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Wolters Kluwer Clinical Drug Information's Request for CMS evaluation of Lexi-Drugs as a compendium for use in the determination of medically-accepted indications of drugs/biologicals used off-label in anti-cancer chemotherapeutic regimens

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Contact:

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Compendium being requested for inclusion:

Lexi-Drugs database delivered on the Lexicomp platforms.

Copy of the Compendium:

Lexi-Drugs is available online: log into online.lexi.com/login

Login: lexicompendial
Password: lexicomp

Action requested of CMS:

Wolters Kluwer Clinical Drug Information requests that CMS exercise its authority pursuant to Medicare Benefits Policy Manual, Chapter 15 Covered Medical and Other Health Services (Rev. 194), 50.4.5.1 (Rev.120) and the process set forth in 42 CFR 414.930 (a) to include Lexi-Drugs in the list of compendia appropriate for identifying medically-accepted indications for off-label uses of drugs/biologicals in anti-cancer chemotherapeutic regimens

Wolters Kluwer Clinical Drug Information is the provider of a complete medication decision support solution including both drug reference information you can look up at the point of care AND drug data that integrates seamlessly into healthcare systems to power medication-related screening and alerts. We are one content provider, operating under a singular vision to develop consistent and clinically relevant information across our Lexicomp®, Medi-Span®, and Facts & Comparisons® applications. When there's shared content and alignment among various drug information resources, that helps improve workflow and communication, reduce confusion, and enhance patient care across an entire healthcare institution or business.

Detailed, Specific Documentation:

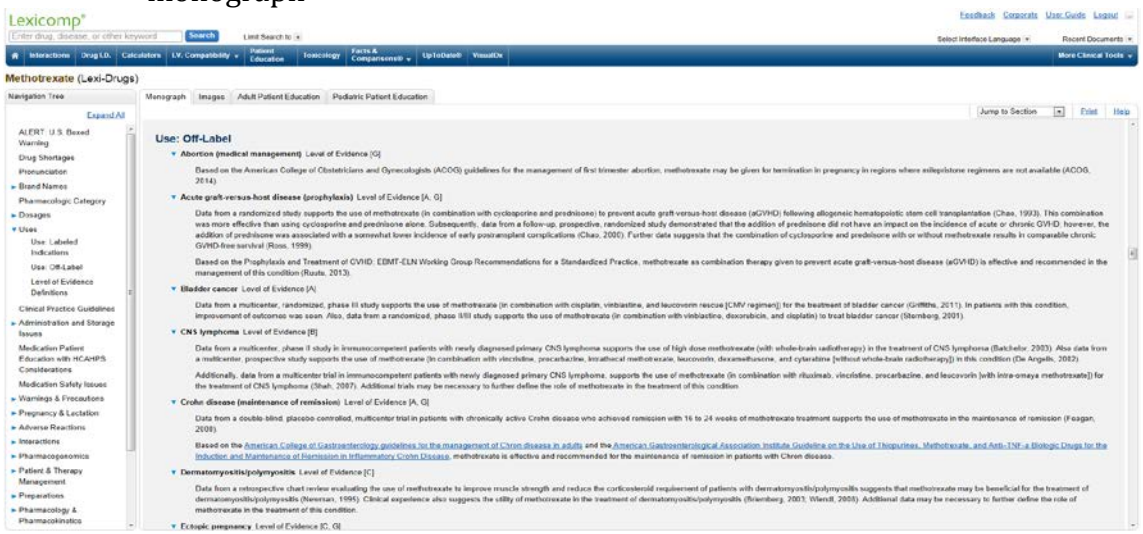
1. Extensive breadth of listings:

   Lexi-Drugs comprises more than 2052 drug monographs and is searchable by generic drug names, brand names, NDC, keyword, and synonyms.

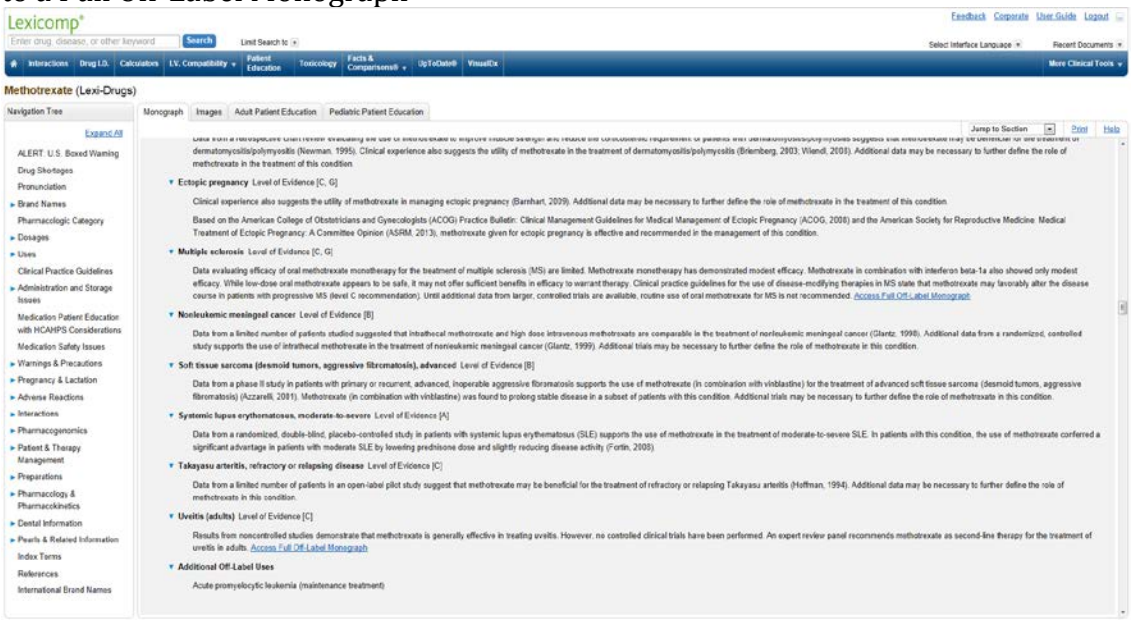
   Drug monographs may include the following content (in addition to other content):

   - Brand names: U.S.
   - Pharmacologic category
   - Uses
     - Use: Labeled Indications
     - Use: Off-Label
       - Includes off-label use, level of evidence, description of use including therapy statements, inline reference (s), links to guideline(s), or a link to a full Off-Label monograph
         - Full Off-Label monograph includes background, evidence rating, patient population, results, safety, doses studied, guidelines, case reports, therapy considerations, and references.
     - Level of Evidence Definitions
   - Use: Unsupported
   - Dosages
   - Clinical Practice Guidelines
   - Administration and Storage Issues
   - Warnings & Precautions
   - Pharmacology & Pharmacokinetics
   - Pregnancy & Lactation
   - Interactions
   - Adverse Reactions
   - Pharmacogenomics
   - Patient & Therapy Management
   - Preparations
   - Related information
   - References

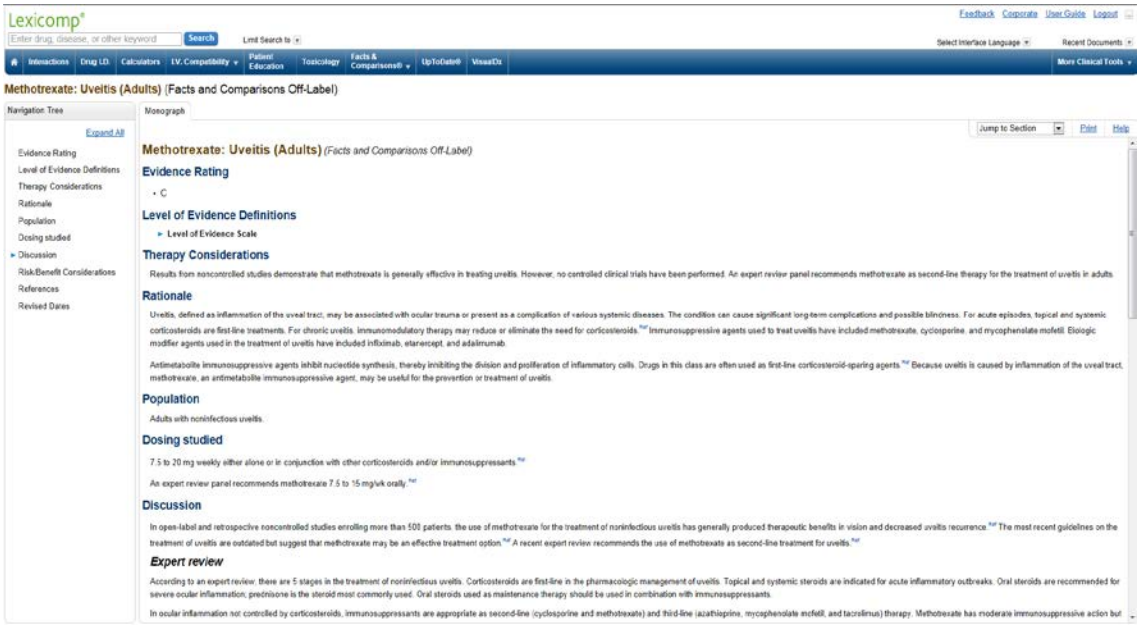
Example of an off-label section within the methotrexate monograph



Example of an off-label use within the methotrexate monograph that links to a Full Off-Label Monograph



Example of a full Off-Label monograph for Methotrexate: Uveitis (Adults)



2. Quick processing from application for inclusion to listing:

   Lexi-Drugs may be updated daily (eg, new drugs, special alerts, major warnings, new labeled indications and dosing information) in a real-time publishing system. Hundreds of changes are incorporated throughout drug monographs per month. The length of time that it takes for changes to be incorporated depends on several factors, including the importance of the change, the amount of documentation needed to be collected and reviewed and the amount of data that is ultimately being incorporated. The goal for publication of more critical edits averages between 1 day and 3 weeks; the goal for more complex edits and guideline incorporation is an average of 1 to 4 months for incorporation into the database. Timeframes are not an implied guarantee of inclusion in content databases.

   An internal surveillance team identifies prescribing information changes as well as changes from primary literature and clinical practice guidelines on a daily basis. Other updates are identified through peer reviewed journal surveillance, routine internal monograph review and updating, an external panel of senior editors and consultants who practice within healthcare systems in the US, and unsolicited client questions. Wolters Kluwer Clinical Drug Information provides drug information to more than 1200 hospitals and health care systems as well as to clients such as UpToDate who link to Lexi-Drugs through their applications. Potential oncology off-label uses could be identified through any of these pathways.

   Wolters Kluwer Clinical Drug Information's surveillance model, coupled with critical appraisal of relevant literature and rigorous grading of such,

demonstrates a commitment toward reflecting the most relevant and highest quality evidence available to-date.

3. **Detailed description of the evidence reviewed for every individual listing**

The following are included for uses listed in the "Use: Off-Label" field in Lexi-Drugs:

- Level of evidence rating (eg, A, B, C and/or G)
- Therapy considerations: Globally summarizes efficacy, outlines areas needing additional study, and raises issues that should be considered prior to prescribing.
- Abbreviated citations that supports the level of evidence (eg, last name author, year). The complete reference for the citation will be incorporated into the reference list within the specific drug monograph.
- Links to Clinical Guidelines and/or full Off-label monographs, if applicable

Lexi-Drugs is not exhaustive of all off-label uses, does not include extensive statistical analysis, and is not intended for use in establishing global drug policies. It is intended to aid the health care professional in quickly identifying published literature regarding a specific drug use. Use of off-label content should help enable a clinician to determine if a specific off-label use is rational. The primary literature for the specific off-label use should be reviewed prior to patient-care decisions.

4. Use of pre-specified published criteria for weighing evidence:
Level of Evidence Scale for Oncology Off-Label Use

A	Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form (eg, results of the introduction of penicillin treatment) to support off-label use. Further research is unlikely to change confidence in the estimate of benefit.
B	Evidence from randomized, controlled trials with important limitations (eg, inconsistent results, methodologic flaws, indirect, imprecise); very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the

	estimate.
C	Evidence from observational studies (eg, retrospective case series/reports providing significant impact on patient care); unsystematic clinical experience; or potentially flawed randomized, controlled trials (eg, when limited options exist for condition). Any estimate of effect is uncertain.
G	Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.

5. Use of prescribed published process for making recommendations:
   Lexi-Drugs database development and maturation is based upon policy and procedure rules laid out within those respective documents. Wolters Kluwer Clinical Drug Information's content is peer-reviewed, evidence-based, and expert-driven. Complex topics are synthesized to promote clear, concise information most suitable for point-of-care use. The clinical content team is comprised of pharmacists with significant clinical and academic experience.

   Clinical editors conduct a review of the foundational information supporting recommendations and highlight differences from current clinical practice that are then investigated through an internal peer review process and an external peer review by practicing clinicians. Information that represents a departure from commonly accepted clinical practice or represents recommendations based on very limited patient exposure warrant further investigation via primary literature and other sources. In cases where there is a consensus that the approach represents a common clinical practice, appropriate supporting literature is cited, along with language that identifies the limited experience.

   To develop this content, specialists within the clinical staff conduct a review of the primary and secondary literature, applicable clinical guidelines and occasionally tertiary reference texts to inform the final synthesis of information in the supporting monographs. Critical evaluation of the literature is paramount, and focuses on determining the validity and reliability of the various clinical and basic science research reports.

   Editorial convention requires a balanced presentation of the clinical data, such that both positive and negative studies are discussed, referenced, and used as the basis for assigning these evidentiary ratings. Study design (ie, blinded, randomized, controlled, multi-centered trials) and methodology (ie, clinically relevant dosing strategies in well described populations, using both intent to treat and per-protocol analyses, as well as valid statistical analyses)

are heavily weighted as the basis for assigning ratings and subsequent clinical recommendations.

Studies of lower quality (eg, case studies, observational studies, retrospective reviews, etc.) are also considered, but content derived from these sources are appropriately assigned a lower strength of evidence and higher level of uncertainty.

Identification of potential Off-label Oncology Use:

- Monitoring of NLM's 119 premier/core journals
- Unbiased evidence-based clinical practice guidelines
- Client request
- External/Internal request generated from drug monograph review
- Survey of drug information centers, list servs, or managed healthcare databases
- Hospital policies for trending prescribing patterns

Literature search/resources: Primary Medical literature, Clinical Practice Guidelines

A process is used in determining the criteria for inclusion of literature: A PubMed search of the last 10 years is used to identify data relevant to the topic. If sufficient material is not available, a search of the previous 5 years is performed as needed. References greater than 15 years old may be used if more recent data is not available to support an off-label use. From the literature search, editors select the relevant data based upon strength of the studies.

Evaluation Process:

Once a potential off-label oncology use for a medication is identified, an internal oncology pharmacist will review the supporting literature, assess and evaluate the evidence, and assign an evidence rating and strength of recommendation for inclusion into Lexi-Drugs based upon the scales below. The off-label use content is reviewed by 4 additional panel members composed of internal and external experts. Each panel member independently reviews and votes on the level of evidence rating and strength of recommendation for inclusion into Lexi-Drugs and identifies any conflicts of interest. Five panel members without a conflict of interest need to participate in the vote. To be listed in Lexi-Drugs, agreement is required from at least 3 of the 5 panel members regarding its inclusion and level of evidence rating.

Process when there is no clear majority among the oncology off-label use review panel: If the panel does not attain a majority vote in favor of an off-label addition, it will not be added to the database. If any member of the review panel has additional details for discussion, a conference call will be arranged to review the off-label use and determine/resolve the disposition of it.

Level of Evidence Scale for Oncology Off-Label Use

Levels of evidence do not pertain to the drug's place in therapy as compared with other agents.

A	Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form (eg, results of the introduction of penicillin treatment) to support off-label use. Further research is unlikely to change confidence in the estimate of benefit.
B	Evidence from randomized, controlled trials with important limitations (eg, inconsistent results, methodologic flaws, indirect, imprecise); or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.
C	Evidence from observational studies (eg, retrospective case series/reports providing significant impact on patient care); unsystematic clinical experience; or potentially flawed randomized, controlled trials (eg, when limited options exist for condition). Any estimate of effect is uncertain.
G	Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.

Strength of Recommendation for Inclusion in Lexi-Drugs for Oncology Off-Label Use

Strong (for proposed off-label use)	The evidence persuasively supports the off-label use (ie, Level of Evidence A).
Equivocal (for proposed off-label use)	The evidence to support the off-label use is of uncertain clinical significance (ie, Level of Evidence B, C). Additional studies may be necessary to further define the role of this medication for the off-label use.

Against proposed off-label use	The evidence either advocates against the off-label use or suggests a lack of support for the off-label use (independent of Level of Evidence). Additional studies are necessary to define the role of this medication for the off-label use.

Removal of oncology off-label uses from the database if no longer applicable: Off-label uses that are already incorporated within the database will be moved into the "Use: Labeled Indications" section if the use gains approval from the FDA. Identification of an off-label use that is no longer supported may occur through literature surveillance and review. This would initiate a similar process where an internal oncology pharmacist reviews and assesses the supporting literature. The off-label use content is reviewed by 4 additional panel members composed of internal and external experts. Each panel member independently reviews and votes on the removal of the off-label use. Five panel members without a conflict of interest need to participate in the vote. To be removed from Lexi-Drugs, a consensus of agreement for removal is required from at least 3 of the 5 panel members. The off-label use will be removed from the off-label use field and may be placed in the "Use: Unsupported" field.

Process when there is no clear majority among the oncology off-label use review panel: If the panel does not attain a majority vote in favor of removal of off label use, it will not be removed from the database. If any member of the review panel has additional details for discussion, a conference call will be arranged to review the off-label use and determine/resolve the disposition of it.

6. Publicly transparent process for evaluating therapies.
   The process for evaluating therapies can be seen in the attached word documents and screen shots. The site that will house this information for public review is www.lexi.com under clinical notes (http://www.lexi.com/home/clinical/). Although the content for the off-label uses in anticancer chemotherapeutic regimens cannot be seen currently on the website, the word documents and screen shots illustrate how it will be deployed on the site. The new off-label use table will be updated on a

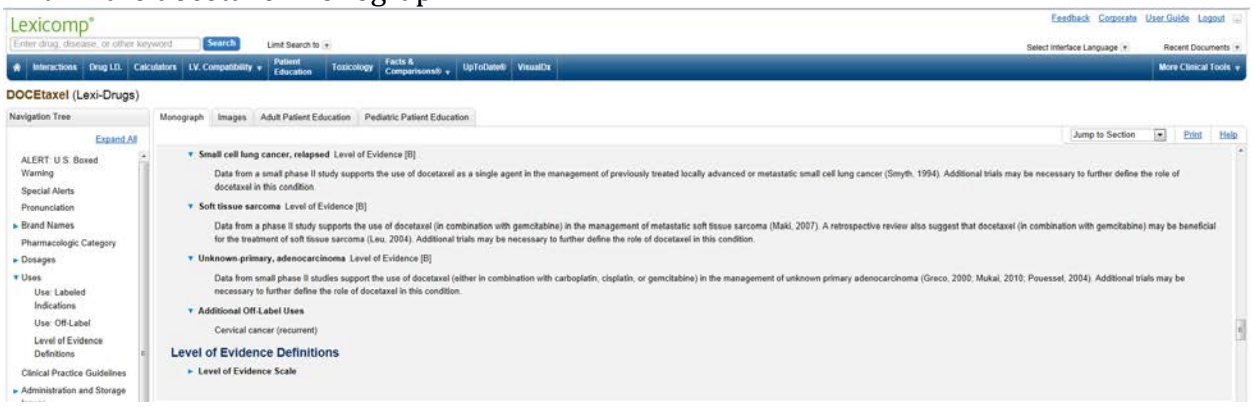
monthly basis with details of the drug and its proposed off-label use, date of review, participating panel members, voting record, and any conflict of interest for the voting panel members.

7. Explicit "Not Recommended" listing when validated evidence is appropriate. An off-label use that is no longer valid based upon previously described review would be removed from the "Use: Off-label" field within Lexi-Drugs. The use may be placed in the "Use: Unsupported" field if, based on clinical judgment, it is determined this information is helpful to Lexi-Drugs users. The "Use: Unsupported" field includes uses (off-label or FDA-approved) that are no longer recommended based on data that indicates use is considered unsafe or of questionable efficacy. The off-label use would also be listed on the publically transparent table titled, Off-label uses removed from the database.

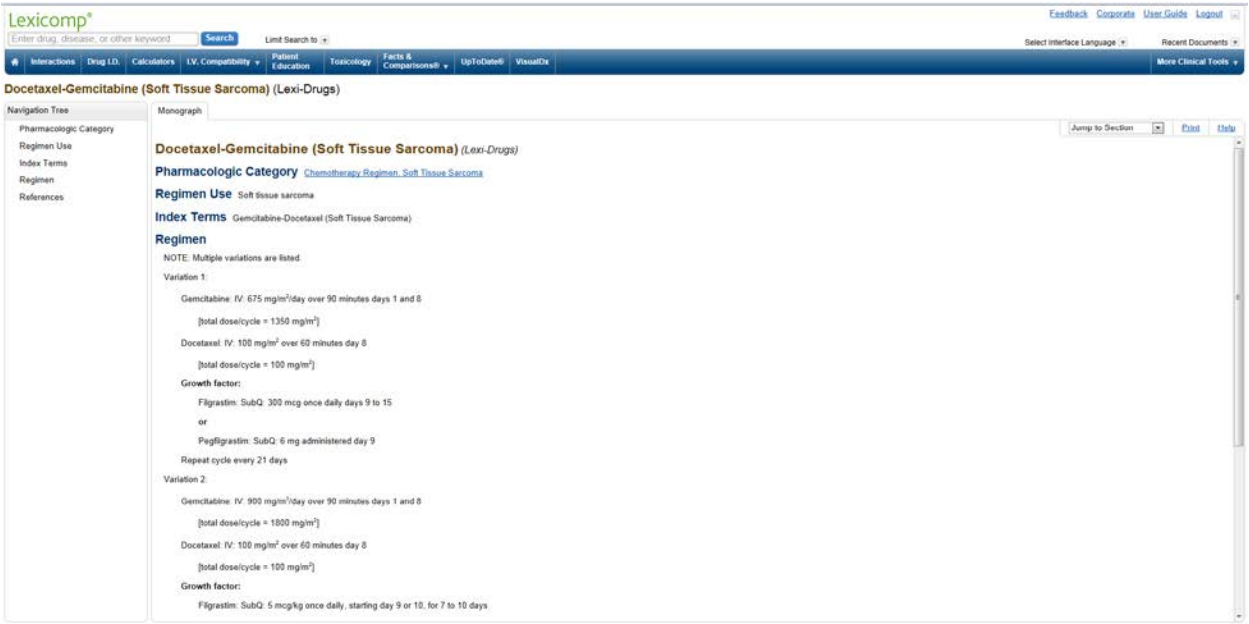
8. Explicit listing and recommendations regarding therapies, including sequential use or combination in relation to other therapies.
   Lexi-Drugs includes other drugs used in combination for an anticancer chemotherapeutic regimen. Within a specific drug monograph, the other drugs in the regimen are listed, but explicit dosing details are identified in the specific drug monograph or in the chemotherapy regimen monograph where the whole regimen is outlined.

   An example to illustrate how combination chemotherapies are for off-label content: Docetaxel-Gemcitabine for soft tissue sarcoma:

   Within the docetaxel monograph:



   Within the chemotherapy regimen monograph:



9. Explicit "equivocal' listing when validated evidence is equivocal.
   When the evidence for an off-label use is equivocal, it will be given a level of evidence rating of B or C.

B	Evidence from randomized, controlled trials with important limitations (eg, inconsistent results, methodologic flaws, indirect, imprecise); or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.
C	Evidence from observational studies (eg, retrospective case series/reports providing significant impact on patient care); unsystematic clinical experience; or potentially flawed randomized, controlled trials (eg, when limited options exist for condition). Any estimate of effect is uncertain.

10. Process for public identification and notification of potential conflicts of interest of the compendium's parent and sibling organization, reviewers, and committee members, with an established procedure to manage recognized conflicts.

    The site that will contain this information for public review is www.lexi.com under clinical notes (http://www.lexi.com/home/clinical/). Attached to the

request are screen shots to visualize the site. In the table titled New off-label uses, each voting member's conflict of interest disclosures will be reported.

The process used to identify and manage conflict of interest disclosures: From the Wolters Kluwer Clinical Drug Information Conflicts of Interest Standard Operating Procedure: "All Wolters Kluwer Clinical Drug Information Personnel involved with Wolters Kluwer Clinical Drug Information's content development process are required to make a formal, written disclosure of real, potential or perceived conflicts of interest related to themselves or their spouses, partners or minor children and Wolters Kluwer Clinical Drug Information content development. Such written disclosure will be collected on the Wolters Kluwer Clinical Drug Information Conflicts of Interest Disclosure Statement. Dissemination and collection of the Wolters Kluwer Clinical Drug Information Conflicts of Interest Disclosure Statement will be coordinated by the Compliance and Documentation Department: prior to providing service to Wolters Kluwer Clinic Drug Information; annually following engagement of services with Wolters Kluwer Clinical Drug Information; and upon any change in circumstances during the engagement of services that presents a real, potential or perceived conflict of interest. The Compliance and Documentation Department is responsible for reviewing and assessing all Wolters Kluwer Clinic Drug Information Conflicts of Interest Disclosure Statement forms. Wolters Kluwer Clinical Drug Information Personnel without identified conflicts of interest will be allowed to provide services to Wolters Kluwer Clinical Drug Information without restriction. Wolters Kluwer Clinical Drug Information Conflicts of Interest Disclosure Statements identifying a real, potential or perceived conflict of interest will be further assessed by the Compliance and Documentation Department to determine, based on the facts and circumstances of each disclosed conflict, what action, if any, is required."

In summary, the Wolters Kluwer Clinical Drug Information surveillance model, coupled with critical appraisal of relevant literature and rigorous grading of such, demonstrates a commitment toward reflecting the most relevant and highest quality evidence available to date. The aim of Lexi-Drugs is to provide healthcare providers (physicians, nurses, pharmacists, and other healthcare providers) with clear and concise drug information in order to help improve patient safety, and elevate the quality of patient care.

Lexi-Drugs, if recognized as a Compendium for Medically-Accepted Indication of Drugs/Biologicals used Off-label in Anticancer Chemotherapeutic Regimens, will continue to focus on identification and assessment of potential off-label uses in oncology through the processes outlined for the Centers for Medicare & Medicaid Services (CMS).

Wolters Kluwer Clinical Drug Information appreciates the opportunity to outline its process and plan required for consideration of Lexi-Drugs as a Compendium for

Medically-accepted indications of drugs/biologicals used off-label in anti-cancer chemotherapeutic regimens.

If you have any questions, please contact Liz Tomsik as listed in the contact listing.

Respectfully submitted,

Elizabeth Tomsik, Senior Director of Content

Wolters Kluwer Clinical Drug Information