AHFS Final Determination of Medical Acceptance: Sevelamer for the Management of Hyperphosphatemia Related to FGFR Inhibitors

Drug: Sevelamer

Off-label Use: FGFR inhibitor-related hyperphosphatemia

Off-label Use for Review:

- Minimal clinical evidence; current recommendations are primarily based on expert opinion

Strength of Evidence: Level 3 (low strength/quality)

Grade of Recommendation: Reasonable choice (accepted, with possible conditions)

Narrative Summary:

The Food and Drug Administration (FDA) has approved three fibroblast growth factor receptor (FGFR) inhibitors (erdafitinib, futibatinib, and pemigatinib) for the treatment of various malignant conditions as genetic alterations in the FGFR gene family may be oncogenic.[10001,10002] One of the most common adverse events associated with FGFR inhibitor therapy is hyperphosphatemia, occurring in 55 to 85% of patients in clinical trials.[10002,10003,10004] The prescribing information for each approved FGFR inhibitor contains general management strategies for hyperphosphatemia occurrence.[10005,10006,10007] These strategies include restricting dietary phosphate intake, avoiding use of agents that may increase serum phosphate, withholding, reducing, or discontinuing the FGFR inhibitor dose dependent upon serum phosphate level and/or clinical manifestations, and potential initiation of an oral phosphate binder. [10005,10006,10007] Sevelamer is an oral phosphate binder available as 2 separate salt forms.[10008,10009] The hydrochloride form is labelled for the control of serum phosphorous in patients with chronic kidney disease (CKD) on dialysis while the carbonate form is labelled for the control of serum phosphorous in adults and children ≥6 years of age with CKD on dialysis. [10008,10009] Sevelamer is generally well tolerated; however, the most common adverse reactions associated with its use are gastrointestinal in nature including dyspepsia, diarrhea, nausea, constipation, flatulence, abdominal distension, and vomiting.[10008,10009]

The published clinical evidence supporting the use of sevelamer as a preferred oral phosphate binder for the management of FGFR inhibitor-related hyperphosphatemia is minimal in nature. There is no consensus on the optimal management strategy and current recommendations are primarily based on expert opinion.[10003,10012] Attieh and colleagues reported an index case involving a 68 year old male with FGFR2-mutated stage IV intrahepatic cholangiocarcinoma who was initiated on futibatinib after undergoing treatment with multiple lines of therapy.[10003] Upon 13 days of futibatinib therapy, the patient developed hyperphosphatemia and was initiated on calcium acetate 1334 mg orally three times daily with meals. [10003] Despite calcium acetate therapy, serum phosphate levels continued to rise (peaking at 6.4 mg/dL) and the patient was subsequently initiated on sevelamer hydrochloride 800 mg orally three times daily with an observed reduction in serum phosphate levels. [10003] Beyond this single case report, protocols from key clinical trials of FGFR inhibitor therapy incorporated sevelamer therapy as a cornerstone of hyperphosphatemia management.[10010,10011]

Based on current evidence, sevelamer for the management of FGFR inhibitor-related hyperphosphatemia, has Level 3 (low strength/quality) evidence supporting its use. [10010] Sevelamer may be preferred over calcium-based phosphate binders in patients with hypercalcemia. [10012] Sevelamer use may be more appropriate in patients experiencing none to limited/mild diarrhea related to FGFR inhibitor therapy. [10012]

Dosage

When sevelamer is used for the management of FGFR inhibitor-related hyperphosphatemia, the usual initial dosage is 800 to 1600 mg orally three times daily with meals with a maximum recommended dose of 2400 mg orally three times daily.[10013]

References:

10001. Food and Drug Administration. Drugs@FDA: FDA-approved drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

10002. Subbiah V, Verstovsek S. Clinical development and management of adverse events associated with FGFR inhibitors. *Cell Reports Med*. 2023;4:101204.

10003. Attieh RM, Upadrista P, Levy AT, Jhaveri KD. Fibroblast growth factor receptor inhibitor-induced hyperphosphatemia: lessons for the nephrologist. *Clin Nephrol*. 2025;103(1):12-18.

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10005. Balversa®. Erdafitinib tablets for oral use prescribing information. Janssen Products, LP: Horsham, PA; October 2025.

10006. Lytgobi®. Futibatinib tablets for oral use prescribing information. Taiho Oncology, Inc.: Princeton, NJ; October 2025.

10007. Pemazyre®. Pemigatinib tablets for oral use prescribing information. Incyte Corporation: Wilmington, DE; June 2023.

10008. Renagel®. Sevelamer hydrochloride tablets for oral use prescribing information. Genzyme Corporation: Cambridge, MA; 2023.

10009. Renvela®. Sevelamer carbonate tablets and powder for oral use prescribing information. Genzyme Corporation: Cambridge, MA; 2023 March.

10010. Goyal L, Meric-Bernstam F, Hollebecque A, et al for the FOENIX-CCA2 study investigators. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. *N Engl J Med*. 2023;388:228-39. Supplementary material.

10011. Loriot Y, Matsubara N, Park SH, et al for the THOR Cohort 1 investigators. Erdafitinib or chemotherapy in advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2023;389:1961-71. Supplementary material.

10012. OncLive. Monitoring and managing hyperphosphatemia. https://www.onclive.com/view/monitoring-and-managing-hyperphosphatemia. February 7, 2024.

10013. Kommalapati A, Tella SH, Board M, et al. FGFR inhibitors in oncology: insight on the management of toxicities in clinical practice. *Cancers*. 2021;13:2968.

Oncology Expert Committee Voting Results and Comments:

First-Round Vote (6 of 7 committee members returned the initial ballot):

Proposed Level of Evidence: Level 3 (Low strength/quality)

Concur with rating: 5 votes

Do not concur with rating: 1 vote; opinion/experience rating

Grade of Recommendation:

Recommended (Accepted): 0 respondents

Reasonable choice (Accepted, with possible conditions): 4 respondents

Not fully established (Unclear risk/benefit or equivocal): 2 respondents

Not recommended (Unaccepted): 0 respondent

Reviewer Comments on Level of Evidence and Grade of Recommendation

Based on the study protocols for these agents and doses of sevelamer used, I think the starting dose recommendation should be changed to 800-1600 mg orally 3 times daily with meals with the same max dose as is already included. We should also consider how to incorporate information from the futibatinib phase II study supplemental materials and the protocol for erdafitinib's phase III data that provides specific recommendations for use of sevelamer to treat hyperphosphatemia due to these agents.

While I agree sevelamer certainly has a place in the treatment of hyperphosphatemia caused by FGFR inhibitors, I do not think there is sufficient evidence to specifically recommend sevelamer over other phosphorus binders. There are several clinical considerations when selecting a phosphorus binder that must also be considered, namely cost to the patient/insurance coverage, pill burden, if they are having diarrhea at baseline as sevelamer specifically can worsen this, and other laboratory values. Lastly, there appears to be minimal evidence to support specific selection of sevelamer based on one case report in FGFR inhibitor use.

In the phase 2 study of pemigatinib in previously treated cholangiocarcinoma, yperphosphatemia was managed using a tiered strategy that incorporated dietary phosphate restriction, followed by initiation of phosphate-binding therapy when serum phosphate levels exceeded 7 mg/dL, and escalation to additional interventions such as diuretics if needed. Serum phosphate was monitored at least twice weekly until normalization. Similarly, clinical protocols and prescribing guidance recommend that hyperphosphatemia management follow institutional practices, including the use of phosphate binders such as sevelamer or other agents, either alone or in combination. These agents are routinely administered with meals to optimize efficacy and tolerability. Protocols for both studies are available, and within the hyperphosphatemia management sections, the use of phosphate binders is explicitly included as part of the recommended management strategy. In the phase 2 FOENIX-CCA2 study of futibatinib, hyperphosphatemia was a common adverse event, and management included dose modifications, dietary interventions, and use of phosphate binders as clinically indicated, further reinforcing that phosphate-binding therapy is an accepted component of toxicity management in this drug class. Collectively, these data demonstrate that while there is no single standardized phosphate binder mandated across trials, the use of phosphate binders is consistently incorporated into FGFR inhibitor protocols as part of routine management of hyperphosphatemia. Based on this information, the off-label use of sevelamer for FGFR inhibitor–induced hyperphosphatemia is reasonable and consistent with clinical trial practice and expert recommendations. However, it is important to acknowledge that the prospective comparative evidence supporting one phosphate binder over another remains limited, with current data largely derived from case reports, institutional practices, and expert opinion.

Although the evidence supporting sevelamer use for FGFR inhibitor-induced hyperphosphatemia is not substantial - the off-label use of sevelamer in this context is supported with expert opinion and case studies. With the dearth of evidence, sequencing recommendations and treatment algorithms are not well-studied nor established. Thereby, opinions may differ to what line sevelamer may be utilized. Given that it is a calcium-free agent, sevelamer is a preferred option if the patient has hypercalcemia since it does not risk the worsening of hypercalcemia and thereby cannot induce further complications such as vascular calcifications. In addition, sevelamer has a 19% rate of diarrhea (grade 3/4 not reported). FGFR inhibitors have reported the following rates of diarrhea (overall, severe): Erdafitinib (63%, 3%); Pemigatinib (47-50%, 2.7-2.9%); Futbatinib (39%, 1%). Given that these agents can cause substantial diarrhea, initiation of sevelamer while the initial FGFR-inhibitor-induced diarrhea is uncontrolled can compound an existing problem. Sevelamer may cautiously be initiated if a patient does not exhibit diarrhea or if the diarrhea is mild and controlled.

More data are needed regarding sevelamer for grade 3 or higher FGFR inhibitor-induced hyperphosphatemia. Especially given that a side effect of sevelamer (diarrhea) is also a side effect of FGFR inhibitors, we'd need to understand the risk of potentiating diarrhea.

There’s no head-to-head trial that compares phosphate binders or alternative therapies in this setting. Only infigratinib explicitly stated that patients used sevelamer in their trial, while others only mention “phosphate binders” in general. This is a tough one to review since it’s supportive care. I would add the potential adverse effects and incidence of ADRs of using sevelamer, such as hypophosphatemia and diarrhea/constipation (one article stated diarrhea while another said constipation). We could also include ways to prevent the hypophosphatemia: do not take sevelamer on days when FGFRi is not taken, use smallest dose possible, adjust diet as needed. Although infigratinib was pulled from the market, their phase 2 data could serve to justify the use of sevelamer for the treatment of hyperphosphatemia in patients taking FGFRi’s.

Consensus Vote (6 of 7 committee members returned the consensus ballot):

Proposed Level of Evidence: Level 3 (Low strength/quality)

Concur with rating: 6 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended (Accepted): 0 respondents

Reasonable choice (Accepted, with possible conditions): 6 respondents

Not fully established (Unclear risk/benefit or equivocal): 0 respondents

Not recommended (Unaccepted): 0 respondent

Final Grade of Recommendation: Reasonable choice (Accepted, with possible conditions)

Participants:

AHFS Staff Members (writing and editing): Michael Gabay PharmD, JD, BCPS

AHFS Oncology Expert Committee Members (reviewing and voting): Chase Ayres PharmD, BCOP; Kathleen Wiley MSN, RN; Rachel Bailen PharmD, BCOP, BCPS; Sandra Cuellar PharmD, BCOP, FHOPA, FASHP; Andrew Li PharmD; Chelsea Gustafson PharmD, BCOP; Isabel Houlzet PharmD, BCPS, BCOP

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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