CLL SOCIETY

VIA ELECTRONIC DELIVERY

May 22, 2023

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

RE: Information Collection Request (ICR) for Negotiation Data Elements (CMS-10847)

Dear Administrator Brooks-LaSure:

CLL Society appreciates the opportunity to submit its comments on the Centers for Medicare & Medicaid Services' (CMS') Information Collection Request (ICR) for Negotiation Data Elements toward implementation of the Drug Price Negotiation Program (DPNP) created under the Inflation Reduction Act (IRA) of 2022.

CLL Society is dedicated to addressing the unmet needs of those within 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. CLL Society is the largest nonprofit focused exclusively on the unmet needs of those living with CLL and SLL.

As a patient advocacy organization, we strive to ensure 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 healthcare providers, patients, and their caregivers. We also recognize that the healthcare landscape extends beyond science, clinical care, and patient support. CLL Society is deeply concerned that while the IRA's DPNP may marginally ease financial burdens for Medicare beneficiaries with CLL/SLL, its implementation has the potential to exert a detrimental force on equitable access to existing treatments and disincentivize research and development for new and better therapeutic options.

As we noted in our comments to CMS' Initial Guidance implementing the DPNP, the decisions the Agency makes now will be incorporated into the decision processes for researchers, investors, and manufacturers as they determine whether to pursue a particular drug candidate for an indication. Similarly, any procedural hurdles to fully engage patients living with CLL/SLL, and the clinicians treating them, will reduce both the breadth and accuracy of the information upon which CMS will base its initial offer and evaluate any manufacturer counteroffer(s). Clinical trial data is an essential

component of evidence on treatment value, but it fails to capture real-world treatment outcomes as it evolves over time.

Our comments provide a brief background on CLL/SLL and focus on data elements within the context of our patient community. We will also outline our concern that the framework articulated in CMS' Initial Guidance, particularly the policy and statutory interpretation determinations on drug selection released as final guidance, increases the burden on stakeholders. These determinations also decrease the ICR's alignment with the statutory concept of determining a maximum fair price (MFP) for single-source "monopoly" drugs. CLL Society remains concerned that the MFP generated from the Initial Guidance and the ICR will be distorted by aggregation of data on alternative therapeutic options as well as unmet needs across multiple NDAs/BLAs with indications in disparate disease states and patient populations.

We continue to urge CMS to fully engage stakeholders so that its policy determinations and exercise of discretion will avoid disrupting incentives to scientific advances that have provided 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 18,000 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 a 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 just yet located within the bloodstream. When the cancer cells are only found in the lymph nodes it is called SLL. When the cancer is found in the bloodstream and possibly elsewhere, including the lymph nodes, it's called CLL.

CLL/SLL is extremely heterogeneous, meaning each person's disease type and the way the disease progresses can be extremely variable. Some individuals experience rapid deterioration due to having an aggressive form of the disease and survive for as little as two years, while others have a less aggressive form of the disease that may never need treatment and they 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 those in our community affected by this disease. Patients now have more treatment options compared to ten years ago when the standard of care was chemoimmunotherapy, which did not necessarily work on all forms of the disease. Now, they can take an oral continuous BTK inhibitor, with or without a monoclonal

antibody, until their disease progresses. Alternatively, patients can choose a shorter time-limited treatment approach that combines venetoclax (which is currently the only approved BCL-2 inhibitor) and a monoclonal antibody. The latter approach enables dose discontinuation until active monitoring reveals that the disease has again progressed to a degree that indicates a different 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. Many are forced to either adjust their dosing due to side effects, take a "drug holiday," or completely discontinue the drug due to intolerance. For patients with relapsed/refractory disease or drug 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 will experience serial relapses over their lifespans, and many will be treated with all available agents at some point during their disease course.

The experience with PI3K inhibitors in CLL/SLL illustrates the inherent difficulties surrounding studying treatments for this rare disease and the heightened risk that drug manufacturers take on when pursuing new therapeutic candidates. Delays in approval that are directly associated with the wait for overall survival data have already dampened research efforts for CLL/SLL and slowed patient access to potentially life-saving therapies. CLL Society has advocated for crossover in clinical trials because it saves lives, but the strategy inherently compromises the "purity" of overall survival data. Since CLL/SLL is not an ideal disease state from a research perspective, new treatments are often approved for other types of cancer and then later approved for CLL/SLL.

As more fully discussed below, CLL/SLL serves as a perfect example as to why there are several unmet needs for those whose disease progresses to the point of being in a life-threatening condition despite the availability of other FDA-approved treatment options. Similarly, existing CLL/SLL treatment options are not interchangeable alternatives for patients when they move through initial treatment, complete response, relapse, second-line treatment, complete response, relapse again, and then progression.

CMS' Initial Guidance increases the burden associated with the ICR and decreases the sufficiency and utility of the information to be collected.

CLL Society understands that CMS is charged with implementing the DPNP on a very tight timeline. Unfortunately, CMS' commitment to timely implementation deprived the Agency of the stakeholder feedback it needed to implement the DPNP, including the ICR, without undue burden on stakeholders and to derive MFPs based on the factors specified in the IRA for each selected drug. Procedural safeguards ensuring public input from impacted stakeholders, including notice and comment, are particularly critical when implementation mechanisms are driven by policy

decisions and legal interpretations that diverge from or are arguably inconsistent with, statutory language.

CLL Society reiterates its request that CMS reconsider its decision to identify a qualifying single-source drug based on common active moiety (drugs) or common active ingredient (biologics). An approach that treats products as the same qualifying single-source drug only when they share an NDA or BLA is within the plain language of the statute. It would reduce the burden on manufacturers complying with the ICR, and it would increase the utility of the collected information in identifying an MFP informed by unmet need, treatment value, and available alternative therapies. It would also eliminate the conflict between the IRA's timeline from NDA/BLA approval to negotiation eligibility and CMS' implementation of the DPNP. For our patients, however, the most important concern is that CMS' interpretation reduces the value of new indications to manufacturers and their shareholders. We understand from anecdotal reports that one or more drug manufacturers have shut down research and development efforts toward NDAs for new uses of existing drugs, due to concern that any new NDA would be subject to an MFP earlier than what was anticipated from the statutory language.

We are also concerned that CMS' implementation creates another substantial set of burdens that are not required under the statute. Although CMS' ICR states that the IRA requires and authorizes CMS to collect information from Primary Manufacturers, the law does not explicitly address situations in which more than one entity meets the definition of a manufacturer for DPNP purposes. Manufacturers often develop drug candidates and license one or more indications to a partner. Research and development costs may be split across multiple entities and a manufacturer with data on those costs may not have access to data on sales volume, revenue, and other data elements required within the ICR. CLL Society expects that more robust stakeholder engagement could have permitted CMS to avoid situations in which a primary manufacturer would be responsible for securing information in the possession of, or even confidential to, a secondary manufacturer. We expect that these scenarios create a substantial burden to manufacturers that is not captured in CMS' estimates.

Stakeholder input on alternative therapies and unmet needs is crucial to identify an appropriate MFP.

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 for 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 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 that are approved for CLL/SLL and expect a response. This is because once a drug within that same BTK inhibitor drug class has failed the patient, all drugs within that same class will also likely fail. All FDA-approved CLL/SLL treatments are, therefore, not a set of alternatives that can be deployed throughout a patient's disease course.

Questions 40 through 43 of the ICR are designed to enable manufacturers and the public to share information on a selected drug, therapeutic alternatives, and the extent to which it addresses an unmet need, and/or represents a treatment advance. We appreciate that CMS intends to develop a mechanism for patients and their providers to weigh in on treatments selected for negotiation. But we remain concerned that the processes for submission could deter patients, treating clinicians, and patient advocacy organizations from submitting feedback and information. CLL Society offers the recommendations below to improve the information CMS is able to obtain from public stakeholders and guide its analysis of unmet needs and therapeutic alternatives:

- CMS should solicit public input on selected treatments and any therapeutic alternatives through regulations.gov and accept comments and input through that portal or through an email address designated to accept public input within the negotiation process. Neither patients nor patient advocacy organizations are familiar with HPMS, and we are unaware of it having been used for similar purposes in the past.

- The 30-day comment period is far too short for patients, patient advocacy organizations, and clinicians to collect and provide meaningful input on selected drugs and their therapeutic alternatives. We ask that CMS provide clear notice of opportunities for stakeholder input and that it accept information from non-manufacturer stakeholders throughout the negotiation process.

- Limitations on the number of words or citations that can be submitted to CMS are unlikely to encourage stakeholder input or to increase the relevant information submitted to the Agency. We ask that CMS remove those limitations and accept public input through regulations.gov or email submission.

- CLL Society is concerned that Section J, **Certification of Submission for Respondents Who Are Not Primary Manufacturers Required for All Respondents Who Are Not Primary Manufacturers,** is identical to the certification required from manufacturers. Patients and their advocacy organizations will likely experience questions and concerns regarding any legal jeopardy associated with informing CMS about their experience with drugs selected for negotiation. The cautionary statement on potential civil or criminal liability will all but foreclose the valuable input from clinicians and researchers that could improve CMS' ability to determine an appropriate MFP.

- Non-manufacturer stakeholders must certify that the information is complete and accurate, but CMS does not provide any guidance on the difference between complete and incomplete submissions.
- Stakeholders would commit to "timely notify CMS if I become aware that any of the information submitted in this form has changed." This may apply to a researcher involved in studies for a selected drug or therapeutic alternative but does not appear applicable to the general public, patients, patient advocacy organizations, or clinicians.
- Any individual or entity electing to submit information must acknowledge that they "also understand that any misrepresentations may also give rise to liability, including under the False Claims Act." We strongly urge CMS to eliminate the certification requirement for non-manufacturer stakeholders.

- The MFP is a single price for each selected and negotiated drug under the Medicare program. The IRA negotiation process outlines considerations such as alternative therapies, unmet needs, and the extent to which a treatment represents an advance in therapeutic options.

    - The instructions preceding questions 40-43 note that declarative statements must be supported by evidence with a citation unless the information concerns personal experience prescribing or taking the drug. CLL Society, like other patient advocacy organizations, is well-positioned to communicate the needs and concerns expressed by our patient communities. We urge CMS to permit and consider patient information submitted by patient advocacy organizations.

    - Information on alternative therapies is indication-specific. CMS' decision to utilize costs of alternative therapies in calculating an initial offer does not appear reasonable unless the selected drug is defined by an NDA/BLA rather than moiety or active ingredient.

        - Due to the approval of new treatment options over the past several years, patients with CLL/SLL are now living longer. However, CLL/SLL patients often experience multiple remissions and relapses throughout their lifespan, so living longer with the disease means there is a good chance they may run out of treatment options the longer they live. All FDA-approved treatment options are not interchangeable as alternative therapies for patients as their disease progresses. Patients may be unable to tolerate an entire drug class or have multiple relapses after being treated with all available therapies.

Options are based on previous treatments, patient-specific factors potentially driving tolerance and/or effectiveness, and the aggressiveness of their disease.

- The definition of unmet medical need CMS intends to adopt for DPNP purposes is narrow. CLL Society urges CMS to acknowledge that there is an unmet need when patients are adversely impacted by a condition ***despite*** the availability or use of treatments.
    - For CLL/SLL patients, the unfortunate reality is that it remains incurable despite significant progress in treatments. Patients who progress after both a BTK and BCL2 inhibitor fail 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.

Conclusion

CLL Society appreciates the opportunity to contribute the perspective of those living with CLL/SLL as CMS implements the DPNP. 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 contact Saira Sultan, CLL Society's Healthcare Advocacy & Policy Consultant at ssultan@cllsociety.org.

Sincerely,

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