NDA 214998/S-010

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Gordon Teg Pipes, PhD
Associate Director, Global Regulatory Sciences Strategy
P.O. Box 5326
Princeton, NJ 08543-5326

Dear Dr. Pipes:

Please refer to your supplemental new drug application (sNDA) dated June 18, 2024, received June 18, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Camzyos (mavacamten) capsules.

This Prior Approval supplemental new drug application provides for the following changes to the labeling and proposed modifications to the approved Camzyos risk evaluation and mitigation strategy (REMS):

- Removal of contraindications for moderate CYP2C19 inhibitors and strong CYP3A4 inhibitors
- Update descriptions of contraindicated medications and medications requiring dose adjustments when used concomitantly with Camzyos
- Advise that Camzyos may be interrupted for “short-term” use (when Camzyos dose modification is not feasible) of a weak to moderate CYP2C19 inhibitor
- Update the echocardiogram monitoring schedule from 12 weeks to 3 - 6 months for patients on a stable dose of Camzyos in the maintenance phase
- Add a post-exercise LVOT gradient assessment that may be considered to further titrate symptomatic patients with normal or near normal Valsalva gradients
- Extend the dispensing limit from 35-day to 90-day supply for patients beyond the first year of treatment with Camzyos.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Camzyos was originally approved on April 28, 2022, and the most recent REMS modification was approved on December 19, 2023. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of changes to the REMS document and REMS materials, as outlined above, to align with the updated labeling being approved as part of this supplement.

Your proposed modified REMS, submitted on June 18, 2024, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on April 28, 2022.

The revised REMS assessment plan must include, but is not limited to, the following:

For each metric, provide data for the 2 previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

Program Implementation and Operations

1. REMS Call Center Reports
    a) Number of calls by participant type (patient, healthcare provider, designee, pharmacy, wholesalers-distributors, other)
    b) Summary of reasons for calls (e.g., enrollment question) and participant type (patients, healthcare provider, designee, pharmacy, other). Limit the summary to the top five reasons for calls by each participant group
    c) If the summary reason for the call(s) indicates a complaint, include details on the nature of the complaint(s) and whether the caller indicated potential REMS burden or patient access issues (current period only; previous and cumulative periods available by Agency request)
    d) If the summary reason for the call(s) indicates an adverse event related to heart failure or a contraindicated drug or drug interaction, include details and the outcome of the call(s) (current period only; previous and cumulative periods available by Agency request)
    e) Percentage of calls to the REMS Call Center that were answered within 20 minutes
    f) The shortest wait time for a call to be answered, the longest wait time for a call to be answered and the median time for a call to be answered
    g) Percentage of calls to the REMS Call Center where the caller abandoned the call before the call was answered
    h) The shortest wait time at which a call was abandoned, the longest wait time before the call was abandoned and the median wait time for a call to be abandoned
2. REMS Certification and Enrollment
    a) Healthcare Providers

i. Number of newly certified healthcare providers and number of active (i.e., who have prescribed at least once during the reporting period) healthcare providers stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), specialty (e.g., Cardiology, Electrophysiology, Geneticist, Other), and geographic region (defined by US Census). If "Other" accounts for >10% of respondents, provide the most common specialties identified. Specifically identify and categorize if a specialty is within cardiology or non-cardiology

b) Number of Designees stratified by role (RPh/PharmD, RN, NP, or PA)

i. Method of healthcare provider and designee certification (online or fax)

c) Number of authorized support staff, stratified by role (medical assistants, LPN, care coordinator, etc.)

i. Method of support staff authorization (online or fax)

d) Pharmacies

i. Number of newly certified pharmacies

ii. Number of active pharmacies (i.e., have dispensed Camzyos)

e) Patients

i. Number of newly enrolled patients and number of active (i.e., received at least one dispense of Camzyos) patients stratified by a combined variable of age and gender and geographic region. Provide the minimum and maximum age of enrolled patients. For gender/age variable use age ranges of:

1. Less than 18 years old
2. 18-40 years old
3. 41-60 years old
4. 61 years old and older

f) Wholesalers-distributors

i. Number of newly contracted wholesalers-distributors and number of active (i.e., have shipped Camzyos) wholesalers-distributors

3. REMS Compliance

a) A copy of the non-compliance plan, including the criteria for non-compliance for healthcare providers, pharmacies, and wholesalers-distributors, actions taken to address noncompliance for each case,

and which event lead to decertification from the Camzyos REMS (Beginning with the 1-year assessment and annually thereafter)

b) Audits

i. A copy of the audit plan for pharmacies and wholesalers/distributors

ii. Report of audit findings for each participant (pharmacies and wholesalers-distributors)

iii. Number of audits expected, and the number of audits performed.

iv. Documentation of completion of training for relevant staff.

v. Documentation of processes and procedures in place for complying with the Camzyos REMS

vi. Verification for each audited participant's site that the designated Authorized Representative remains the same. If different, document that the pharmacy has re-certified with the name and contact information for the new Authorized Representative

vii. Number and types of deficiencies noted for each group of audited participants as a percentage of audited participants

viii. For each Audited Pharmacy, number of the following deficiencies (numerator) divided by the number of dispenses audited at that pharmacy (denominator):

1. Healthcare provider not certified, and prescription dispensed
2. Patient not enrolled and prescription dispensed
3. Drug Interaction and Counseling Checklist not completed, and prescription dispensed
4. Audit of Drug Interaction and Counseling Checklist forms that identified a drug was dispensed but a required action not taken
5. Authorization denied and prescription dispensed

ix. For participants with deficiencies noted, the number that successfully completed a Corrective and Preventative Action (CAPA) plan and as a percentage of those for which a CAPA plan was requested

x. For any participants who did not complete the CAPA Plan, a description of actions taken

c) Healthcare provider noncompliance (For each non-compliance event, the source of the report, a description of the event, the root cause analysis of the event, and corrective actions taken)

   i. Number of healthcare providers who were non-compliant with the Camzyos REMS program requirements. Provide as a percentage of active healthcare providers

   ii. Number of healthcare providers who were de-certified and reasons for de-certification also provide as a percentage of active healthcare providers. Include if any healthcare providers were re-certified

d) Pharmacies (For each non-compliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions taken)

   i. Number of pharmacies for which non-compliance with the Camzyos REMS is detected (numerator) divided by all pharmacies dispensing Camzyos (denominator)

   ii. Total number of unauthorized Camzyos prescriptions dispensed

   iii. The number of non-certified pharmacies that dispensed Camzyos (numerator) divided by all pharmacies that dispensed Camzyos (denominator).

   iv. Number of Camzyos prescriptions dispensed by non-certified pharmacies (numerator) divided by all prescriptions Camzyos dispensed (denominator) and the actions taken to prevent future occurrences.

   v. Number of Camzyos prescriptions dispensed that were written by non-certified healthcare providers (numerator) divided by all dispensed prescriptions (denominator). For prescriptions dispensed that were written by non-certified healthcare providers, provide the root cause analysis and the actions taken to prevent future occurrences.

   vi. Number of Camzyos prescriptions dispensed to non-enrolled patients (numerator) divided by all dispensed prescriptions (denominator). For prescriptions dispense to non-enrolled patients provide a root cause analysis and the actions taken to prevent future occurrences.

   vii. Number of Camzyos prescriptions dispensed to non-enrolled patients based on a prescription from a non-certified healthcare provider (numerator) divided by all dispensed prescriptions (denominator). For prescriptions dispensed to non-enrolled patients based on a prescription from a non-certified healthcare

provider provide a root cause analysis and the actions taken to prevent future occurrences.

viii. Number of times a Camzyos prescription was dispensed because a certified pharmacy bypassed the Camzyos REMS authorization processes (numerator) divided by all certified pharmacies (denominator). Provide a root cause analysis and including a description of how the events were identified and any corrective actions taken.

ix. Number of pharmacies decertified (numerator), reasons for decertification, and actions to address non-compliance. Provide as a ratio the numerator divided by all certified pharmacies (denominator)

e) Wholesalers-distributors (For each non-compliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions taken)

i. Number of contracted wholesalers-distributors for which non-compliance with the Camzyos REMS is detected (numerator) divided by the number of contracted wholesalers-distributors (denominator)

ii. Number of wholesalers-distributors suspended from distributing, reasons for the suspension, and actions to address non-compliance

iii. Number of times Camzyos was distributed to a non-certified pharmacy (numerator) divided by the number of distributions of Camzyos (denominator)

4. Utilization Data

a) Number of prescriptions (new and refills) dispensed, stratified by:

i. Healthcare provider degree/credentials and geographic region

ii. Patient demographics (age and gender, and geographic region)

b) Number of unique healthcare providers who wrote prescriptions dispensed in the reporting period (active healthcare providers)

c) Number of unique patients receiving Camzyos, stratified by age, gender, and geographic region

d) Number of unique patients receiving an early dispense of Camzyos stratified by reason for early dispense (e.g., travel, weather-related or other environmental emergency, other reason [state reason])

i. Number and percentage of early dispense authorizations issued, stratified by reason

ii. Number of humanitarian events during the reporting period for which early dispenses were allowed

iii. Change in dispensing cadence (e.g, number of days early that dispenses were authorized, including median, mean, and range number of days early that dispenses were authorized), stratified by reason

iv. Number of unauthorized early dispenses, root cause analysis, corrective actions, and outcomes

v. A summary analysis of adverse events of heart failure due to systolic dysfunction reported among patients who received an early dispense during the reporting period (e.g., number of cases, causality assessment, etc.)

e) The number of prescriptions dispensed when the prescription:

i. Will be dispensed with a REMS authorization

ii. Will be dispensed from a Certified pharmacy

iii. Written by a Certified prescriber

iv. Written for an Enrolled patient

v. Has a completed Patient Status form that documents an appropriately timed ECHO

vi. Has a completed Drug Interaction and Counseling Checklist that documents appropriate actions were taken prior to authorization.

5. Burden to the Healthcare System and/or Barriers to Patient Access

a) Reports to the Camzyos REMS Call Center indicating a burden to the healthcare system or barriers to patient access. Assessment of whether burden is attributable to the REMS, insurance, health care availability, other

Safe Use Behavior

6. Patient Status Forms

a) Number of Patient Status Forms expected, received, and outstanding as of the REMS assessment cut-off date

b) Number of first patient shipments sent prior to receipt of a Patient Enrollment Form (numerator) divided by all patients who were dispensed Camzyos (denominator).

c) Number of unique patients who had a Patient Status Form submitted who the healthcare provider confirmed reviewing the echocardiogram

for (numerator) divided by number of unique patients who had a Patient Status Form submitted (denominator)

d) Number of unique patients who had a Patient Status Form submitted who the healthcare provider authorized treatment for (numerator) divided by number of unique patients who had a patient status form submitted (denominator)

e) Number of Patient Status Forms outstanding from previous reporting periods that were completed in the current reporting period (numerator) divided by the number of outstanding Patients Status Forms from the previous reporting period (if applicable)

f) Number of Patient Status Forms on which the healthcare provider indicated that the patient experienced a clinical heart failure event requiring hospitalization

g) Number of Patient Status Forms on which the healthcare provider indicated the patient experienced a decrease in LVEF to <50%

h) Number of patients who were not authorized to receive Camzyos as indicated on the Patient Status Form

7. Patient Enrollment Forms

a) Number of unique patients who have a treatment start date >90 days after the date the **Patient Enrollment Form** was submitted, along with the minimum, maximum, and mean days of initial therapy delay, and reasons for the delay

8. Drug Interaction and Counseling Checklist for Pharmacies

a) Number of unique patients who had a Drug Interaction and Counseling Checklist completed prior to their initial dispensing of Camzyos (numerator) divided by the number of patients who initiated therapy with Camzyos (denominator).

b) Number of prescriptions dispensed that had a Drug Interaction and Counseling Checklist completed prior to dispensing (numerator) divided by the number of prescriptions dispensed for Camzyos (denominator).

c) Number of Drug Interaction and Counseling Checklist that identified concurrent contraindicated medicines (numerator) divided by the total number of Drug Interaction and Counseling Checklists completed (denominator)

d) For those Drug Interaction and Counseling Checklists that identified a concurrent contraindicated medicines indicate the source of the drug interaction and action taken after healthcare provider was contacted including:

i. Source

1. Interacting drug prescribed by Camzyos certified healthcare provider/designee
2. Interacting drug prescribed by other healthcare provider
3. Interacting drug purchased over the counter by patient

ii. Action taken

1. Camzyos discontinued
2. Contraindicated drug discontinued

e) Number of Drug Interaction and Counseling Checklists that identified a concurrent medicine that required a dosage reduction (numerator) divided by the total number of Drug Interaction and Counseling Checklists completed (denominator).

f) For those Drug Interaction and Counseling Checklists that identified a concurrent medicine that required a dosage reduction indicate source of drug interaction and action taken after healthcare provider was contacted including:

i. Source

1. Interacting drug prescribed by Camzyos certified healthcare provider/designee
2. Interacting drug prescribed by other healthcare provider
3. Interacting drug purchased over the counter by patient

ii. Action taken

1. Camzyos discontinued
2. Camzyos dose decreased
3. Other medicine(s) discontinued

g) Any information obtained from audits, or self-reported by pharmacies that indicated that a patient did receive a contraindicated medicine, while taking Camzyos expressed by the number of patients who received at least one shipment (dispensing) of Camzyos who were also taking a concurrent contraindicated medicines (numerator) divided by the total number of patients with at least one shipment (dispensing) of Camzyos (denominator)

i. For all occurrences, include the contraindicated drug name, dose, and duration of therapy

9. Knowledge Assessments (provide data at the 1-year and 2-year assessment reports only)

   a) Number of completed Healthcare Provider Knowledge Assessments, including the method of completion and number of attempts to complete

   b) A summary of the most frequently missed Healthcare Provider Knowledge Assessment questions

   c) A summary of potential comprehension or perception issues identified with the Healthcare Provider Knowledge Assessment

   d) Number of completed Pharmacy Authorized Representative Knowledge Assessments, including the method of completion and number of attempts to complete

   e) A summary of the most frequently missed Pharmacy Authorized Representative Knowledge Assessment questions

   f) A summary of potential comprehension or perception issues identified with the Pharmacy Authorized Representative Knowledge Assessment

Overall Assessment of REMS Effectiveness

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 214998 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 214998 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 214998 /S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 214998 /S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 214998/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 214998/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 214998

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain

documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

APPROVAL & LABELING

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 enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.
Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[1] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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, please contact Maryam Changi, Regulatory Project Manager, at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiology and Nephrology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- REMS

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/

MARY R SOUTHWORTH
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