Gita A. Toyserkani, Pharm.D.; Megan Moncur, M.S.; Jeanne Perla, Ph.D.; Claudia Karwoski, Pharm. D.
DDMAC	Mathilda Fienkeng, Pharm.D.; Twyla Thompson, Pharm.D.
Controlled Substance Staff	JianPing Gong, M.D., Ph.D.; Lori A. Love, M.D., Ph.D.; Stephen Sun, M.D.; Michael Klein, Ph.D.

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DDMAC=Division of Drug Marketing, Advertising and Communications

1. Introduction

Archimedes Development Limited has submitted this application for a fentanyl nasal spray product intended to treat episodes of breakthrough pain in cancer patients who are already being treated with round-the-clock doses of an opioid analgesic for their background cancer pain. There are four transmucosal fentanyl products already approved for this indication: Actiq, a lozenge on a stick approved in 1998; Fentora, a buccal tablet approved in 2006; Onsolis, a buccal soluble film approved in 2009; and Abstral, a sublingual tablet approved January 7, 2011. As with the Fentora, Onsolis, and Abstral applications, this is a 505(b)(2) application referencing NDA 20-747 for Actiq, and the evidentiary basis for a finding of efficacy for Lazanda is a single, adequate and well-controlled clinical trial of a design based on the original studies performed for Actiq. The major regulatory concerns related to this application have been the development of an adequate Risk Evaluation and Mitigation Strategy (REMS) and concerns related to the spray device, including a large

Reference ID: 2968278

quantity of residual fentanyl after maximal use, potentially unsafe priming procedures, ease of access to the fentanyl solution, and the potential for inadvertent excess dosing and surreptitious abuse due to flaws in the dose-counter mechanism.

Based on the CMC, microbiology and risk mitigation concerns described in my review of the original submission (see Appendix), a Complete Response (CR) Letter was issued to Archimedes on June 30, 2010. This response to the CR Letter was received on September 30, 2010. I will only address the outstanding approvability issues in my review of the applicant's response. The reader is referred to my initial review and the reviews from the various disciplines for additional detail.

2. Background

The approvability issues and the information necessary to address them, as stated in the CR Letter, are reproduced below:

1. The container-closure system is inadequate to prevent accidental exposure to the fentanyl solution by patients, caregivers, and household contacts.
    a. The (b) (4) pump assembly can be removed from the glass bottle with moderate effort and no tools.
    b. The top of the pump assembly can be easily separated from the bottom of the mechanism, allowing fentanyl solution to leak out.
2. The container-closure system is inadequate to ensure an accurate accounting of the number of sprays delivered.
    a. If the top of the pump was removed and then replaced, it could be indexed at various positions along the dose counter and would no longer accurately reflect the number of sprays delivered.
    b. It is possible to actuate a dose without causing the dose counter to advance.
3. The method of disposing the residual fentanyl solution, discarding the container in the trash, does not adequately protect household contacts from accidental exposure to the fentanyl solution. Similarly, the proposed method of (b) (4) does not adequately protect household contacts from accidental exposure to fentanyl solution.
4. An assay for detecting *Burkholderia cepacia* in the drug product, and inclusion of a specification for the absence of *Burkholderia cepacia* in the drug product, were not submitted.
5. A commitment to testing for *Burkholderia cepacia* contamination in the Purified Water, USP, (b) (4).

To address these deficiencies:

1. Provide a container closure system that does not result in leakage of fentanyl solution with accidental or minor tampering.

Reference ID: 2968278

2. Provide a container closure system with a dose counting mechanism that cannot be manipulated and that is always accurate.

3. Reduce the volume of fentanyl solution such that there is either no residual following use of the product or provide a method for disposing of the residual such that it cannot be accidentally accessed.

4. Submit an assay for detecting *Burkholderia cepacia* in the drug product, and include absence of *Burkholderia cepacia* in the drug product specifications.

5. Commit to testing for Burkholderia cepacia contamination in the Purified Water, USP (b) (4).

3. CMC

The following summary of the applicant's response to the CMC deficiencies has been reproduced from pages 4 through 8 of Dr. Shibuya's review:

> As described in the reviews for the first cycle and in Drs. Julia Pinto's (CMC reviewer) and Luke Yip's (Clinical Reviewer) current reviews, the product is packaged in a glass bottle topped with a plastic spray apparatus (see Figure 1).

Figure 1: Drug product presentation

Source: NDA resubmission of 30 Sep 2010, M3, 32p7, container-closure-system, page 3/29 of pdf

> The device requires four priming strokes in order to accurately deliver the intended 100 mcL volume for each spray. The device is designed to deliver eight full sprays (a single dose could be one or two sprays). Following the eighth spray, as much as (b) (4) of fentanyl remain in the bottle. It is possible to express additional sprays after the eight metered sprays. However, the sprays decrease in volume as the residual fentanyl solution in the bottle decreases.

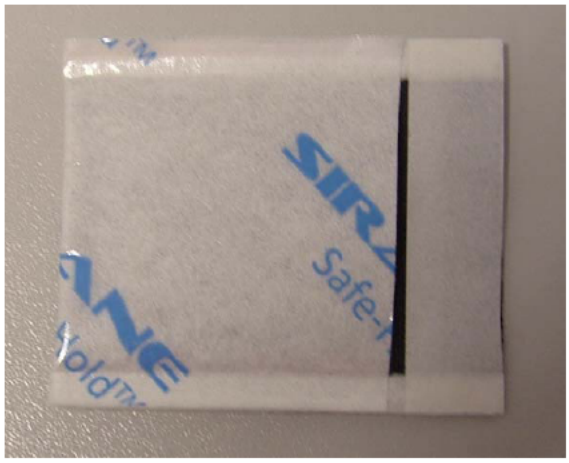
The device has been modified to address Deficiencies 1 and 2. Briefly, the glass bottle has more lugs and the spray device has additional teeth to engage the lugs. This renders it difficult to separate the plastic spray device and glass bottle. The spray device has been redesigned to make it difficult to separate the top and bottom of the device while making it easier to advance the counter mechanism.

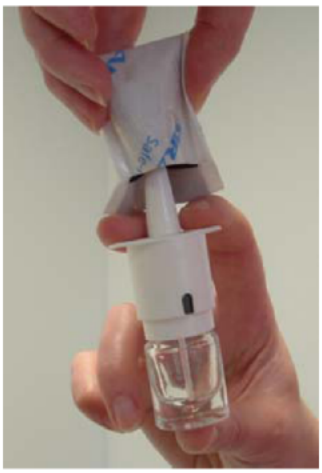
To address the issue of the disposal of waste and residual fentanyl after use, the Applicant has designed an activated carbon-lined pouch, shown in Figure 2. The schematic of the pouch design (Figure 3) shows that it is constructed much like a diaper except that it is lined with activated carbon-cloth, designed to adsorb fentanyl.

Figure 2: Absorbent pouch

a) Absorbent pouch (unsealed) containing inner lining of carbon cloth

b) Illustration of use of pouch to capture sprays





Source: Resubmission dated 9/30/10, 3.2.P.2.4 (Container Closure System), page 40/281 of pdf

Figure 3: Schematic showing layers of pouch

OUTSIDE

Application of sprays

Source: Resubmission dated 9/30/10, 3.2.P.2.4 (Container Closure System), page 40/281 of pdf

The Applicant conducted extraction studies using simulated saliva, simulated gastric fluid, and simulated intestinal fluid which were included in the 30 September 2010

resubmission. Minimal fentanyl was extracted under those conditions which used an extraction time of two hours.

Upon a request by the Agency, additional extraction studies were conducted to test a wider range of solvents and more rigorous conditions. The extraction conditions were:

- Fentanyl amount: entire contents of 4 mg/mL bottle, left to stand for 20 hours
- Extraction volume: 40 mL
- Temperature: 70˚F
- Time: (up to 24 hours)
- Other: minimal agitation (gentle shake prior to sampling)
- Aliquots were taken at each sampling time and the volume taken replenished

Tables 2 and 3 show summary results from the additional extraction studies.

Table 2: Summary results from expanded extraction studies

Extraction medium	**% Fentanyl retained on pouch after extraction**				**Total amount extracted at 24 hr (mcg)**
	1 hr	**3 hr**	**6 hr**	**24 hr**	
Water (intact)	100	99.7	99.2	99.4	33
Water (segmented)	97.7	99.7	100.0	100.0	0
0.1 M HCl (intact)	97.6	100.0	95.6	99.6	21
0.1 M (HCl (segmented)	97.4	97.8	99.2	99.9	7
0.1 M NaOH (intact)	99.3	100	99.0	99.6	22
0.1 M NaOH (segmented)	99.4	99.8	100	100	0
Acetone (intact)	73.7	69.4	70.8	77.0	1201
Acetone (segmented)	71.8	69.1	70.8	76.5	1291
Methanol (intact)	84.9	81.9	84.2	90.8	474
Methanol (segmented)	79.7	84.1	87.6	94.4	275
Ethanol (intact)	98.3	93.4	88.1	85.1	740
Ethanol (segmented)	77.7	77.8	79.5	84.3	801
Ethanol/water (segmented)	94.5	98.0	99.1	99.7	14

*all contents of a 4mg/mL FNS bottle were sprayed into the pouch, which was then left to stand for 20 hours prior to extraction.

Source: Submission to NDA dated 21 February 2011, Attachment 1 to Cover Letter, page 6 of 12 of pdf

Table 3: Summary results from several ethanol extraction studies

Sample tested	% Fentanyl retained on pouch after extraction				Final amount extracted (mcg)
	1 hr	3 hr	6 hr	24 hr	
Prime + dose + disposal sprays ethanol only	77.7	77.8	79.5	84.3	801
Prime + dose + disposal sprays ethanol only after only 2 h standing	60.1	66.0	71.9	83.6	821
Prime + disposal sprays ethanol only after only 2 h standing	71.7	71.7	70.7	73.6	539
Prime + dose + disposal 50% v/v ethanol:water	94.5	98.0	99.1	99.7	14
Prime + dose + disposal after only 2 h standing 50% v/v ethanol:water	91.1	97.5	99.1	99.9	4
Prime + disposal sprays 50% v/v ethanol:water	96.7	98.7	99.3	99.9	2
Prime + disposal sprays - carbon separated 50% v/v ethanol:water	92.7	94.0	95.0	96.3	55
Prime + dose + disposal sprays - carbon separated 50% v/v ethanol:water	96.3	97.1	97.6	98.3	71

* unless otherwise stated in column 1, all contents of a 4mg/mL FNS bottle were sprayed into the pouch, which was then left to stand for 20 hours prior to extraction,

Source: Submission to NDA dated 21 February 2011, Attachment 1 to Cover Letter, page 7 of 12 of pdf

> Table 3 shows that the most effective extraction medium was acetone which resulted in a yield of more than 30% in three hours. On face, the other extraction media were much less effective.
>
> However, when the percent remaining in solid phase (pouch) is assessed over the extraction time, in both tables, some of the conditions show a peculiar trend in that the amount extracted with less time is greater than the amount extracted at 24 hours (maximum extraction time). The Applicant provided no explanation for these results.

Based on the information provided by the sponsor, Dr. Pinto concluded the following, which has been reproduced from page 7 of her review:

> Therefore, from the CMC quality standpoint, the Applicant has adequately addressed the deficiencies sited in review #1 including providing a pouch as protection from accidental exposure to the environment. However, the burden of developing an "addict-proof"

Reference ID: 2968278

> disposal system has not been met. Therefore while CMC recommends approval based on the quality of the drug product, assessment of the abuse potential of the pouch, is deferred to the clinical and CSS staff. If Clinical and/or CSS deems the pouch as it is currently designed to be a risk, then CMC recommends that the Applicant develop a different, more robust addict-proof disposal system.

The applicant responded to the microbiology deficiencies with additional data. Dr. Fong reviewed that data and concluded that the applicant's response was adequate.

4. Nonclinical Pharmacology/Toxicology

See Appendix

5. Clinical Pharmacology/Biopharmaceutics

See Appendix

6. Clinical Microbiology

There are no clinical microbiology concerns for this application.

7. Clinical/Statistical-Efficacy

See Appendix

8. Safety

The following has been reproduced from pages 9 and 10 of Dr. Shibuya's review:

> There has been little activity in the clinical development program for this product between review cycles. Following the initial submission, the Applicant continued to collect data for Study CP045/06. This is an open-label safety study in opioid-tolerant cancer patients with breakthrough pain. This resubmission contains data on 81 such patients.
>
> Dr. Luke Yip conducted the safety review for these additional data. Given the limitations in interpretability of data from this class of drugs (TIRFs), the additional safety data did not reveal any new or unexpected safety signals.
>
> During the five months between data lock for the first review cycle and data lock for the resubmission (October 2009 to March 2010), of the 81 patients followed, 8 died, 7 experienced non-lethal Serious Adverse Events, and 2 discontinued due to adverse events. Dr. Yip reviewed each case and found that the study drug was unlikely to have contributed to the event. Instead, the major safety findings were typical of patients with advanced cancer and included events such as progression of disease, pulmonary embolism, line sepsis, pneumonia, and intestinal obstruction.

For this open-label safety data, the incidence and types of common adverse events appeared similar to those reported in the original submission and there were no issues with local irritation reported.

Upon a request from the Agency, the Applicant also submitted a summary of the available postmarketing safety data from non-U.S. countries. As described in Dr. Yip's review, Lazanda is approved and marketed under the tradename "PecFent" in the EU. At the time the postmarketing safety summary was submitted (January 2011), "PecFent" had been marketed in Europe for, at most, three months. The summary states that, at that time, approximately (b) (4) had been sold and there were no new safety signals detected.

9. Advisory Committee Meeting

The review team determined that an advisory committee meeting was unnecessary for this new formulation of fentanyl as there were no unusual issues related to its safety or efficacy compared to the previously approved products in the class, and there was adequate expertise within the Agency to address the product concerns related to the device and the risk management program.

10. Pediatrics

See Appendix

11. Other Relevant Regulatory Issues

The applicant has submitted information and data to address the deficiencies noted in the CR Letter. The spray bottle has been redesigned and can now only be opened with unusual effort; and, after complete dosing and disposal of residual fentanyl into the activated charcoal pouches, there is a minimal and not visually apparent quantity of fentanyl in the capillary tube inside the spray bottle. Additionally, the product now includes a child-resistant container into which the patient or caregiver will place the spray bottle and pouch prior to disposal. The activated charcoal pouches intended to be distributed with the drug product provide considerable improvement in patient/household contact safety. However, they provide a novel means to drug disposal and their use is not intuitive and requires a rather complex procedure. Therefore, the review team concluded that the applicant would need to demonstrate that patients and caregivers can properly follow the instructions as outlined in the product labeling by performing a "label comprehension" study prior to approval. It will also be important to assess whether patients and caregivers will be compliant with using the pouches for drug disposal. The division acknowledges that the latter is not something that can be adequately assessed in a clinical study. Therefore, we will allow the sponsor to capture that data by appropriate means in the post-marketing period as part of the REMS program, i.e., results of surveys conducted of patients' understanding and knowledge of the serious risks and safe use of Lazanda.
.

Late in this review cycle, in response to the review team's concerns about [redacted] the applicant agreed to perform a study to test whether [redacted] of the pouches was feasible. They conducted the study and submitted those results along with the results of a label comprehension and human factors study, and the review clock was extended by three months to allow for adequate review of this amendment to the application. The following conclusions and recommendations have been reproduced from page 6 of Dr. Holmes review of the actual use study for DMEPA:

> The Instructions for Use section of the Lazanda Medication Guide will satisfactorily achieve its objective of ensuring that participants will understand how to effectively use and dispose of Lazanda if the REMS is successfully implemented and followed for this product. The REMS requires that healthcare professionals instruct patients on Lazanda's use when writing a prescription for Lazanda.
>
> Additionally, DMEPA and DRISK made some recommendations concerning the final IFU used in the study including recommending that the Applicant provide a figure to more clearly show the plastic strip on the pouch and added an instruction to place the cap back on the Child Resistant Container (CRC) prior to throwing the container in the trash. These recommendations will be captured in the Division of Risk Management's review of the Medication Guide (which includes the IFU). These minor revisions do not require retesting of the Instructions for Use. Furthermore, because the disposal method of the pouch has been revised [redacted] to placing the pouch in the CRC since the IFU has been tested, DMEPA would typically recommend that the revised instruction for use undergo at least one more round of testing similar to the ones conducted in this protocol with at least 15 participants and using the same objectives and measurements. However, none of the participants in the study had trouble placing the nasal spray container into the CRC or disposing the CRC in the trash. Additionally, there is sufficient room to fit the pouch and nasal spray into the CRC. Thus, DMEPA finds that the change in disposal instructions for the pouch would be unlikely to result in any confusion since participants have already demonstrated they can places the nasal spray container in the CRC without error.

In regard to the abuse liability of the product, as shown in Table 2 above, it is clear from the data that fentanyl can be extracted from the pouches in readily available organic solvents. However, this would take considerable effort on the part of the abuser, and there are numerous approved, high potency, opioid drug products which would most likely be more attractive to those intent on diversion or abuse. In addition, the REMS for Lazanda will require clear direction to patients and caregivers regarding proper storage and disposal to avoid diversion.

The following summary of the CSS conclusions and recommendations has been reproduced from page 3 of Dr. Gong and Mr. Hunter's review of June 17, 2011:

> **Conclusions**
>
> 1. The submitted data from the facile experiments is insufficient to determine the [redacted] of the pouch.
>
> 2. A significant number of patients in the label comprehension study spontaneously reported their reluctance and resistance to complying with instructions to [redacted]

Reference ID: 2968278

disposal recommendations, and without alternative disposal recommendations, patients may engage in unsafe disposal practices.

3. Additionally, due to the potential for significant patient non-adherence to a disposal method that is unacceptable to some patients for various reasons, the proposed disposal instructions directing patients to (b) (4) should be reconsidered as an acceptable method of disposal.

Recommendations

1. CSS continues to recommend that the Sponsor consider developing a method to inactivate or destroy residual drug, or set up a mail-back program to collect the used pouch and used device to dispose residual drug.

2. To mitigate risks associated with accidental unintentional exposure to the drug contained in the pouch, CSS alternatively recommends that patients be instructed to place the sealed pouch containing residual drug into the supplied child resistant container and place it in the household trash.

12. Labeling

The review team and the applicant have reached agreement on the product labeling which includes a MedGuide and Instructions for Use.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The applicant has provided sufficient data to support the efficacy and safety of Lazanda, when used according to the product label and the product REMS. Therefore, the benefits of the product outweigh the risks and this application can be approved.

- Required Postmarketing Risk Evaluation and Mitigation Strategy

  The applicant revised their REMS as part of their response to the CR letter and, after extensive discussions, the review team and the applicant have agreed on a final REMS that is consistent with our expectations for REMS for transmucosal immediate-release fentanyl (TIRF) products. The following has been reproduced from page 11 of the DRISK REMS team's review:

Reference ID: 2968278

An individual REMS will be implemented by Archimedes until a single-shared TIRF REMS system has been approved. The proposed LAZANDA REMS, submitted June 29, 2011, includes all the elements put forth in the Agency's TIRF REMS for a single-shared system, and addresses all comments conveyed to the sponsor, to date (as described in Section 1.2 of this document). The REMS elements include a Medication Guide, Elements to Assure Safe Use, an Implementation System, and a Timetable for Submission of Assessments.

The DRISK Review Team finds the proposed REMS for LAZANDA, as submitted June 29, 2011 (and appended to this review) to be acceptable.

- Other Post-Marketing Requirements

  None

Reference ID: 2968278

Appendix

12 PAGES HAVE BEEN WITHHELD AS DUPLICATIVE. SEE THE MEDICAL REVIEW SECTION FOR THE WITHHELD REVIEW.

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

/s/

BOB A RAPPAPORT
06/30/2011