BOSTON MEDICAL CENTER HEALTHNet PLAN

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WELL SENSE HEALTH PLAN

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Pharmacy Policy

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators – Unified Formulary

Policy Number: 9.148
Version Number: 2
Version Effective Date: 1/1/2022

Product Applicability	☐ **All Plan+ Products**
Well Sense Health Plan	**Boston Medical Center HealthNet Plan**
☐ New Hampshire Medicaid	☒ MassHealth ACO
	☒ MassHealth MCO
	☐ Qualified Health Plans/ConnectorCare/Employer Choice Direct
	☐ Senior Care Options

Note: Disclaimer and audit information is located at the end of this document.

Policy

Reference Table:

Drugs That Require PA	No PA
Kalydeco® (ivacaftor) PD	
Orkambi® (lumacaftor/ivacaftor) PD	
Symdeko® (tezacaftor/ivacaftor) PD	
Trikafta® (elexacaftor/tezacaftor/ivacaftor) PD	

PD=preferred drug. In general, MassHealth requires a trial of the preferred drug or clinical rationale for prescribing a non-preferred drug within a therapeutic class.

Procedure:

Approval Diagnosis:	Cystic Fibrosis
Approval Criteria: **Kalydeco®** (ivacaftor) Cystic Fibrosis with one	Prescriber provides documentation of **ALL** of the following: 1. Appropriate diagnosis (*specific gene mutation MUST be noted)** 2. Member is ≥ 4 months of age 3. Request does not exceed 2 units/day‡ 4. Baseline body mass index (BMI) and percent predicted forced

mutation in the CFTR gene that is responsive to ivacaftor*	expiratory volume in one second ($ppFEV_1$) † *Notes:* • *Members < 4 months old will be evaluated on a case-by-case basis, evaluating available literature. Please forward request to the Clinical Reviewer for follow-up.* • ** Please refer to Appendix for full list of approved mutations.* • *† If member is ≤ 6 years of age, ppFEV1 does not have to be performed* • *‡ Please review for potential drug drug interactions as highlighted in appendix section* • *Previous prior authorizations for CFTR modulators should be end-dated if member is switched to Kalydeco*
Approval Criteria: **Orkambi**® (lumacaftor/ivacaftor) Cystic Fibrosis with two copies (homozygous) of the F508del-CFTR mutation	Prescriber provides documentation of **ALL** of the following: 1. Appropriate diagnosis *(specific gene mutation MUST be noted)* 2. Member is ≥ 2 years of age 3. Request does not exceed 4 tablets/day or 2 packets/day‡ 4. Baseline BMI and $ppFEV_1$ † *Notes:* • *Members < 2 years old will be evaluated on a case-by-case basis, evaluating available literature. Please forward request to the Clinical Reviewer for follow-up.* • *† If member is ≤ 6 years of age, ppFEV1 does not have to be performed* • *‡ Please review for potential drug drug interactions as highlighted in appendix section* • *Previous prior authorizations for CFTR modulators should be end-dated if member is switched to Orkambi*
Approval Criteria: **Symdeko**® (tezacaftor/ivacaftor) Cystic Fibrosis with two copies (homozygous) of the F508del-CFTR mutation or at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor*	Prescriber provides documentation of **ALL** of the following: 1. Appropriate diagnosis *(specific gene mutation MUST be noted)** 2. Member is ≥ 6 years of age 3. Request does not exceed 2 tablets/day‡ 4. Baseline BMI and $ppFEV_1$ *Notes:* • *Members < 6 years old will be evaluated on a case-by-case basis, evaluating available literature. Please forward request to the Clinical Reviewer for follow-up.* • ** Please refer to Appendix for full list of approved mutations.* • *‡ Please review for potential drug drug interactions as highlighted in appendix section* • *Previous prior authorizations for CFTR modulators should be end-dated if member is switched to Symdeko*
Approval Criteria: **Trikafta**® (elexacaftor/tezacaftor/ivacaftor)	Prescriber provides documentation of **ALL** of the following: 1. Appropriate diagnosis *(specific gene mutation MUST be noted)** 2. Member is ≥ 6 years of age 3. Request does not exceed 3 tablets/day‡ 4. Baseline BMI and $ppFEV_1$

Cystic Fibrosis with at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive to elexacaftor/tezacaftor/ ivacaftor*	*Notes:* • *Members < 6 years old will be evaluated on a case-by-case basis, evaluating available literature. Please forward request to the Clinical Reviewer for follow-up.* • **Please refer to Appendix for full list of approved mutations.* • ‡ *Please review for potential drug drug interactions as highlighted in appendix section* • *Previous prior authorizations for CFTR modulators should be end-dated if member is switched to Trikafta*
Denial Criteria:	Cases that do not meet the approval criteria will be denied.
	If a request is denied and the prescriber has additional clinical documentation, a **new** prior authorization request must be submitted.
Duration of Authorization:	Prior authorization may be issued for **6 months.**
Recertification Criteria:	Prescriber provides documentation of any positive response to therapy either on the PA form or in medical records (e.g., improvement in BMI, $ppFEV_{1,}$ decrease in clinical exacerbations, etc.). Recertifications may be issued for **12 months**. If request does not document a response to therapy, please call office to attempt to gather information. In addition, check member adherence to Orkambi®, Kalydeco®, Symdeko®, or Trikafta® and report any gaps in pharmacy fills to office. **If unsuccessful within compliance time, issue a provisional one month approval and change outgoing message to alert office to information needed on resubmission**. If office/prescriber is unable to provide any documentation of positive response to therapy following an initial six months of continuous treatment, please address rationale for continuation of therapy with prescriber.

Appendix:

Stability

Stability on a medication requiring a prior authorization is not a reason to bypass approval criteria.

Additional Information

FDA-Approved Mutations

CFTR Gene Mutations Responsive to Trikafta					
3141del9	*E822K*	*G1069R*	*L967S*	*R117L*	*S912L*
546insCTA	*F191V*	*G1244E*	*L997F*	*R117P*	*S945L*
A46D	*F311del*	*G1249R*	*L1077P*	*R170H*	*S977F*
A120T	*F311L*	*G1349D*	*L1324P*	*R258G*	*S1159F*
A234D	*F508C*	*H139R*	*L1335P*	*R334L*	*S1159P*
A349V	*F508C;S1251N* †	*H199Y*	*L1480P*	*R334Q*	*S1251N*
A455E	*F508del* *	*H939R*	*M152V*	*R347H*	*S1255P*
A554E	*F575Y*	*H1054D*	*M265R*	*R347L*	*T338I*
A1006E	*F1016S*	*H1085P*	*M952I*	*R347P*	*T1036N*
A1067T	*F1052V*	*H1085R*	*M952T*	*R352Q*	*T1053I*
D110E	*F1074L*	*H1375P*	*M1101K*	*R352W*	*V201M*
D110H	*F1099L*	*I148T*	*P5L*	*R553Q*	*V232D*

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CFTR Gene Mutations Responsive to Trikafta					
D192G	*G27R*	*I175V*	*P67L*	*R668C*	*V456A*
D443Y	*G85E*	*I336K*	*P205S*	*R751L*	*V456F*
D443Y;G576A;R668C †	*G126D*	*I502T*	*P574H*	*R792G*	*V562I*
D579G	*G178E*	*I601F*	*Q98R*	*R933G*	*V754M*
D614G	*G178R*	*I618T*	*Q237E*	*R1066H*	*V1153E*
D836Y	*G194R*	*I807M*	*Q237H*	*R1070Q*	*V1240G*
D924N	*G194V*	*I980K*	*Q359R*	*R1070W*	*V1293G*
D979V	*G314E*	*I1027T*	*Q1291R*	*R1162L*	*W361R*
D1152H	*G463V*	*I1139V*	*R31L*	*R1283M*	*W1098C*
D1270N	*G480C*	*I1269N*	*R74Q*	*R1283S*	*W1282R*
E56K	*G551D*	*I1366N*	*R74W*	*S13F*	*Y109N*
E60K	*G551S*	*K1060T*	*R74W;D1270N †*	*S341P*	*Y161D*
E92K	*G576A*	*L15P*	*R74W;V201M †*	*S364P*	*Y161S*
E116K	*G576A;R668C †*	*L165S*	*R74W;V201M;D1270N †*	*S492F*	*Y563N*
E193K	*G622D*	*L206W*	*R75Q*	*S549N*	*Y1014C*
E403D	*G628R*	*L320V*	*R117C*	*S549R*	*Y1032C*
E474K	*G970D*	*L346P*	*R117G*	*S589N*	
E588V	*G1061R*	*L453S*	*R117H*	*S737F*	

* *F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data.
† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko					
546insCTA	*E92K*	*G576A*	*L346P*	*R117G*	*S589N*
*711+3A→G **	*E116K*	*G576A;R668C †*	*L967S*	*R117H*	*S737F*
*2789+5G→A **	*E193K*	*G622D*	*L997F*	*R117L*	*S912L*
*3272-26A→G **	*E403D*	*G970D*	*L1324P*	*R117P*	*S945L **
*3849+10kbC→T **	*E588V*	*G1069R*	*L1335P*	*R170H*	*S977F **
A120T	*E822K*	*G1244E*	*L1480P*	*R258G*	*S1159F*
A234D	*E831X*	*G1249R*	*M152V*	*R334L*	*S1159P*
A349V	*F191V*	*G1349D*	*M265R*	*R334Q*	*S1251N*
*A455E **	*F311del*	*H939R*	*M952I*	*R347H **	*S1255P*
A554E	*F311L*	*H1054D*	*M952T*	*R347L*	*T338I*
A1006E	*F508C*	*H1375P*	*P5L*	*R347P*	*T1036N*
A1067T	*F508C;S1251N †*	*I148T*	*P67L **	*R352Q **	*T1053I*
D110E	*F508del ^*	*I175V*	*P205S*	*R352W*	*V201M*
*D110H **	*F575Y*	*I336K*	*Q98R*	*R553Q*	*V232D*
D192G	*F1016S*	*I601F*	*Q237E*	*R668C*	*V562I*
D443Y	*F1052V*	*I618T*	*Q237H*	*R751L*	*V754M*
D443Y;G576A;R668C †	*F1074L*	*I807M*	*Q359R*	*R792G*	*V1153E*
*D579G **	*F1099L*	*I980K*	*Q1291R*	*R933G*	*V1240G*
D614G	*G126D*	*I1027T*	*R31L*	*R1066H*	*V1293G*
D836Y	*G178E*	*I1139V*	*R74Q*	*R1070Q*	*W1282R*
D924N	*G178R*	*I1269N*	*R74W*	*R1070W **	*Y109N*
D979V	*G194R*	*I1366N*	*R74W;D1270N †*	*R1162L*	*Y161S*
*D1152H **	*G194V*	*K1060T*	*R74W;V201M †*	*R1283M*	*Y1014C*
D1270N	*G314E*	*L15P*	*R74W;V201M;D1270N †*	*R1283S*	*Y1032C*
E56K	*G551D*	*L206W**	*R75Q*	*S549N*	
E60K	*G551S*	*L320V*	*R117C**	*S549R*	

* Clinical data for these mutations in Clinical Studies.
^ A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in Table 6 to be indicated.
† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Kalydeco

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*711+3A→G **	*F311del*	*I148T*	*R75Q*	*S589N*
*2789+5G→A **	*F311L*	*1175V*	*R117C**	*S737F*
*3272-26A→G **	*F508C*	*I807M*	*R117G*	*S945L**
*3849+10kbC→T **	*F508C;S1251N †*	*I1027T*	*R117H**	*S997F **
A120T	*F1052V*	*I1139V*	*R117L*	*S1159F*
A234D	*F1074L*	*K1060T*	*R117P*	*S1159P*
A349V	*G178E*	*L206W **	*R170H*	*S1251N**
*A455E **	*G178R**	*L320V*	*R347H**	*S1255P**
A1067T	*G194R*	*L967S*	*R347L*	*T338I*
D110E	*G314E*	*L997F*	*R352Q**	*T1053I*
D110H	*G551D **	*L1480P*	*R553Q*	*V232D*
D192G	*G551S **	*M152V*	*R668C*	*V562I*
*D579G **	*G576A*	*M952I*	*R792G*	*V754M*
D924N	*G970D*	*M952T*	*R993G*	*V1293G*
*D1152H **	*G1069R*	*P67L**	*R1070Q*	*W1282R*
D1270N	*G1244E **	*Q237E*	*R1070W**	*Y1014C*
E56K	*G1249R*	*Q237H*	*R1162L*	*Y1032C*
E193K	*G1349D**	*Q359R*	*R1283M*	
E822K	*H939R*	*Q1291R*	*S549N**	
*E831X**	*H1375P*	*R74W*	*S549R**	

* Clinical data exist for these mutations.
† Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

Requests for Mutations other than the FDA-Approved Indications

Requests for mutations other than those listed above in the individual approval criteria or in the specific package inserts should be denied non-FDA approved indication.

Drug-Drug Interactions Requiring Dose Adjustments for the CFTR Modulator

All requests for CFTR modulators should be reviewed for drug interactions. If the request notes member is currently being treated with the specific agents below (or there is recent history of claims) that are not recommended for use in combination with the requested regimen or requires a dose reduction of the CFTR modulator, prescriber should address the management of drug interaction on resubmission. Consult clinical reviewer, if necessary.

Kalydeco® (ivacaftor)

<table>
<tr><th>Concomitant Drug Class: Drug Name</th><th>Effect on Concentration</th><th>Recommendations</th></tr>
<tr><td>Strong Inhibitors of CYP3A
(e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin)</td><td>↑ ivacaftor by 8.5 fold</td><td>Reduction in Kalydeco® dose as follows:
<table>
<tr><th>Age</th><th>Kalydeco® dose</th></tr>
<tr><td>≥ 6 years old</td><td>150 mg twice weekly</td></tr>
<tr><td>6 months to < 6 years
Weight 5 kg to < 7 kg</td><td>25 mg packet twice weekly</td></tr>
<tr><td>6 months to < 6 years
Weight 7 kg to < 14kg</td><td>50 mg packet twice weekly</td></tr>
<tr><td>6 months to < 6 years
Weight ≥ 14 kg</td><td>75 mg packet twice weekly</td></tr>
<tr><td colspan="2">Concomitant use of moderate or strong CYP3A inhibitors is not recommended in children < 6 months of age. Food containing grapefruit should be avoided.</td></tr>
</table></td></tr>
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<table>
<tr><th>Concomitant Drug Class:
Drug Name</th><th>Effect on Concentration</th><th>Recommendations</th></tr>
<tr><td>Moderate Inhibitors of CYP3A
(e.g., fluconazole, erythromycin)</td><td>↑ ivacaftor by 3 fold</td><td>Reduction in Kalydeco® dose as follows:
<table><tr><th>Age</th><th>Kalydeco® dose</th></tr><tr><td>≥ 6 years old</td><td>150 mg once daily</td></tr><tr><td>6 months to < 6 years
Weight 5 kg to < 7 kg</td><td>25 mg packet once daily</td></tr><tr><td>6 months to < 6 years
Weight 7 kg to < 14kg</td><td>50 mg packet once daily</td></tr><tr><td>6 months to < 6 years
Weight ≥ 14 kg</td><td>75 mg packet once daily</td></tr></table></td></tr>
<tr><td>Strong Inducer of CYP3A
(e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John’s wort)</td><td>↓ ivacaftor by 9 fold</td><td>Do NOT administer together.</td></tr>
</table>

Orkambi® (lumacaftor/ivacaftor)

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
Strong Inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin)	↑ ivacaftor by 4.3 fold	No dose adjustment is necessary when CYP3A inhibitors are initiated in patients already taking Orkambi. However, when initiating Orkambi in patients currently taking strong CYP3A inhibitors (e.g., itraconazole), reduce Orkambi dose to one tablet daily or one packet of oral granules every other day for the first week of treatment. Following this period, continue with the recommended daily dose. If Orkambi is interrupted for more than one week and then re-initiated while taking strong CYP3A inhibitors, patients should reduce Orkambi dose to one tablet daily or one packet of oral granules every other day for the first week of treatment re-initiation. Following this period, continue with the recommended daily dose.
Strong Inducer of CYP3A (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John’s wort)	↓ ivacaftor by 57%	Do NOT administer together.
CYP3A Substrates	May decrease therapeutic effect of other agent	Lumacaftor is a strong inducer of CYP3A. Co-administration of lumacaftor with ivacaftor, a sensitive CYP3A substrate, decreased ivacaftor exposure by approximately 80%. Administration of ORKAMBI may decrease systemic exposure of medicinal products which are substrates of CYP3A, thereby decreasing the therapeutic effect of the medicinal product. Co-administration of ORKAMBI is NOT recommended with sensitive CYP3A substrates or CYP3A substrates with a

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
		narrow therapeutic index such as: Benzodiazepines: midazolam, triazolam Immunosuppressants: cyclosporine, everolimus, sirolimus, and tacrolimus
Please refer to package insert for additional information on potential for lumacaftor/ivacaftor to affect other drugs.		

Symdeko® (tezacaftor/ivacaftor)

<table>
<tr><th>Concomitant Drug Class: Drug Name</th><th>Effect on Concentration</th><th>Recommendations</th></tr>
<tr><td>Strong Inhibitors of CYP3A
(e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin)</td><td>↑ ivacaftor by 15.6 fold as well as ↑ tezacaftor by 4 fold</td><td>Reduction in Symdeko® dose as follows:
<table>
<tr><th>Age</th><th>Symdeko® dose</th></tr>
<tr><td>6 to < 12 years old weight < 30 kg</td><td>Day 1: One (tezacaftor 50 mg/ivacaftor 75 mg) tablet QAM (No ivacaftor dose in PM)
Day 2: No dose
Day 3: No dose
Day 4: One (tezacaftor 50 mg/ivacaftor 75 mg) QAM (No ivacaftor dose in PM)
Repeat</td></tr>
<tr><td>6 to < 12 years old Weight ≥ 30 kg or age ≥ 12 years old</td><td>Day 1: One (tezacaftor 100 mg/ivacaftor 150 mg) tablet QAM (No ivacaftor dose in PM)
Day 2: No dose
Day 3: No dose
Day 4: One (tezacaftor 100 mg/ivacaftor 150 mg) QAM (No ivacaftor dose in PM)
Repeat</td></tr>
</table></td></tr>
<tr><td>Moderate Inhibitors of CYP3A
(e.g., fluconazole, erythromycin)</td><td>↑ ivacaftor by 3 fold as well as ↑ tezacaftor by 2 fold</td><td>Reduction in Symdeko® dose as follows:
<table>
<tr><th>Age</th><th>Symdeko® dose</th></tr>
<tr><td>6 to < 12 years old weight < 30 kg</td><td>Day 1: One (tezacaftor 50 mg/ivacaftor 75 mg) tablet QAM (No ivacaftor dose in PM)
Day 2: One ivacaftor 75 mg tablet QAM
Day 3: One (tezacaftor 50 mg/ivacaftor 75 mg) tablet QAM (No ivacaftor dose in PM)
Day 4: One ivacaftor 75 mg tablet QAM</td></tr>
</table></td></tr>
</table>

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
		6 to < 12 years old Weight ≥ 30 kg or age ≥ 12 years old: Day 1: One (tezacaftor 100 mg/ivacaftor 150 mg) tablet QAM (No ivacaftor dose in PM) Day 2: One ivacaftor 150 mg tablet QAM Day 3: One (tezacaftor 100 mg/ivacaftor 150 mg) tablet QAM (No ivacaftor dose in PM) Day 4: One ivacaftor 150 mg tablet QAM Repeat Food or drink containing grapefruit should be avoided
Strong Inducer of CYP3A (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort)	↓ ivacaftor by 89% as well as ↓ tezacaftor	Do NOT administer together.

Trikafta® (elexacaftor/tezacaftor/ivacaftor)

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
Strong Inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin)	↑ ivacaftor by 8.5 to 15.6 fold as well as ↑ tezacaftor by 4 fold and ↑elexacaftor by 2.8 fold	Reduction in Trikafta® dose as follows: Day 1: Two tablets (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) QAM (No ivacaftor dose in PM) Day 2: No dose Day 3: No dose Day 4: Two tablets (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) QAM (No ivacaftor dose in PM) Repeat
Moderate Inhibitors of CYP3A (e.g., fluconazole, erythromycin)	↑ ivacaftor by 3 fold as well as ↑ tezacaftor by 2 fold	Reduction in Trikafta® dose as follows: Day 1: Two tablets (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) QAM (No ivacaftor dose in PM) Day 2: One ivacaftor tablet Day 3: Two tablets (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) QAM (No ivacaftor dose in PM) Day 4: One ivacaftor tablet Repeat Food containing grapefruit should be avoided
Strong Inducer of CYP3A	↓ ivacaftor by	Do NOT administer together.

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
(e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort)	89% as well as ↓ elexacaftor and tezacaftor	

Compelling cases - Clinical and/or Supervisor Review

If clinical review/supervisor is not available and compliance is an issue, please approve or deny based on your professional clinical judgment and forward to clinical review for follow-up.

Responsibility and Accountability

Policy History

Original Approval Date	Original Effective Date	Policy Owner	Approved by
5/13/2021	7/1/2021	Pharmacy Services	Pharmacy & Therapeutics (P&T) Committee

Policy Revisions History			
Review Date	**Summary of Revisions**	**Revision Effective Date**	**Approved by**
5/13/2021	Created policy for MH Unified Formulary, policy date 3/15/21. Replaces policy MA9.100 Cystic Fibrosis	7/1/2021	P&T Committee
7/23/2021	Updated policy to reflect 6/23/21 dated changes from MH. Verbiage was updated for age criteria for all drugs. Guideline was also updated to include FDA-expanded age indication for Trikafta ≥ 6 years of age.	9/1/2021	P&T Committee
8/12/2021	Annual P&T Reivew: no changes	1/1/2022	P&T Committee

Next Review Date

8/2022

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Other Applicable Policies

References

Reference to Applicable Laws and Regulations, if Any

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