CLL SOCIETY

**VIA ELECTRONIC DELIVERY**

April 14, 2023

The Honorable Chiquita Brooks-LaSure
Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Baltimore, MD 21244–1850

**RE: Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026**

Dear Administrator Brooks-LaSure:

CLL Society appreciates the opportunity to submit its comments on the Centers for Medicare & Medicaid Services' (CMS') Initial Guidance on implementation of the Drug Price Negotiation Program created under the Inflation Reduction Act of 2022 (IRA).

CLL Society is dedicated to addressing the unmet needs of the chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) community through patient education, advocacy, support, and research. Our patients live with a chronic, rare cancer of the immune system. We are the largest nonprofit focused exclusively on the unmet needs of patients living with CLL and SLL.

We strive to fulfill our primary mission of ensuring that patients have access to safe and effective treatment options by informing patients and caregivers about the rapidly changing therapeutic landscape and the importance of clinical trials, supporting, and building patient networks, engaging in research, and educating providers and patients. As an organization, we also recognize that the healthcare landscape extends beyond science, clinical care, and patient support. Legislative, regulatory, and policy initiatives have the potential to exert a considerable and increasing force on equitable access to existing treatments and the development of new therapeutic options.

CLL Society expects that the IRA provisions capping Part D out-of-pocket costs will bring substantial relief to our patient community. Just as importantly, CMS' implementation of a "smoothing" mechanism will allow patients to spread their out-of-pocket costs over the year and avoid the all-too-common scenario of having to base treatment decisions on their financial concerns rather than their medical needs.

While the drug price negotiation program may have a marginal impact on healthcare costs for patients with relatively common conditions, as well as CLL and SLL patients who are not currently receiving active treatment, it will likely have no impact on out-of-pocket costs for patients requiring

active therapy. There is little doubt that the decisions CMS makes now on the price negotiation program will become part of the complex calculations researchers, investors, and drug manufacturers make when determining whether to pursue a particular drug candidate for a specific indication. We fear that without a proactive intent to preserve the fragile cost/benefit balance in small population diseases, CMS will inadvertently tip the scales away from innovation in CLL and SLL as well as other related blood cancers.

Our comments provide a brief background on the disease and focus on the potential impact that the policies and processes within CMS' Initial Guidance might have on our patient community. We urge CMS to exercise its implementation discretion to ensure that our health system continues to welcome the rapid scientific advances in our understanding of disease mechanisms and targeted treatment approaches that have driven hope for blood cancer patients and their families.

## Background

CLL is a chronic blood cancer of a type of white blood cell called the B-lymphocyte. In CLL there is a progressive accumulation of too many mature B-lymphocytes. CLL is the most common leukemia in adults in the United States, with around 21,000 cases diagnosed annually. Besides being a type of leukemia, it is also classified as a type of non-Hodgkin's Lymphoma (NHL). So CLL is both leukemia and lymphoma at the same time. SLL is simply a different manifestation of the same disease and is best understood as a different stage of CLL where there are not a significant number of cancer cells yet located in the bloodstream. When the cancer is only found in the lymph nodes it is called SLL. When the cancer is found in the bloodstream and possibly elsewhere, including lymph nodes, it's called CLL.

CLL/SLL is extremely heterogeneous, meaning each person's disease course and progression can be extremely variable. Some experience rapid deterioration due to having an aggressive form of the disease and survive for as little as two years, while some who have a less aggressive form of the disease will never need treatment and can expect to have a normal life expectancy.

Targeted therapies such as BTK inhibitors and the BCL2 inhibitor known as venetoclax offer substantial efficacy against CLL/SLL and have transformed care for our patient community. Patients now have more treatment options compared to just years ago when the standard of care was chemoimmunotherapy. They can take continuous daily oral therapy with a BTK inhibitor, with or without a monoclonal antibody, until their disease progresses. Alternatively, patients can choose a short-term time-limited treatment approach that combines venetoclax and a monoclonal antibody. The latter approach enables dose discontinuation until active monitoring reveals that another treatment is needed.

Although most CLL/SLL patients can expect a response to initial therapy, nearly all current treatment options are palliative and not curative. Most patients will experience one or more

relapses during the course of their disease, and many are forced to either change treatments, take a "drug holiday," or adjust dosing due to drug intolerance. For patients with relapsed or refractory disease (or treatment intolerance), treatment decisions are highly individualized based on prior therapies, prior response, the reason for discontinuation of previous therapy, comorbidities, biomarker characteristics, patient preference, and therapeutic goals. Patients can experience serial relapses, and many will be treated with all available agents at some point during their disease course.

The unfortunate reality is that despite significant progress in treating CLL/SLL, it remains an incurable cancer. Patients progressing after both BTK and BCL2 inhibitors face a poor prognosis with few treatment options other than PI3K inhibitors. Unfortunately, the use of PI3K inhibitors for hematologic malignancies has recently come under scrutiny due to safety and efficacy concerns. Manufacturers have voluntarily withdrawn indications for idelalisib in both follicular lymphoma (FL) and SLL, and duvelisib in FL. Additionally, umbralisib was completely withdrawn from the market. The FDA's recent ODAC meeting recommended the withdrawal of duvelisib. If this comes to pass, there will be no available PI3K inhibitor approved as a single agent in CLL, and none at all in SLL.

The experience with PI3K inhibitors in CLL/SLL illustrates the inherent difficulties surrounding studying this disease and the heightened risk manufacturers take on when pursuing new therapeutic candidates. Delays associated with the wait for overall survival data have already dampened research efforts and slowed patient access to potentially life-saving therapies. We have advocated for crossover in clinical trials to save lives, but the strategy inherently compromises the "purity" of survival data. Since CLL/SLL is not an ideal disease state from a research perspective, "new" treatments are often first approved for other cancers and then later approved for CLL/SLL under FDA's accelerated approval mechanism. Research and development efforts in CLL/SLL could be significantly deterred due to the combination of increased payer hesitance to fully cover and pay for accelerated approval therapies, and the likelihood that a CLL/SLL indication would render an existing drug ineligible for the IRA orphan exclusion to price negotiation, slowing new drug development in CLL/SLL and other rare cancers. We are concerned that this evolving landscape, viewed holistically, poses dire consequences for CLL/SLL patients as they exhaust available treatment options.

**CMS should extend the time for stakeholder feedback on the Initial Guidance.**

CLL Society has reviewed the complex set of policies within the Initial Guidance with an eye toward identifying concerns within our patient and provider communities and making recommendations to address those concerns. We had hoped that CMS would fulfill its commitment to prioritize transparency and robust engagement in implementing the price negotiation program. Unfortunately, CMS has issued "final" guidance to implement policy decisions we did not anticipate in light of the statutory language, that importantly warrant public input and will likely drive the success or failure of the program. To the extent that CMS reached out to the patient advocacy

community in advance of issuing the Initial Guidance, we were unaware of the approach CMS was considering, much less the opportunity to shape alternative approaches.

We are also concerned that the Agency exposes itself to legal challenges that will inject considerable uncertainty among manufacturers, investors, and even private payers. Uncertainty is a highly disruptive force that can stall or deter access to the resources that fuel innovation. We urge CMS to consider stakeholder feedback received through the 30-day comment process and extend the time for additional comments on the entirety of the Initial Guidance. Going forward, we also respectfully request that CMS develops a review process that allows for a consistent and open dialogue with the patient community. For the countless patients hoping for new treatments and equitable access to existing options, the stakes are too high for CMS to prioritize expedience over inclusion and consideration.

**Orphan Drug Exclusion**

CLL Society appreciates CMS' interest in stakeholder ideas that might facilitate orphan drug development. We also generally support the Agency's decision to extend the orphan drug exclusion to drugs with a single designation (as opposed to a single indication). The small and emerging biotechnology companies responsible for over 80% of orphan product development are particularly vulnerable to landscape changes that can impact the recoupment of research and development costs.

The risk/benefit analysis is particularly complex within the context of CLL/SLL treatments. As noted above, BTK inhibitors offer considerable improvements in care for our patients but can result in drug intolerance requiring discontinuation. Zanubrutinib is a BTK inhibitor with an orphan designation and approval in the treatment of mantle cell lymphoma (2019) that has demonstrated fewer cases of atrial fibrillation than ibrutinib and no cardiac-related deaths. CLL/SLL patients taking zanubrutinib also have a higher response rate and a longer time to disease progression. The January 19, 2023, announcement that FDA had approved zanubrutinib for both CLL and SLL was particularly significant in that it worked well in patients with difficult-to-treat cancers (i.e., those with a mutated gene called TP53, or a chromosomal alteration known as a 17p deletion). We believe it is unlikely that the manufacturer would have invested in the studies required for this set of approvals if its label expansion would have rendered the drug ineligible for the orphan drug exclusion.

The reduced side effect profile for zanubrutinib will enable patients to remain on treatment longer, but once their disease progresses, they cannot simply switch to one of the other irreversibly binding BTK inhibitors approved for CLL/SLL and expect a response. This is because once a drug within that same drug class has failed the patient, all drugs within that same class will likely fail. The January 27, 2023, accelerated approval of reversibly binding BTK inhibitor pirtobrutinib for the treatment of mantle cell lymphoma was a significant advance in lymphoma treatment, as it is

indicated for relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, ***including a BTK inhibitor.*** This treatment has already demonstrated the potential to address a significant unmet need in CLL/SLL patients who have been failed by an irreversibly binding BTK inhibitor. We are pleased that Eli Lilly is moving forward with their clinical trials in CLL, and our patient communities are hopeful that these studies will result in an FDA-approved treatment for patients who have exhausted their existing options. As the drug price negotiation program becomes a tangible reality for manufacturers, however, there is a very real danger that it will drive decisions on the drug candidates and/or indications manufacturers and investors are willing to pursue.

The sets of incentives encouraging the development of treatments for small-population diseases have generally worked well to expand treatment options and improve survival for patients with CLL/SLL and other blood cancers. The IRA's narrow exclusion for orphan drugs, however, creates a landscape in which multiple designations for a promising therapy will negate eligibility for the exclusion, thereby substantially complicating analyses on the potential for favorable return on investment. Manufacturers may face pressures to focus on an orphan indication with the largest patient population rather than the disease state that is most suitable for clinical trials. This could impact the time it takes to move a product from bench to market, increase costs associated with securing a first approval, and deter studies in Waldrenstrom's Macroglobulinemia and other blood cancers with extremely small patient populations.

We are similarly concerned that manufacturers will face considerable tension between their legal and fiduciary obligations to shareholders and their perceived moral obligation to cancer patients. Any decision to invest in research toward an expanded label that could ultimately disqualify the drug from the orphan drug exclusion would appear to be unsupportable if the follow-on indication population is small. Manufacturers may also face difficulties securing approval from their directors, shareholders, and investors to continue confirmatory studies for accelerated approval indications with small addressable populations if withdrawing those indications would make a drug eligible for the orphan drug exclusion. We do not believe Congress or the Administration sought to limit research and development in orphan diseases generally or in rare cancers. Manufacturers secured orphan designations well before the IRA was enacted and could not have considered that a relatively narrow designation would later drive consequences to research and development in other indications.

We believe researchers, investors, and manufacturers should be rewarded, not penalized, for investing in research and development to secure FDA approval for new indications (rather than relying on off-label use). It would be a tremendous tragedy if Congress' efforts to improve healthcare affordability created an environment in which future treatments like Pirtobrutinib would never be indicated for CLL/SLL (or mantle cell lymphoma) despite their potential to transform patient care. These concerns are compounded by the fact that the same considerations exist for other treatments with orphan designations outside CLL/SLL. Zanubrutinib, for example,

was first approved in 2019 for mantle cell lymphoma. Its MCL approvals, as well as the label expansion in relapsed or refractory marginal zone lymphoma (MZL), were granted through the accelerated approval mechanism and remain contingent upon the completion of confirmatory studies. Zanubrutinib's orphan designation is for mantle cell lymphoma, and each additional indication is outside that narrow designation, including the label expansions for CLL/SLL and WM that were secured through FDA's traditional approval mechanism. CLL Society expects that the IRA will make approval histories like that of Zanubrutinib a thing of the past, despite the significant benefit conferred to blood cancer patients from manufacturer-sponsored studies in multiple indications.

CLL Society asks that CMS support and pursue Congressional action to remove the single orphan designation/indication requirement for orphan drug exclusion eligibility. The statutory language as it stands leaves manufacturers with a no-win proposition and jeopardizes patient access to promising therapies without any benefit to the Medicare program or society as a whole. We also urge CMS to implement a stop-gap measure through its demonstration authority that would maintain the status quo with regard to payment mechanisms (e.g., ASP-based), and apply to orphan drugs that do not have annual utilization in any one indication that exceeds 200,000 patients.

In addition, we urge CMS to enable manufacturers to submit evidence demonstrating eligibility for the orphan drug exclusion.

**Definition of Qualifying Single Source Drug**

CLL Society urges CMS to reconsider its decision to identify a qualifying single source drug, and its dosage forms and strengths, by referring to common active moiety (drugs) or common active ingredient (biologics). The approach that CMS has chosen is not mandated by the statutory language. In fact, the IRA appears to require that products be treated as the same qualifying single-source drug only when they share an NDA or BLA. The determination of negotiation eligibility for products approved through an NDA [or BLA] is based on whether seven [eleven] years have passed since the NDA approval without reference to moiety [ingredient], reference product, or similar indicia of an intent to apply the term as broadly as set forth in the Initial Guidance.

We are also concerned that CMS' implementation creates a substantial set of burdens that were not envisioned when the IRA was enacted. For example, CMS' illustrative scenarios included one for which two manufacturers could be identified as a qualifying single-source drug. One of these manufacturers (the NDA/BLA holder) would be the primary manufacturer responsible for participating in the negotiation process, submitting complete and accurate information, and ensuring access to the maximum fair price (MFP). The primary manufacturer would be responsible for securing information that might be in the possession of, or even confidential to, the secondary manufacturer. The secondary manufacturer has no IRA-related obligations, yet its activities or

omissions could place the primary manufacturer in legal jeopardy in the form of substantial fines and penalties.

Manufacturers could not have foreseen the new landscape CMS' definition of a qualifying single source drug has created, and there may be no recourse available to primary manufacturers unable to comply with CMS' IRA requirements without information and other cooperation from secondary manufacturers. Neither the burden to primary manufacturers nor the substantial leverage that a secondary manufacturer might have in negotiating its compliance have been subjected to the notice and comment usually required when a significant burden is imposed on stakeholders. In fact, CMS did not acknowledge or discuss what, if any recourse it envisions would be available to primary manufacturers in its Initial Guidance.

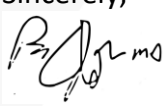
We urge CMS to reconsider its approach in advance of any legal challenges that might be asserted by manufacturers concerned that they have legal obligations with which they are logistically unable to comply. As noted above, we are concerned primarily with the uncertainty accompanying legal challenges to the implementation of laws designed to benefit patients. This is especially important if CMS' implementation of the new Part D out-of-pocket cost refinements is contingent upon moving forward with the IRA drug price negotiation program, and we ask that CMS inform the patient community that this is not the case.

**Conclusion**

Once again, we appreciate the opportunity to contribute the perspectives of those within the CLL/SLL patient and caregiver community as CMS implements the drug price negotiation provisions of the IRA. We strongly urge the Agency to expand the window for stakeholder feedback on this important and complex step toward drug selection and negotiation. The patient community has not had sufficient time to determine how the Initial Guidance changes incentives and disincentives, or whether it is more likely to benefit or harm patients. We look forward to a continuing dialogue throughout the IRA implementation process and welcome the opportunity to discuss our comments or the experience of CLL/SLL patients generally.

Thank you for your consideration of these comments. If you have any questions, please feel free to contact me or Saira Sultan, CLL Society's Healthcare Advocacy & Policy Consultant, via email at saira.sultan@connect4strategies.com.

Sincerely,



Brian Koffman, MDCM, MSEd
Co-Founder, Chief Medical Officer, & Executive Vice President
CLL Society