DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21855/S-009

SUPPLEMENT APPROVAL

Bionphama, Inc.
Attention: Usha Sankaran
Associate Vice President, Regulatory Affairs
600 Alexander Road, Suite 2-4B
Princeton, NJ 08540

Dear Ms. Sankaran:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 1, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for loperamide hydrochloride capsules, 1 mg and 2 mg.

This "Prior Approval" supplemental new drug application provides for:

- Loperamide HCl 2 mg carton count-size no greater than 24-count limited to blister packaging only.
- Loperamide HCl 1 mg carton count-size no greater than 48-count limited to blister packaging only.
- After "**Ask a doctor before use if you have**" the bullet "a history of abnormal heart rhythm" has been added to the end of the list.
- After "**Ask a doctor or pharmacist before use if you are taking**", the statement "a prescription drug. Loperamide may interact with certain prescription drugs" follows, and "antibiotics" has been removed.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and package configurations.

Taking higher-than-recommended doses of loperamide can cause serious cardiac events, including torsades de pointes, cardiac arrest, ventricular tachycardia, syncope, and death.[1] [2] Evidence suggests that package limitations and use of unit-dose packaging may reduce

[1] Rose BJ. High doses of loperamide can cause serious cardiac events. Pharm Today (2016); 22:34.
[2] FDA Drug Safety Communication: *FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse* is available at https://www.fda.gov/Drugs/DrugSafety/ucm504617.htm.

medication overdose and death.[3] [4] [5] To support ongoing efforts to encourage the safe use of loperamide hydrochloride, we are approving packages that contain a maximum of 48 mg loperamide hydrochloride in unit-dose packaging. If you intend to market or distribute packages containing more than 48 mg loperamide hydrochloride or capsules that are not in unit-dose packaging, submit a prior approval supplement that includes data showing the proposed changes will not adversely impact the safety of the product.

LABELING

Submit final printed labeling, as soon as they are available, but no more than 30 days after they are printed. The final printed labeling must be identical to the enclosed labeling identified in the below table submitted December 3, 2018, and must be in the "Drug Facts" format (21 CFR 201.66), where applicable.

Submitted Labeling	Date Submitted
4-count carton (blister), 2 mg	December 3, 2018
6-count carton (blister), 2 mg	December 3, 2018
8-count carton (blister), 2 mg	December 3, 2018
12-count carton (blister), 2 mg	December 3, 2018
18-count carton (blister), 2 mg	December 3, 2018
24-count carton (blister), 2 mg	December 3, 2018
4-count immediate container (blister), 2 mg	December 3, 2018
6-count immediate container (blister), 2 mg	December 3, 2018
8-count immediate container (blister), 2 mg	December 3, 2018
12-count immediate container (blister), 2 mg	December 3, 2018
6-count carton (blister), 1 mg	December 3, 2018
6-count immediate container (blister), 1 mg	December 3, 2018

The final printed labeling should be submitted electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2017, Revision 4)*. For administrative purposes, designate this submission "**Final Printed**

[3] Turvill JL, et al. Change in occurrence of paracetamol overdose in UK after introduction of blister packs. The Lancet (2000); 355:2048-2049.
[4] Hawton K, et al. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: Interrupted time series analysis (2013); 346:f403.
[5] Chan TYK. Improvements in the packaging of drugs and chemicals may reduce the likelihood of severe intentional poisonings in adults. Human & Experimental Toxicology (2000); 19:387-391.

Labeling for approved NDA 21855/S-009." Approval of this submission by FDA is not required before the labeling is used.

DRUG REGISTRATION AND LISTING

All drug establishment registration and drug listing information is to be submitted to FDA electronically, via the FDA automated system for processing structured product labeling (SPL) files (eLIST). At the time that you submit your final printed labeling (FPL), the content of labeling (Drug Facts) should be submitted in SPL format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. In addition, representative container or carton labeling, whichever includes Drug Facts, (where differences exist only in the quantity of contents statement) should be submitted as a JPG file.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call CAPT Janice Adams-King, Safety Regulatory Project Manager, at (301) 796-3713.

Sincerely,

{See appended electronic signature page}

Valerie Pratt, MD
Deputy Director for Safety
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURES:
Carton and Container Labeling

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/

VALERIE S PRATT
01/31/2019 02:25:33 PM