AMERICAN SOCIETY OF HEMATOLOGY
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December 22, 2021

Troyen Brennan, MD, Chief Medical Officer
CVS Health
One CVS Drive
Woonsocket, RI 02895

Dear Dr. Brennan,

I am writing on behalf of the American Society of Hematology (ASH) to express concern about the recent decision by CVS to limit some commercial health plan formularies to only one direct oral anticoagulant (DOAC), Xarelto (rivaroxaban), and warfarin. ASH is gravely concerned about the impact this will have on patients and urges CVS to reconsider moving forward with this policy change.

ASH represents more than 18,000 clinicians and scientists worldwide who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy.

As you know, DOACs are used to treat acute venous thromboembolism (VTE), a common and serious blood clotting condition that includes both deep-vein thrombosis (DVT) and pulmonary embolism (PE). CVS's decision to limit formularies to one DOAC will force beneficiaries to switch their anticoagulation therapy. In many instances, however, it is more clinically appropriate and safer to treat a patient with apixaban rather than rivaroxaban. For example, apixaban can be given to patients with a greater degree of renal insufficiency.[1] The use of rivaroxaban in patients with creatinine clearance <15 mL/min is contraindicated. However, product labeling for apixaban permits its use in patients with end-stage kidney disease and emerging data indicate that apixaban is an option in these patients.

Additionally, apixaban has a lower bleed risk than rivaroxaban. In a meta-analysis directly comparing apixaban to rivaroxaban in patients with acute VTE, both major and minor bleeding events were significantly higher in the rivaroxaban group. The paper also notes that previous studies have shown apixaban to be safer in patients with advanced age, baseline active cancer, chronic kidney disease, and provoked VTE.[2] The increasing use of anti-platelet therapy in patients on DOACs due to the expanding use of cardiovascular procedures particularly in the aging population increases further the risk of bleeding if apixaban is replaced by rivaroxaban especially if there is concurrent renal insufficiency. Rivaroxaban has also consistently demonstrated higher rates of gynecologic bleeding compared to other DOACs and apixaban is a preferred alternative in this patient population. And in a number of studies, especially in older patients, rivaroxaban

has been associated with increased rates of gastrointestinal bleeding when compared to apixaban.[3,4]

An additional study including more than 37,000 patients found that apixaban was associated with a lower risk of recurrent VTE and a lower rate of major bleeding compared with rivaroxaban. While comparative effectiveness studies like this one have limitations, they provide some of the best available evidence in the absence of clinical trials.[5]

Decisions surrounding any medication choice, including anticoagulation, are based on clinicians' expertise, scientific evidence, as well as patients' preferences and values and are made through a shared decision-making process. By allowing this change to move forward, insurance companies are the ones making complicated medical decisions – this approach is neither a safe nor effective way to practice medicine. ASH believes all treatment decisions should be made between a physician and their patient.

Given the serious impact this will have on patients, ASH urges CVS to reconsider this decision and to not move forward with limiting formularies to only include one DOAC. Thank you for your consideration. ASH would be pleased to provide you with copies of any of the literature cited in this letter. If you have any questions or if the Society can ever serve as a resource to you, please reach out to Leslie Brady, ASH Policy and Practice Manager, at lbrady@hematology.org or 716-361-2764 (cell).

Sincerely,

Jane Winter, MD
President

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[1] Hanni Claudia, Petrovitch Elizabeth, Ali Mona, et al. Outcomes associated with apixaban vs warfarin in patients with renal dysfunction. Blood Advances 2020;4:23662371. 10.1182/bloodadvances.2019000972.

[2] Aryal MR, Gosain R, Donato A, et al. Systematic review and meta-analysis of the efficacy and safety of apixaban compared to rivaroxaban in acute VTE in the real world. *Blood Adv.* 2019;3(15):2381-2387. doi:10.1182/bloodadvances.2019000572

[3] Graham, D.J., Reichman, M.E., Wernecke, M., Hsueh, Y.H., Izem, R., Southworth, M.R., Wei, Y., Liao, J., Goulding, M.R., Mott, K. and Chillarige, Y., 2016. Stroke, bleeding, and mortality risks in elderly Medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. JAMA internal medicine, 176(11), pp.1662-1671.

[4] Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD, Stein CM. Association of Oral Anticoagulants and Proton Pump Inhibitor Cotherapy With Hospitalization for Upper Gastrointestinal Tract Bleeding. JAMA. 2018 Dec 4;320(21):2221-2230. doi: 10.1001/jama.2018.17242. PMID: 30512099; PMCID: PMC6404233.

[5]Dawwas GK, Leonard CE, Lewis JD, Cuker A. Risk for Recurrent Venous Thromboembolism and Bleeding With Apixaban Compared With Rivaroxaban: An Analysis of Real-World Data. *Ann Intern Med.* 2021 Dec 7. doi: 10.7326/M21-0717. Epub ahead of print. PMID: 34871048.