CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204957Orig1s000

OTHER ACTION LETTERS

NDA 204957

COMPLETE RESPONSE

B. Braun Medical, Inc.
901 Marcon Blvd.
Allentown, PA 18109

Attention: Cindy Katsempris
Director, Regulatory Affairs

Dear Ms. Katsempris:

Please refer to your new drug application (NDA) dated and received December 13, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen in the PAB container, 500mg/50mL and 1000mg/100mL.

We acknowledge receipt of your amendment dated October 24, 2019, which constituted a complete response to our March 27, 2019, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

(1) During a recent inspection of B. Braun Medical Inc. (FEI 2021236), drug product manufacturer for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

(2) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

CARTON AND CONTAINER LABELING

(3) We acknowledge receipt of the revised draft carton and container labeling on October 24, 2019. We reserve our comments on the acceptability of the packaging labels for the next review cycle.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

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[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- Present tabulations of the new safety data combined with the original application data.

- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We refer to the following deficiency communicated to you in our March 27, 2019, complete response (CR) letter and in further detail in our March 25, 2019, information request letter that preceded the CR letter: “Provide updated letters from Mallinckrodt that clearly indicate a specific date upon which your application can be approved.”

Your October 17, 2019, response to the CR letter (i.e., resubmission received October 24, 2019) stated: “Updated letters from Mallinckrodt (titled “update waiver (b) (4), “update waiver (b) (4) “update consent approval”), clearly indicating a specific date (October 12, 2018) upon which our application can be approved are provided in Module 1.3.5.2.” We note that legal review of these updated letters is still pending at this time and therefore we have not made a determination as to whether this is still deficient.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing

If you have any questions, call Jaimin Patel, Regulatory Project Manager, at (301) 796-0412.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Acting Director
Division of Anesthesiology, Addiction Medicine and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

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/

RIGOBERTO A ROCA
04/24/2020 12:37:37 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204957

COMPLETE RESPONSE

B. Braun Medical, Inc.
901 Marcon Blvd.
Allentown, PA 18109

Attention: Cindy Katsempris
Director, Regulatory Affairs

Dear Ms. Katsempris:

Please refer to your New Drug Application (NDA) dated and received December 13, 2016, and your amendments, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Acetaminophen Injection in the PAB Container, 500 mg/50 mL and 1000 mg/100 mL.

We acknowledge receipt of your amendment dated September 27, 2018, which constituted a complete response to our September 28, 2017, action letter.

FACILITY INSPECTIONS

1. During a recent inspection of the B. Braun Medical, Inc. manufacturing facility (FEI 2021236), our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection.

   Information needed to resolve deficiency:
   Satisfactory resolution of the observations is required before this application may be approved.

REGULATORY

We refer to the following outstanding deficiencies communicated to you in further detail in our March 25, 2019, information request:

2. Provide updated letters from Mallinckrodt that clearly indicate a specific date upon which your application can be approved.

3. Submit documentation that notice of paragraph IV certification to the '(b) (4) and '(b) (4) patents, which includes (b) (4) and (b) (4) use codes, was sent to the patent owner/NDA holder.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

1. Replace the terminology (b) (4) with "single dose" on your proposed carton and container labels and in Section 16 of the proposed PI labeling text.

2. The container label of one unit and the carton labeling of 4 units should have different NDC package codes (last 2 digits of the NDC) to minimize the risk for confusion. Thus, revise the NDC numbers so that the carton labeling and vial labels use a different NDC package code (last 2 digits of the NDC).

3. It is unclear why there is space for (b) (4) included on the carton because (b) (4) Thus, remove (b) (4) or provide your rationale for including.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

- Present tabulations of the new safety data combined with the original application data.

- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues, however, they should be addressed in your complete response to this action:

1. Your reporting of leachables compounds at and above (b) (4) mcg/mL (i.e., (b) (4) mcg/day taking into consideration the maximum daily dose of acetaminophen) is not acceptable as this exceeds the recommended qualification threshold of 5 mcg/day. Identify all leachable compounds above 5 mcg/day and submit a toxicological risk assessment for any newly identified compound that exceeds the 5 mcg/day threshold of concern.

2. You have not provided adequate safety justification for the unknown compound at RRT (b) (4) Identify this unknown compound and submit an accompanying toxicological risk assessment.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Ogochukwu Ogoegbunam, PharmD, BCGP, Regulatory Project Manager, at (240) 402-8807.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/

SHARON H HERTZ
03/27/2019 01:34:14 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204957

COMPLETE RESPONSE

B. Braun Medical, Inc.
901 Marcon Blvd.
Allentown, PA 18109

Attention: Cindy Katsempris
Director, Regulatory Affairs

Dear Ms. Katsempris:

Please refer to your New Drug Application, dated and received December 13, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen Injection in the PAB Container, 500 mg/50 mL and 1000 mg/100 mL.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

During a recent inspection of the B. Braun Medical, Inc. manufacturing facility (FEI 2021236), our field investigator observed product specific and GMP compliance issues at the facility and conveyed that information to the representative of the facility at the close of the inspection.

Information needed to resolve deficiency:
Satisfactory resolution of the observations is required before this NDA may be approved.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

Container Labels

1. Revise the stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000."

2. Relocate the statement, "CAUTION: DO NOT ADD SUPPLEMENTARY MEDICATION" to under the statement "For Intravenous Use Only" to increase its prominence and minimize the risk of healthcare professionals overlooking this important information.

3. Relocate the package type statement to below the statement "CAUTION: DO NOT ADD SUPPLEMENTARY MEDICATION" to increase its prominence.

Carton Labeling

4. See Item 1, above.

5. Relocate the statement, "CAUTION: DO NOT ADD SUPPLEMENTARY MEDICATION" from the side panel to a prominent location on the principal display panel to minimize the risk of healthcare professionals overlooking this important information.

6. Relocate the NDC number to the top third of the principal display panel in accordance with 21 CFR 207.35(b)(3)(i).

7. Add the lot number in accordance with 21 CFR 201.10(i)(1). Ensure that there are no other numbers located in close proximity to the lot number where they can be mistaken as the lot number. 1

8. Add the expiration date in accordance with 21 CFR 201.17. Ensure that there are no other numbers located in close proximity to the expiration date where they can be mistaken as the expiration date.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

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[1] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009; 14(15):1-3.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
   - Present tabulations of the new safety data combined with the original application data.
   - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments and recommendations that are not approvability issues that should be addressed prior to a subsequent NDA resubmission:

1. Tighten the drug product specification for 4-aminophenol and 4-nitrophenol based on long-term stability data to as low as technically feasible.
2. In your leachables study, 3 unknown compounds (RT [redacted] (b) (4)) under normal conditions as well as 5 unknown compounds (RT [redacted] (b) (4)) under accelerated conditions were present in your leachable samples. As we cannot conduct a

toxicological risk assessment on unknowns, either provide identification for these unknown compounds along with an adequate toxicological risk assessment or confirm that these compounds are present in other FDA-approved products that use the same container closure system at comparable total daily intake levels.

3. The safety of [redacted] (b) (4) has not been adequately addressed by the submitted 28-day and 14-day toxicology studies. Either provide data that demonstrates [redacted] (b) (4) and related compounds are present at comparable total daily intake levels in other FDA-approved products that use the same container closure system or conduct an adequately designed 14-day toxicology study that identifies a NOAEL that establishes adequate safety margins.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Ogochukwu Ogoegbunam, PharmD, Regulatory Project Manager, at (240) 402-8807.

Sincerely,

{See appended electronic signature page}

Ellen Fields, MD, MPH
Deputy Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

ELLEN W FIELDS
09/28/2017