PMR/PMC Development Template

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

NDA: 22-266

PMR/PMC Title:

Assessment of pharmacokinetics, safety, and efficacy of Onsolis for the treatment of breakthrough pain in pediatric patients with cancer

PMR/PMC Schedule Milestones:

Protocol Submission: January 2011
Study Start Date: [redacted] b(4)
Final Report Submission: [redacted]

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

   It is appropriate to defer pediatric studies and have them conducted as a PMR because the product is ready for approval in adults and it was necessary to assess safety in adults prior to beginning pediatric studies.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 3.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☒ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

     No pharmacokinetic data, efficacy or safety available for the pediatric population
     The requirements to conduct pediatric studies under PREA have led to the PMR.

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

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

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

   Not applicable.

4. If not required by regulation, characterize the review issue leading to this **PMC**

   Not applicable

5. What type of study or clinical trial is required or agreed upon (describe)?

   Required:
   - ☐ Pharmacoepidemiologic study (list risk to be evaluated)
   - ☐ Registry studies
   - ☒ Primary safety study or clinical trial (list risk to be evaluated) Safety in pediatric patients
   - ☐ Subpopulation (list type)
   - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   - ☐ Thorough Q-T clinical trial
   - ☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)

- ☐ Nonclinical study (laboratory resistance, receptor affinity)
- ☒ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing studies
- ☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☒ Other (provide explanation) pediatric efficacy studies

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- ☐ Dose-response study performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☒ Other (provide explanation) Safety and PK studies

6. Is the PMR/PMC clear and feasible?
   - ☒ Are the schedule milestones and objectives clear? Yes
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility? Yes

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

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
CDER/OND/ODE II/DAARP

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

/s/

Ellen Fields
6/17/2009 11:08:46 AM
MEDICAL OFFICER

Larissa Lapteva
6/17/2009 06:15:50 PM
MEDICAL OFFICER

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, June 05, 2009 12:43 PM
To: 'David T. Wright'
Cc: Compton, Kimberly
Subject: RE: REMS comments and responses to your questions

Thanks Dave. I did send this to the team yesterday before I left.

And, in case you were wondering why we asked if the [redacted]ad been printed, we had a late request from DDMAC for a revision in that document and told them that if it had been finalized and printing had begun (as we had verbally reach agreement on it in the past) we would not pass along their request, but since it appears there is still time to amend the document and the change does not appear to major, we will need to pass along their request. b(4)

[redacted] b(4)

Could you run this past the team on your end and if it is acceptable, let me know by return email and then when you submit the finalized versions of everything, you can just make the change in that version going forward.

In general, our plan now is to see if anyone else on the team has any other comments or not, and if not, ask BDSI to go ahead and submit the finalized versions of these officially and then we should just be able to QC those and make sure they are OK with the team while the pkg is wending its way through the clearance process outside the review team.

As always, I will keep you posted on whatever I know as soon as I know it. Sharon agreed that for our TC on June 9, the main focus will be discussion of review status and action timing as well as to try to tie up any outstanding items so we can consider the package complete (at the Division level at least). We have invited the same team members as we've had for most of our previous TCs—myself, Sharon Hertz, Mary Willy, Jeanne Perla, Ellen Fields, Elizabeth Kilgore, Mary Dempsey, Chris Wheeler, Agnes Plante, Marcia Britt and Brian Gordon. I am not sure if any of them will attend, but that is the possible list of attendees on our end.

Thanks
Kim

From: David T. Wright [mailto:DTWright@bdsinternational.com]
Sent: Thursday, June 04, 2009 5:53 PM
To: Compton, Kimberly
Subject: RE: REMS comments and responses to your questions
Importance: High

Kim:

Thanks for sending the below comments! Our initial responses follow:

1. Comment 1 – I can confirm that the thumbnails will link to the final REMS materials as provided on 22 May.
2. Comment 2 – I believe that the REMS website is consistently www.OnsolisFocus.com throughout all REMS materials but will recheck.
3. Comments 3 to 6 – I can confirm that BDSI accepts these comments and will make these revisions. Revised MS Word documents will be sent via email as soon as possible (tomorrow for all materials except the website which may require an additional day or two).
4. Comment 7 – [redacted] Thus, nothing has been printed. b(4)

In addition, regarding the confirmed teleconference for 09 June, given the minor nature of the comments received today, BDSI assumes that the agenda for this teleconference is to discuss the review status and action timing. We also assume that the Agency attendees be limited to DAARP and other relevant senior staff. Are these assumptions correct? (Note that BDSI wants to limit the sponsor attendees involved in review status and action timing discussions.)

Thanks for your assistance!

Best regards, Dave

David T Wright, PhD, RAC
Director, Regulatory Affairs
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From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Thursday, June 04, 2009 4:35 PM
To: David T. Wright
Cc: Compton, Kimberly
Subject: REMS comments and responses to your questions

HI Dave,

In response to your questions from yesterday, below are our replies.

1. Website Educational Materials – Will BDSI receive the pending Agency comments later today? These are provided below.

2. All other REMS materials – Are these materials agreed or will BDSI receive further Agency comments? If

there are further comments, when will BDSI receive such comments? A few additional REMS comments are provided below along with the web comments; otherwise the Division does feel we have agreement on the other REMS materials. However, we must point out that these materials must still undergo final review by other groups in the Agency (outside of the review team) and it is always possible they will recommend changes to the agreed-upon materials. While we do not anticipate additional changes, it is always possible. We would convey any recommended changes as soon as we received them but do not have an estimate of when that might be.

3. All other NDA documents, including the PI/MG for ONSOLIS – Are these documents agreed or will BDSI receive further Agency comments? If there are further comments, when will BDSI receive such comments? Similar to the situation in Number 2 above, the Division does feel we have agreement on the labeling materials. However, we must point out that these materials as well must still undergo final review by other groups in the Agency (outside of the review team) and it is always possible they will recommend changes to the agreed-upon materials. Again,while we do not anticipate additional changes, it is always possible. We would convey any recommended changes as soon as we received them but do not have an estimate of when that might be.

4. Container and carton labeling – Is it possible for BDSI to receive final approval of these labels to minimize delays between NDA approval and product launch? If so, when will BDSI receive such approval? You indicate in your summary of the recent May 29 meeting with the Division which you provided in your email yesterday that approval for carton and container labeling could be provided prior to NDA approval:

> When asked if the Agency could approve the ONSOLIS container and carton labeling now to minimize the time between NDA approval and product launch, Dr Hertz stated that this was possible and that she would determine how to accomplish this soon.

However, we must point out, as we have previously, that (although we do not anticipate this), it is always possible that when the application materials undergo final review, additional changes may be recommended and so while we have indicated that these pieces are currently acceptable as proposed, we have no mechanism to provide early approval or official clearance of them prior to approval of the application. We apologize if that was unclear in our meeting discussions.

Below, please see our remaining additional comments on the REMS program materials. These mainly deal with the draft web materials sent by email on May 26, but include a few other minor points/clarifications as well.

1. We were unable to follow the links on the webpage (as it is not live) to the linked

educational pieces so could not confirm that the enrollment forms on the website were updated to reflect changes we'd previously agreed upon. Please confirm this.

2. Ensure that the website address is consistent throughout all the literature/material for Onsolis.

3. Page 20 of the web shot from the May 26, 2009 email submission states:

[redacted] b(4)

4. Add a "d" in front of "none of these apply" to Question 1 on the Prescriber KAB survey.

5. Change "[redacted]" to "pharmacies" on Form FF 16 as indicated below: b(4)

The FOCUS™ Program for ONSOLIS™ requires that [redacted] re-enroll every 2 years. Your enrollment period will end on MM-DD-YYYY. b(4)

6. [redacted] b(4)

7. [redacted] b(4)

We still continue to work as hard as we are able to finalize this application and provide you with as timely feedback and accurate information as soon as it is known to us.

Thanks

Kim

Kimberly Compton

Kimberly Compton, R.Ph.

Regulatory Project Manager

Division of Anesthesia, Analgesia and

Rheumatology Products (HFD-170)

301-796-1191

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

/s/

Kimberly Compton
6/9/2009 06:30:19 PM
CSO