Technology Assessment

Technology Assessment Program

COMPENDIA FOR COVERAGE OF OFF-LABEL USES OF DRUGS AND BIOLOGICS IN AN ANTICANCER CHEMOTHERAPEUTIC REGIMEN

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Compendia for coverage of off-label uses of drugs and biologics in an anticancer chemotherapeutic regimen

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Introduction

The topic of this assessment is the evaluation of drug compendia for the purpose of informing the Centers for Medicare & Medicaid Services (CMS) on decisions about coverage of off-label uses of drugs and biologics in anticancer treatment. This coverage is dictated by Section 1861(t)(2)(B) of the Social Security Act, which describes the reliance upon recommendations in compendia, specifically the AMA Drug Evaluations (AMA-DE; no longer in existence), American Hospital Formulary Service Drug Information (AHFS-DI[1]), and United States Pharmacopeia Drug Information (USP-DI[2]).

Rapidly advancing medical technologies, drugs, and biological agents can improve survival and quality of life (QoL) of patients. Physicians and researchers often discover uses of drugs other than those for which they have been approved by the U.S. Food and Drug Administration (FDA). The term "off-label" can mean many things: "[U]sing an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease; treating unrelated, unindicated diseases; and treating the indicated disease but varying from the indicated dosage, regimen, or patient population may all be considered off-label use."[3] The medical treatment in oncology practice is complex, with uncertain patient outcomes. According to a study by the U.S. General Accounting Office (GAO) in 1991, the off-label use of anticancer drugs was as high as 33 percent of all anticancer drug prescriptions. Today 50 to 75 percent of all uses of anticancer therapy are off-label according to the National Comprehensive Cancer Network (NCCN) estimates.[4] Cancers are life-threatening illnesses, and advances in anticancer drug research can outpace approval rates by the FDA; this can result in an increased use of off-label drugs in oncology practice. The increased off-label use of drugs in cancer therapy may be due to several other reasons as well: the lack of, or failure of, standard treatments; lack of FDA approved treatments for rare cancers; and lack of an established proven therapy in the face of terminal illness.

Listings of off-label indications in drug compendia affect not only reimbursement decisions, but also utilization. Several studies have suggested that oncologists alter their preferred treatment due to reimbursement restrictions and costs of certain drugs.[5,6] Laetz[6] published the national survey conducted by GAO among oncologists on the prevalence of off-label use, the extent of reimbursement denials, and the effect of reimbursement denials on the treatment of cancer patients. As many as 40 percent of oncologists reported altering their preferred therapies due to cost or other reimbursement barriers. More recently, Dornbusch[5] conducted a survey among 310 oncologists after publication of Phase III clinical trial data evaluating the use of bevacizumab in non-small cell lung carcinoma (NSCLC). More than 50 percent of the respondents said they planned to use off-label bevacizumab in NSCLC as soon as reimbursement is secure.

In order to inform potential future coverage determinations, CMS has commissioned a technology assessment from the Agency for Healthcare Research and Quality (AHRQ) to summarize the process by which anticancer drugs are added to various compendia, as well as the evidence collection methodology for listed drugs and their indicated uses. The Duke Evidence-based Practice Center (Duke EPC) and the Tufts-New England Medical Center EPC (Tufts-NEMC EPC) were asked by AHRQ to prepare this report and present at a Medicare Coverage Advisory Committee (MCAC) meeting on March 30, 2006.

Scope and Key Questions

The key questions addressed in this report are:

1. *How do the methods used to develop compendia listings compare to methods used to develop published guidelines, systematic reviews, and narrative reviews? How do they compare to the publication criteria of journals?*

2. *Describe the compendia on the following:*
    a. *Breadth of listings*
    b. *Speed of throughput from application to listing*
    c. *Use of pre-specified, published criteria for weighing evidence*
    d. *Use of pre-specified, published process for making recommendations*
    e. *Level of public transparency in the process of evaluating therapies*
    f. *Public notification of reviewers' and committee members' conflict(s) of interest, including institutional funding sources*
    g. *Public notification of all funding sources of the compendium and its parent and sibling organization(s), including unrestricted grants and gifts*

3. *For chosen drugs/biologics and their off-label indications, evaluate the compendia on the following:*
    a. *Level of detail of the evidence reviewed*
    b. *Any recommendations that are made (i.e., explicit "Not Recommended" listings or explicit "Equivocal" listings when evidence is equivocal)*
    c. *Silence, i.e. no listing, when evidence is equivocal*
    d. *Presence of bias (i.e., "Recommended" when evidence is equivocal or "Not Recommended" when evidence is equivocal)*

4. *Is there an analysis of potential harms and potential benefits in the assessment of biologics and chemotherapeutic agents included in the compendia? If yes, what components are used, and how are they quantified?*

5. *Which compendia have listings on the off-label uses of drugs/biologics chosen for this report? If these drugs/biologics and specified off-label indications are included in compendia:*
    a. *How do each compendium's listings compare with its own stated methods?*
    b. *How do each compendium's listings compare to those of other compendia for the same drugs/biologics and off-label indications?*
    c. *How do they compare to the EPC's own review of the evidence?*

6. *Do the two current compendia in use by Medicare for the determination of off-label uses of anticancer drugs and biologics in anticancer treatment, the AHFS and the USP-DI, adhere to their stated criteria and processes in making recommendations?*

The overall goal of this report is to evaluate a selected set of documents that may be considered to be drug compendia using certain pre-specified criteria to determine to what extent

these compendia use evidence-based approaches in their collection, review, and reporting of the literature. This report does not address or make any assessments of the overall quality or usefulness of these compendia for the purposes of clinician education, assistance with patient management, or prescriber decisionmaking.

The following compendia are evaluated:

- American Hospital Formulary Service- Drug Information (AHFS-DI)[1]
- United States Pharmacopeia- Drug Information (USP-DI; available through Thomson MICROMEDEX)[2]
- DRUGDEX Information System (also available through Thomson MICROMEDEX)[2,7]
- Facts & Comparisons[8]
- National Comprehensive Cancer Network Drugs and Biologics Compendium (NCCN)[9]
- Clinical Pharmacology[10]

This list does not include all documents that may be considered either to be or to be similar to drug compendia. CMS, AHRQ, and the two EPCs agreed on this list as the most relevant for the purposes of this review. For some of these compendia, several different versions or related documents may exist. When necessary, we chose the version that was both most accessible and had the most detailed information.

Given the large number of anticancer agents and cancers, it was not be possible to evaluate all possible agent-cancer combinations for off-label indications. With input from CMS and AHRQ, the EPCs identified several combinations for evaluation. These combinations were selected to reflect newer and older agents, common and rare cancers, and both biologics and drugs.

Fourteen agent-cancer combinations were evaluated:

- Bevacizumab (Avastin®) for breast and lung cancer (approved by the FDA in February 2004 for colorectal cancer);
- Oxaliplatin (Eloxatin®) for breast and lung cancer (approved by the FDA in 2004 for colorectal cancer);
- Irinotecan (Camptosar®) for breast cancer (approved by the FDA in 1998 for colorectal cancer);
- Docetaxel (Taxotere®) for esophageal, gastric, and ovarian cancers (approved by the FDA in 1999 for locally advanced or metastatic non-small cell lung cancer [NSCLC]);
- Gemcitabine (Gemzar®) for biliary tract, bladder, and ovarian cancers (approved by the FDA in 1996 for pancreatic cancer);
- Rituximab (Rituxan®) for chronic lymphocytic leukemia (CLL; approved by the FDA in 1997 for non-Hodgkin's lymphoma); and
- Erlotinib (Tarceva®) for head and neck, and pancreatic cancers (approved by the FDA in 2004 for NSCLC).

Among all new cancer cases in women, breast cancer is estimated to comprise 32 percent and ovarian cancer 2.9 percent. Among all new cancers in both men and women, the rate of lung cancer is 12 percent; esophageal is 1 percent; gastric is 2 percent; bladder cancer is 4 percent; head and neck cancer is 3 percent; pancreatic cancer is 2 percent; chronic lymphocytic leukemia is 0.7 percent; and biliary tract cancer is 0.6 percent.[11]

The Duke EPC and the Tufts-NEMC EPC jointly produced this report. The Duke EPC

addressed key questions 1 and 2 concerning the methods of the compendia. Both EPCs addressed the remaining questions, which dealt with the reporting of information by the compendia and the assessment of the availability of literature evidence for the agent-cancer combinations selected for evaluation in this report. For the literature review, common methods were used to identify potentially relevant studies, abstract data, and report results wherever feasible to enhance the consistency of this report. The Introduction, Methods, and Discussion sections of the report were written jointly by the two EPCs, while the various Results sections represent non-overlapping independent work of each EPC that shared the same methodological approach.

Methods

The project was divided into four distinct components: (1) a description of the methods used by the compendia; (2) a comprehensive search by the EPCs for studies on the 14 selected off-label indications; (3) a description of the compendia listings and evidence cited for the same 14 off-label indications; and (4) an analysis of the compendia's listings in relation to their stated methodologies.

Description of the Methods Used by the Compendia

In theory, compendia are like reports of systematic reviews in that they identify, appraise, and synthesize a body of evidence. It is useful to evaluate to what extent compendia describe their methods for search, selection, and summarization of evidence, and to what extent they follow their stated methods. Compendia are also like guidelines in that they endorse certain drugs for particular clinical indications; this is particularly evident in the case of off-label indications. It is useful to evaluate to what extent compendia describe their methods for developing recommendations, and to what extent they meet standards for clinical practice guidelines. The QUOROM consensus statement[12] and the AGREE instrument[13] – which were originally developed for assessing the reporting quality of reports of meta-analyses and clinical practice guidelines, respectively – provide reasonable frameworks for these evaluations of drug compendia.

We reviewed evaluation criteria in the QUOROM statement and the AGREE instrument and eliminated duplicate and non-applicable items. The remaining items were used to guide our evaluation of published compendia methods, as well as interviews with compendia editors.

We did not use explicit scoring rules as described in the AGREE instrument, nor did we report explicit "yes" or "no" decisions on QUOROM items. Rather, these documents were used as conceptual models to organize our inquiry into the methods used by drug compendia.

We planned a five-step process to gather information from the compendia as follows:

Step 1: Abstract descriptive information about each compendium based on printed or other publicly available information into a table using the conceptual framework described above.

Step 2: Send the table completed in Step 1 to the publisher of each compendium and schedule an interview with appropriate personnel. In each case, we scheduled 1-hour telephone interviews with the most senior editor and any additional staff they recommended.

Step 3: Interview compendium staff to supplement published information about methods used for evidence synthesis and decisionmaking. We conducted interviews with at least two members of our research team present. We prepared minutes from the calls based on written notes taken by each of the participants. Interviews were not audio recorded.

Step 4: Revise table to include additional information gained on interview and send

revised table to compendium staff to get confirmation or alternative views.

Step 5: Combine the descriptive information on all six compendia compiled in Steps 1-4 into a series of tables to allow comparison across compendia on various topics.

During the conduct of the study, we decided to eliminate the first review by compendia editors and thus did not send a draft of the table before our telephone interviews. After the interviews, when we sent the editor a draft table summarizing the compendium's methods, we blinded them to data from the other compendia, so that each editor saw only data about his or her own publication.

Ultimately, we organized the information from our inquiry for brevity and clarity, with special attention to the domains in which the compendia differ.

EPC Review of Published Studies on the 14 Off-Label Indications

Literature Search

We searched MEDLINE and MEDLINE In-Process & Other Non-indexed Citations (formerly called PreMEDLINE) to identify human studies published in English that investigated the targeted agent-cancer combinations and reported outcomes of interest. We also searched the American Society of Clinical Oncology (ASCO) annual meeting abstracts for the years 2004 and 2005 for recently reported but as yet unpublished studies. The MEDLINE search strategies used are provided in Appendix A.

Study Selection

We included all study designs including clinical trials (Phase I, Phase I/II, Phase III, or Phase IV), case reports, and retrospective case series that reported any of the following outcomes: tumor response, survival, quality of life, symptomatic improvement, or adverse effects. We excluded review articles, studies that described only predictors of response, pharmacokinetic studies, and animal or in vitro studies.

Data Abstraction

We retrieved and reviewed published abstracts and/or full-text articles on eligible studies for each of the agent-cancer combinations. Key data were abstracted into evidence tables (Appendix B). One investigator abstracted the data, and a second verified the abstraction. The abstracted data included: author; year of publication; dose of agent for the indicated use; co-intervention(s); comparator(s); brief description of the cancer stage; indicated line of treatment (first or greater); study design; and outcomes (tumor response rate; survival rates; duration data for survival and progression-free survival; QoL; symptoms; and adverse effects reporting by severity, by organ and frequency). We recorded quantitative data on the tumor response and survival outcomes, and p-values related to comparisons with baseline or comparator treatments, but recorded only qualitative data on QoL, symptoms, and adverse effects (whether reported by severity, by organ

system, or by frequency). For full-text articles, we attempted to obtain the required data from the study abstract wherever possible, but retrieved the full text when the abstract provided insufficient information.

Synthesis

To facilitate comparisons, for each of the agent-cancer combinations we created summary tables that list the number of articles identified by study design, describe the outcomes reported, and synthesize data for key outcomes, focusing on the efficacy outcomes of tumor response and survival.

Description of Compendia Listings and Evidence Cited for the 14 Agent-Cancer Combinations

We evaluated all versions of the compendia available to us (print and electronic), but recorded data from the most current and complete versions; in every case, this was an electronic version. We abstracted data from each of the six compendia for each of the 14 agent-cancer combinations. Data abstracted included: whether the off-label indication was explicitly stated; how the indication was graded; comments on further refinement regarding the stage of cancer; method of treatment; route of administration; and use of mono- or combination therapy. We recorded outcomes mentioned specifically in connection with the off-label use, as well as toxicity data. We also recorded the presence of citations to evidence on the off-label indication; the number, identity, and years of the citations; and the date of the most recent update of the compendium monograph or entry.

Analysis of Compendia Listings in Relation to their Stated Methodologies

For each of the 14 agent-cancer combinations, we constructed a matrix to show all the articles, abstracts, and other publications identified from any source (whether from the EPC review or from the compendia citations), with an indication of which compendia cited each publication. For this purpose, publications were stratified by study design, and abstracts were noted separately.

We evaluated each compendium listing in relation to the known literature, identified as described above, and in relation to the compendium's stated methodology as follows:

(1) Given the compendium's stated criteria for selecting evidence (study design, methodological quality, etc.), was all the relevant evidence meeting those criteria cited?
(2) Given the date of the most recent update of the compendium listing, was all eligible and available evidence cited?
(3) Given the eligible, available evidence, was the compendium's decision on listing (listing versus no listing) consistent with our own assessment?

Results

Methods Used by the Compendia

Information on the methods used by the compendia is summarized in Tables 1a-1f. The tables are based on information obtained from published versions of the compendia, as well as from interviews with compendia editors. A draft of each compendium's table entries was reviewed by the compendium's editor. Comments and corrections from the editor were incorporated into the final tables.

Written information describing the editorial policies of the compendia was found in each compendium, usually in the front matter of printed volumes. Electronic publications were less consistent in where this information could be found. In one instance, the current print edition's methods were noted by the editor to be obsolete, with current methods accurately described on the web site (USP-DI[2]). Another compendium made available an unpublished document that described the methods for evidence identification and evaluation in greater detail than the ordinarily available information (AHFS-DI[1]).

We evaluated all versions easily available to us, including print and electronic versions (Table 1a); however, many compendia publish data in multiple electronic formats. We chose a single electronic version to evaluate for each compendium. Our choice was guided by timeliness of access (we preferred on-line versus a mailed CD-ROM) and cost (we used existing institutional licenses when available). Different electronic platforms had different update cycles varying from daily to quarterly; a quarterly update cycle would result in as much as a 3-month delay for a user to see updated information.

We gleaned the stated purposes of the compendia from introductory published material and paraphrase these in Table 1b. None of the compendia published a "statement of purpose" explicitly labeled as such; however, all had descriptions of their intended use, users, and scope that seemed to set forth their purpose. In addition, AHFS-DI[1] had a lengthy description of its history that puts the purpose of this publication in historical context.

The scope of pharmaceutical products covered varied across compendia, particularly with regard to inclusion of non-prescription (OTC) and investigational drugs, and non-U.S. drugs. The compendia generally provided at least the same scope of information on each drug as is required for FDA labeling; some included much more information.

All of the compendia include non-FDA approved indications (Table 1b). They vary in their approach to indicating the off-label use: AHFS-DI uses † (dagger sign; although # [number sign] appears in the on-line HTML-format document); Clinical Pharmacology uses † (dagger sign); USP-DI uses [ ] (square brackets); DRUGDEX uses the phrase "Non FDA-labeled indications"; Facts & Comparisons uses "unlabeled use"; and NCCN provides no indication of off-label use. Most of the compendia had criteria for the conditions under which a non-FDA approved indication would be included. We queried editors regarding how such decisions were made, and in all cases the decision to include a non-FDA approved indication required a judgment by editorial staff regarding the quality and quantity of evidence, and the magnitude of benefit versus harms. In addition, several editors mentioned that a high degree of interest or evidence of use in practice would also be considered in deciding whether to include an off-label listing, particularly in the case of an equivocal indication, where the editorial decision would be to remain silent rather than list an indication that would be qualified as equivocal.

The policy on equivocal evidence (Table 1f) is not clear; however, the scales used for rating

evidence and for grading recommendations (Table 1d) were clearly articulated for four of the six compendia. These scales have important implications for the latitude editors may exercise in listing non-FDA approved indications based on equivocal evidence. For example, DRUGDEX[7] includes an efficacy rating of Class IIb (Evidence is inconclusive) which can be used to qualify recommendations of strength IIa (Recommended in some cases) or III (Not recommended). Similarly, USP-DI[2] uses the same underlying grades, but publishes "Acceptance not established" or "Not accepted." AHFS-DI[1] and NCCN[9] have evidence rating schemes and editorial policies that would allow a non-approved indication that can be qualified as equivocal. Facts & Comparisons[8] has a scale for grading recommendations, but commented that in the particular situation of non-labeled indications where evidence is equivocal, the de facto editorial policy is to remain silent; the "Not recommended" category is rarely used. Clinical Pharmacology[10] does not currently have rating systems in place to qualify a listed indication as based on equivocal evidence and also endorsed a de facto policy of silence.

The explicitness with which recommendations were linked to supporting evidence (Table 1f) varied a great deal across compendia. We regarded an explicit link as having been made only when specific citations to literature (published or unpublished) were provided – we did not interpret a rating of evidence as an explicit link, since the specific data could not be identified. Citations were present only in electronic versions.

Validity assessment was a component of the editorial process for each of the compendia; however, little description of this process was provided in published material. In interviews, editors described the critical appraisal process used by editorial staff. These processes were most clearly articulated by the Thomson MICROMEDEX[2,7] and AHFS-DI[1] editors; in addition, AHFS-DI provided a detailed written description of its evidence evaluation process that includes ample documentation of recent methodological literature.

Staffing and conflict of interest policies are described in Table 1e.

Table 1a: General description of compendia

Compendium	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Publisher	American Society of Health-System Pharmacists	Gold Standard, Inc.	Thomson MICROMEDEX	Wolters Kluwer Health	National Comprehensive Cancer Network	Thomson MICROMEDEX
Inception	1959	1994	~1977	1947	2004	1980
Print version, update cycle	Annual, selected monograph updates offered on-line as available	NA	NA	Annual Updates monthly (loose-leaf version only)	At least annual or when new evidence reported or new FDA approvals	Annual, selected monograph updates offered on-line
Edition assessed	2005	NA	NA	2006	NA	2005
Electronic version, update cycle	On-line, CD-ROM, PDA Updated continuously	On-line, Intranet, CD-ROM Updates continuous (on-line), monthly (Intranet), or quarterly (CD-ROM)	On-line, CD-ROM Updated weekly (on-line) or quarterly (CD)	On-line, CD-ROM Updates monthly (NB – now updated continuously)	Web-only Updated continually	Web CD-ROM Updates daily (Update Website), quarterly (via Healthcare Series, CD), or monthly (flatfiles)
Date accessed and source	2/17/06 Institutional subscription (Stat!Ref)	1/19/06 Institutional subscription	1/20/2006 Institutional subscription	2/17/06 Drug Facts & Comparisons database in Facts & Comparisons 4.0	2/17/06 Free access via internet	1/18/2006 Individual subscription
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Table 1b: Purpose of compendia as stated and vis-à-vis unlabeled uses

Compendium	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Stated purpose	"To provide an evidence-based foundation for safe and effective drug therapy"	"To provide [usable, concise] information on U.S. FDA-approved drugs including prescription and non-prescription (OTC) pharmaceuticals"	"To deliver unbiased drug information for those who prescribe, order, dispense, or administer medications"	To provide "timely, accurate, comprehensive, unbiased, comparative information on prescription and non-prescription medications" to "pharmacists and other health care professionals"	"To support decision-making about the appropriate use of drug and biologic therapy in treating patients with cancer"	To provide complete, yet concise, well-documented information on the "safe and effective use of medication once it was prescribed" for clinicians who prescribe, order, dispense, or administer medications
Scope	Comprehensive U.S. prescription and OTC drugs and biologics	Comprehensive U.S. prescription and OTC drugs; selected investigational drugs and dietary supplements	Comprehensive U.S. and non-U.S. prescription, OTC, and investigational drugs	Comprehensive U.S. prescription, OTC, and investigational drugs (and Canadian trade names)	All anticancer drugs recommended in NCCN Clinical Practice Guidelines in Oncology (NB – these guidelines are estimated to cover 97% of patients with cancer)	Comprehensive U.S. prescription drugs, including U.S. and Canadian trade names
Condition for non-FDA approved indications	**Included** when supported by evidence "in published medical literature and medical practice"	**Included** when the use represents current practice and a dosage regimen has been established and documented for the indication. Generally referenced to original clinical research.	**Included**	**Included** if "legitimate" and "appropriate"	**Included** only if included in NCCN Clinical Practice Guidelines in Oncology	**Included**

Table 1c: Methods for evidence identification by drug compendia

Compendium	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Monograph updating interval	Max: 3-5 years Min: 4-6 weeks	Max: 2 years Min: 1 week	Max: None Min: 6 weeks	Max. None Min: 1 month	Max: 1 year Min: 4-8 weeks	Max: None Min: 6 weeks
Methods to search for evidence	Continuous surveillance of multiple evidence sources	Continuous surveillance of multiple evidence sources	- Weekly automated searches of medical literature - Daily review of (1) key med journal TOCs and (2) alerts from FDA, NIH, CDC, etc.	Continuous surveillance from multiple evidence sources	Literature searches done yearly by staff; supplemented by suggested citations of 19 member inst. plus Clinical Practice Guideline panel members	See DRUGDEX
Sources	- Drug and medical information databases e.g., PubMed, Toxline,www.cancer.gov, www.guidelines.gov, The Cochrane Library, MedWatch) - Relevant medical journals - Government, professional association and industry reports - Routine monitoring of major peer-reviewed medical journals and bibliographic databases	- Official FDA-approved drug label - Primary medical and pharma journals - Abstracting services - Reference texts - Drug compendia - Pharmacology texts - Herbal and Alt Medicine texts - Medical texts - Special resource texts -Drug interaction texts -Nutrition and IV therapy texts	- Drug and medical information databases e.g., PubMed, Toxline,www.cancer.gov, www.guidelines.gov, The Cochrane Library, MedWatch) - Relevant medical journals	- Drug and medical information databases e.g., PubMed, Ovid - Relevant medical journals and textbooks - Government, professional association and industry reports - Routine monitoring of major peer-reviewed medical journals and bibliographic databases	- Primary evidence: Ovid/PubMed, journals, professional association meeting abstracts - Secondary and tertiary: textbooks, websites	See DRUGDEX
Criteria for selecting evidence	Emphasis placed on well-designed, controlled studies, published meta-analyses and systematic reviews, cost-effectiveness analyses	Phase III or IV clinical investigation in the U.S.; lower level evidence at discretion of editorial staff	Designed to be broad; emphasis placed on well-designed, controlled studies, but may include case reports	Well designed, English-language Phase II, III, or IV clinical investigation in the U.S. or meta-analyses; ≥ 30 subjects, ≤ 5 years old; no case reports or animal data	Per NCCN Clinical Practice Guideline panels	Emphasis placed on well-designed, controlled studies; does not generally include case reports

Table 1d: Methods for evidence evaluation by drug compendia

Compendium	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Process of validity assessment	Assessment involves building evidence table for each study, noting study limitations as described in well-referenced document	Subjective, by editorial staff	- Editorial staff assessment based on accepted techniques (e.g. Cho-Bero instrument (1996)) - External reviewers for off-label oncology or potentially controversial indications or when evidence is equivocal	Subjective, by editorial staff	Subjective, based on expert panel	See DRUGDEX
Use of pre-specified, published criteria for weighing evidence	Yes 1-High strength/quality (good RCT or meta-analysis, or overwhelming observational evidence) 2-Moderate strength/quality (RCT with methodologic limitations, inconsistent or indirect evidence, meta-analysis of heterogeneous RCTs, strong observational evidence) 3-Low strength/quality (observational, case reports, case series, seriously deficient RCTs) 4-Opinion/experience NB – strength of endpoint added at each level for cancer uses	No criteria currently used NB – a system is under development; based on AHRQ publications	Yes A-Meta-analysis of RCTs with homogeneity, or multiple, well-done RCTs involving large numbers of patients B-Meta-analysis of RCTs with heterogeneity, RCTs with small numbers of patients or with methodological flaws, or nonrandomized studies C-Expert opinion or consensus, case reports or case series No Evidence	No Professional judgment	Yes High (RCTs or meta-analysis) Lower (Phase II trials or large cohort studies, ranging to individual practitioner experience)	See DRUGDEX
Grading recommendations	A-Recommended B-Reasonable choice C-Not fully established D-Not recommended (considered inappropriate, obsolete or unproven)	No scale used for grading recommendations NB – a system is under consideration; certain add-on modules (e.g., ACP PIER) include grading for recommendations	Strength of recommendation: I: Recommended IIa: Recommended in most cases IIb: Recommended in some cases III: Not recommended Efficacy:	Professional judgment	1-High/Uniform 2A-Lower/Uniform 2B-Lower/Non-uniform 3-Any/Major disagreement	Accepted (FDA + off-label) Acceptance not established Not accepted (inappropriate, obsolete, unproven)

Compendium	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
			Class I – Effective Class IIa – Evidence favors efficacy Class IIb – Evidence is inconclusive Class III - Ineffective			

Table 1e: Staffing and protection from conflict of interest by drug compendia

Compendium	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Staffing of evidence assembly/synthesis task	Profession staff of drug information analysts and editors (n = 20; mostly pharmacists)	- Professional staff (board-certified) of pharmacists as senior editors (n = 8) - Review by Managing editors (n = 2 pharmacists) - Occasional external review	Clinical professional editorial staff, teams of editors with content expertise track certain drugs/therapeutic areas, monitor evidence, and perform reviews/updates	- Team of 6 clinical editors and 6 pharmacists - Outside pharmacist consultants on contract sometimes used	Prepared by staff, interpreted by disease-specific expert panels (comprised of faculty from NCCN member institutions)	See DRUGDEX
Staffing of monograph preparation	- 20 full-time staff - Occasional use of free-lance writers	- 12 full-time staff - Occasional use of free-lance writers	> 100 full-time staff	17 technical editors and 4 pharmacists	20 staff (listed on web page), including 4 MDs, 3 PhDs, 1 PharmD	See DRUGDEX
Staffing of reviews of drug monographs	External (unpaid)	- Internal mostly - External (paid) as needed	External (paid)	- Internal mostly - External (paid; sometimes used)	Reviewers from member institutions (unpaid)	See DRUGDEX
Conflicts of interest disclosure	Staff: Yes Consultants: Yes Reviewers: Yes	Staff: Yes Consultants: Yes Reviewers: No	Disclosure policy: - Not disclosed if board member paid < $25,000 by pharma company - Disclosure if income $25,000-$100,000 -Exclusion if paid >$100,000	Staff: Yes Consultants: Yes Reviewers: Yes	Staff: Yes Consultants: NA Reviewers: Yes	See DRUGDEX
Funding source, public notification of funding sources	- Funded by subscription and licensing fees only - IRS form 990 publically available - Annual external independent audit reported to membership	Funded by subscription and licensing fees only	Funded by subscription and licensing fees	Funded by subscriptions and data licensing	- Member dues pay staff, operating costs - Industry grants pay distribution costs	Funded by subscriptions

Table 1f: Methods for recommendations by drug compendia

Compendium	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Explicit link between recommendation and supporting evidence	Electronic version only	- Most off-label uses referenced to primary literature - Off-label use review and referencing is a standard part of editorial update process	- Yes - Process involves explicit evidence retrieval	Provided on request (not published)	Yes (in Clinical Practice Guidelines – compendium does not list supporting evidence, but all recommendations in compendium correspond to recommendation in Clinical Practice Guideline)	Web version only
Policy on equivocal evidence	Describe evidence as equivocal; listing vs. silence may depend on evidence of use, perceived interest	- Silence - NB – in absence of an off-label use in indications/dosages section, use may be mentioned	Listing with efficacy rating of IIa or IIb	Silence ("Not recommended" category rarely used)	- Silence usually - NB - Sometimes recommendation listed with less than full consensus (2B or 3); sometimes listed as investigational (clinical trial only)	Listing with "Acceptance not established" or silence (listing may depend on use/interest)
Method for formulating recommendations	- Editors review evidence, draft recommendation; reviewed by other editorial staff - External review for comment	- Editor reviews evidence and drafts recommendation; reviewed by other editorial staff - External review for comment	- Editor reviews evidence and drafts recommendation; reviewed by senior editorial staff - External review for comment	Editor reviews evidence and drafts recommendation; reviewed by other editorial staff	-Panel develops initial draft and circulates to member institutions for comment -Staff collate comments - Panel reconvenes to formulate guidelines - Annual update meetings to review guidelines	See DRUGDEX
Outcomes considered – benefits	Explicitly specified hierarchy of outcomes* for oncology drugs	Implicit	Implicit	Implicit	Explicit	Implicit
Outcomes considered – harms	Emphasis placed on efficacy; harms rarely explicitly considered for oncology drugs NB – Comparative toxicity typically discussed in Uses section when information available	Emphasis placed on efficacy; safety also considered in off-label listing if expected or known to be different from labeled safety data	Implicit NB – Strength of Recommendation scale addresses the concept of usefulness (risk-benefit ratio) as well as efficacy	Emphasis placed on efficacy; harms rarely explicitly considered for oncology drugs	- Harms always considered; sometimes are deciding factor in Clinical Practice Guideline recommendations - Harm data not explicitly presented in the compendium	Implicit NB – Acceptance rating scale addresses the concept of usefulness (risk-benefit ratio) as well as efficacy

Compendium	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
	from RCTs; adverse effects info available from labeled uses of the drug					

*Overall survival, cause-specific mortality, quality of life, recurrence/progression/response.

Studies Identified in the EPC Literature Review

The MEDLINE search identified 1314 potentially relevant citations (Table 1g). An additional 18 unique citations were identified for some topics from the Cochrane Central Registered of Controlled Trials (CENTRAL). Finally, 179 abstracts were identified from the American Society of Clinical Oncology (ASCO) website.

Table 1g: Number of citations identified for each agent-cancer combination

Agent	Cancer	MEDLINE, MEDLINE In-Process & Other Non-indexed Citations	CENTRAL	ASCO abstracts
Bevacizumab	Breast	48	4	12
	Lung	47	0	19
Oxaliplatin	Breast	33	2	9
	Lung	70	2	37
Irinotecan	Breast	137	1	13
Docetaxel	Esophageal/Gastric*	87	5	40
	Ovarian	139	4	-
Gemcitabine	Biliary tract	57	-	3
	Bladder	107	-	17
	Ovarian	407	-	7
Rituximab	Chronic lymphocytic leukemia	149	-	15
Erlotinib	Head and neck	16	-	2
	Pancreas	17	-	5
Totals:		**1314**	**18**	**179**

*A combined esophageal and gastric search strategy was used.

The publications thus identified were screened to determine whether they met the EPC inclusion criteria. Results of this screening process are described for each agent-cancer pair below.

Bevacizumab (Avastin®) for Breast Cancer

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). It is designed to inhibit tumor neovascularization and is not directly cytotoxic. Therefore, it is usually administered in combination with traditional cytotoxic treatments such as chemotherapy, radiation therapy, or hormonal therapy. Bevacizumab is FDA approved for the first-line treatment of metastatic colorectal cancer in combination with 5-fluorouracil (5-FU) chemotherapy. It has also been evaluated for off-label use in breast cancer.

Systematic Review by EPC

A total of 64 articles and abstracts were identified through the EPC literature search. Of these, 10 met the EPC inclusion criteria.

Table 2a describes the study types of the included studies and the outcomes reported. Appendix B (Evidence Table 1) reports details from each of the 10 studies. The literature review identified seven clinical trials, of which two were Phase III, three Phase II, and two Phase I/II,

involving a total of 1330 subjects. An additional 1782 subjects were involved in other types of studies, including a retrospective review to evaluate the risk of arterial thrombotic events (N = 1745; included subjects with breast, colorectal, and lung cancer, with the number of breast cancer subjects unknown) and two clinical research reports focused on the mechanism of action of bevacizumab in breast cancer (N = 37).

Table 2a: Study types and outcomes reported – bevacizumab for breast cancer

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	10	3112[a]	2003-5	7	2	2	-	7
Phase III	2 (20%)	1177 (38%)	2005	2	2	2	-	2
Phase II	3 (30%)	70 (2%)	2004-5	3	-	-	-	2
Phase I/II	2 (20%)	83 (3%)	2003-5	1	-	-	-	1
Other[b]	3 (30%)	1782[a] (57%)	2004	1	-	-	-	2
No. of above published as abstracts	9 (90%)	2650[a] (85%)	2003-5	6	1	1	-	6

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.
[a] Includes an unclear number of subjects with colorectal and lung cancer.
[b] Studies of mechanism of action or adverse effects.

Peer-reviewed Phase III trials. The two Phase III studies were the largest clinical trials in this review, and both evaluated tumor response, survival, quality of life (QoL), and adverse effects.[14,15] Neither study reported the impact of the interventions on symptoms.

The study of bevacizumab (15 mg/m^2 q3wks) plus capecitabine *vs* capecitabine alone was published in full text in the *Journal of Clinical Oncology* in February 2005.[15] The study involved women with heavily-pretreated metastatic breast cancer (80 percent with 1-2 prior regimens for metastatic breast cancer). The addition of bevacizumab significantly increased tumor response (19.8 percent *vs* 9.1 percent; p = 0.001) but did not influence progression-free survival (the primary endpoint), overall survival, or QoL. Bevacizumab-treated participants had more hypertension requiring intervention (17.9 percent *vs* 0.5 percent).

The Phase III study of bevacizumab (10mg/m^2 q 2wks) plus paclitaxel *vs* paclitaxel alone as first-line treatment in metastatic or locally-recurrent breast cancer was published in abstract form only.[14,16] A 2003 brief summary of this same study published in *Clinical Breast Cancer* was referenced by the NCCN compendia, but did not meet the EPC inclusion criteria.[16] At the 2005 ASCO meeting these data were presented by Dr. K. Miller as part of an oral presentation on bevacizumab and similar therapies (slides publicly available through the ASCO website), but a specific abstract about the trial was not included in the 2005 ASCO abstract book. The abstract was presented at the earlier San Antonio Breast Cancer meeting. The addition of bevacizumab significantly increased tumor response (28.2 percent *vs* 14.2 percent; p < 0.0001), improved progression-free survival (10.97 vs 6.11 months; p = 0.001), and improved overall survival (p for survival analysis = 0.01). QoL analyses had not been completed at the time of the presentation. Bevacizumab-treated participants had more hypertension requiring intervention (13.3 percent *vs* 0 percent), proteinuria (2.4 percent *vs* 0 percent), and nephropathy (0.3 percent and 0 percent).

Longer followup is planned for further assessment of the impact of bevacizumab on overall survival.

Peer-reviewed Phase II and I/II trials. Of the five Phase II and I/II trials, one was randomized.[17] All were reported in abstract form. Four assessed patients with metastatic breast cancer and one evaluated the use of bevacizumab in the neoadjuvant setting. Co-interventions included erlotinib, docetaxel, letrozole, and "chemotherapy." Tumor response, defined as complete plus partial responses, ranged from 3 to 11 percent. Survival and QoL data were not presented. Three of five (60 percent) studies discussed adverse effects.

The neoadjuvant study was also the only randomized study; it compared docetaxel plus bevacizumab to docetaxel alone, and the distinction between the two regimens on outcomes was not clear within the abstract. Doses ranged from 3 to 20 mg/m^2 every 2 to 3 weeks.

Compendia Listings

Treatment indication and toxicities. Table 2b summarizes the compendia's discussions of the off-label use of bevacizumab for treatment of breast cancer. Only DRUGDEX and NCCN explicitly stated whether there was an off-label indication for the drug in the setting of this cancer. DRUGDEX stated "level III" – not clearly recommended – and NCCN stated "indicated." NCCN did not report on toxicities due to bevacizumab. All other compendia, regardless of whether they discussed an off-label indication for breast cancer or not, discussed toxicities, including severity and frequency of adverse effects, and which organs have been reported to be affected. Only USP-DI discussed bevacizumab-related toxicities specifically among patients being treated for breast cancer.

Table 2b: Summary of compendia listings – bevacizumab for breast cancer

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
Off-label indication explicitly stated	No	No	Yes	No	Yes	No
Sub-category of indication (accepted or acceptance not established)	-	-	Efficacy: Adult, Evidence is inconclusive Recommendation: Adult, Class III Strength of Evidence: Adult, Category B	-	2A	-
Stage of cancers	-	-	Metastatic breast cancer	-	Recurrent or metastatic	-
Method of treatment (first line or other)	-	-	Pre-treated patients	-	Other	-
Routes of administration	-	-	IV	-	NR	-
Uses of the agent (monotherapy or combination)	-	-	Monotherapy	-	Combination	-
Comparator discussed (placebo, standard treatment, other agents)	-	-	NR	-	NR	-
Outcomes mentioned for the off-label use (survival, tumor response, other)	-	-	Duration of confirmed response, tumor burden, ECOG status	-	Disease-free survival; overall survival	-
Toxicity reporting	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: Yes Severity: No By organ: Yes Frequency: No	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: No Indication-specific: No Severity: No By organ: No Frequency: No	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes
Dose indicated for the off-label use	-	-	3, 10, or 20 milligrams/kilogram (mg/kg) every 2 weeks	-	10 mg/kg IV days 1 & 15, cycled every 28 days	-
Number of evidence citations	-	-	1 (+ 1)[a]	-	1	-
Range of years of citations	-	-	2001	-	2003	-
Sources of evidence (abstracts/published articles)	-	-	Abstract	-	Abstract	-
Number of abstracts cited [years]	-	-	1 [2001]	-	1 [2003]	-
Number of published articles cited [years]	-	-	1 review [2002]	-	0	-
Date of last update	1/10/2006	12/06/2005	NR	NR	12/05/20005	7/25/2005

[a] 1 article cited; 1 additional review article included in the reference list.

Studies cited in compendia versus studies identified in EPC review. Only DRUGDEX and NCCN provided any references (Table 2b); one reference was cited by each. Neither of the two references cited by these compendia met the EPC criteria for inclusion, as both were old abstracts (about different studies) with a more recent update available. Neither compendia cited the published full-text Phase III trial of bevacizumab plus capecitabine *vs* capecitabine alone. Only NCCN cited the Phase III study of bevacizumab plus paclitaxel *vs* paclitaxel alone, but in doing so referred to an old abstract.

A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 2c.

Table 2c: Articles cited by compendia vs. articles identified by EPC – bevacizumab for breast cancer

Reference	EPC	AHFS-DI	USP-DI	DRUGDEX	F & C	NCCN	Clin Pharm	Notes
Reviewed by compendia:	-	No	No	Yes	No	Yes	No	-
Phase III								
Miller, 2005[15]	x							
Miller, 2005[14]	x							Same study
Miller, 2003[16]						x[a]		
Phase II								
Rugo, 2005[18]	x							
Dickler, 2004[19]	x							
Overmoyer, 2004[17]	x							
Phase I/II								
Traina, 2005[20]	x							
Cobleigh, 2003[21]	x							Same study
Cobleigh, 2001[22]				x[b]				
Phase I								
(none)								
Other								
Denduluri, 2005[23]	x							
Skillings 2005[24]	x							
Wedam, 2004[25]	x							
Pegram, 2002[26]				*				Review

[a] Not identified by EPC because abstract older than abstract search cut-off and non-ASCO; however, an update of this trial was presented at ASCO by Miller et al. and review of their slides was available for EPC review.
[b] Not identified by EPC because it is an old abstract with updated abstract in 2003 (See Cobleigh[21]).
* Non-cited reference.

Recommendations and supporting evidence. DRUGDEX states that there is inconclusive evidence for a clear recommendation of bevacizumab for breast cancer, indicating a recommendation of level III (not clearly recommended) based upon evidence strength B. Its cited reference was a 2001 abstract from Cobleigh,[22] a non-randomized Phase II trial with an updated abstract published 2 years later. It specified that the place for bevacizumab is as monotherapy for metastatic breast cancer and stated that more studies are needed.

NCCN cites a 2A indication for bevacizumab in breast cancer, with lower quality evidence, but uniform agreement about this conclusion. It specified that bevacizumab should be used in combination at doses and in patients consistent with the Miller study of bevacizumab plus paclitaxel. Its cited reference was a 2003 abstract of this Phase III trial, which was updated recently, but the update was not cited. No toxicity data are provided, despite clear information

about toxicity in the Miller studies.

Summary. Listings of bevacizumab for breast cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Two of the six compendia (DRUGDEX and NCCN) discuss bevacizumab for treatment of breast cancer.
- *Specificity of clinical information:* DRUGDEX offers a dose range and mentions several outcomes, including duration of response, tumor burden, and ECOG status, but without describing precise estimates of benefit. NCCN cites evidence of improvement in disease-free and overall survival, but does not quantify the magnitude of benefit. NCCN offers specific dosing information for bevacizumab and paclitaxel based on the single cited trial.
- *Evidence rating:* Both DRUGDEX and NCCN provide explicit evidence ratings for the off-label indication of bevacizumab for breast cancer. DRUGDEX rates the evidence as "inconclusive" based on lower level evidence (RCTs with small numbers of patients or methodological flaws, or nonrandomized studies). It cites one Phase I/II trial and a review article. NCCN lists the off-label use based on "lower" level evidence but with "uniform" consensus (category 2A), citing a single Phase III trial.
- *Recommendation statements:* DRUGDEX states that use of bevacizumab is "not recommended" based on lower level evidence, which it describes as "inconclusive;" this statement applies to use in previously treated patients with metastatic disease. NCCN endorses the off-label use for first-line treatment of metastatic breast cancer based on lower level evidence, but with uniform consensus (category 2A), citing a single trial.
- *Toxicity:* Toxicities related to bevacizumab are reported in most of the compendia, but only USP-DI notes toxicities specifically in patients with breast cancer.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it does not include breast cancer as an off-label indication for bevacizumab. It emphasizes well-designed, controlled, published studies, but does not cite the two Phase III studies identified in the EPC review. The last update was 1/17/06, but 2005 data, including the two Phase III trials, are not cited.
- USP-DI specifies that it includes off-label indications, but it does not include breast cancer as an off-label indication for bevacizumab. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff, but it does not cite the Phase III studies identified in the EPC review. The last update was 12/6/05, but 2005 data are not cited.
- DRUGDEX specifies that it includes off-label indications, and it does include breast cancer as an off-label indication for bevacizumab. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites an old narrative review, but does not cite the two Phase III studies identified in the EPC review. The date of the last update is not reported, but 2005 data are not cited.
- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it does not include breast cancer as an off-label indication for bevacizumab.

It emphasizes Phase II, III, and IV studies with over 30 subjects, but does not cite the clinical trials identified in the EPC review that meet these criteria, including two Phase III studies. The date of the last update is not stated, but 2005 data are not cited.

- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is an off-label indication for bevacizumab in breast cancer as per the guideline. The last update was 12/5/05, but 2005 data are not cited.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it does not include breast cancer as an off-label indication for bevacizumab. It emphasizes prospective trials, but does not cite the two Phase III studies or the other clinical trials identified in the EPC review. The last update was 7/25/05, but early 2005 data are not cited.

Bevacizumab (Avastin®) for Lung Cancer

As stated above, bevacizumab is a humanized monoclonal antibody against VEGF. It is designed to inhibit tumor neovascularization and is not directly cytotoxic. Therefore, it is usually administered in combination with traditional cytotoxic treatments such as chemotherapy, radiation therapy, or hormonal therapy. Bevacizumab is FDA approved for the first-line treatment of metastatic colorectal cancer in combination with 5-FU chemotherapy. It has also been evaluated for off-label use in lung cancer.

Systematic Review by EPC

A total of 66 articles and abstracts were identified through the EPC literature search. Of these, five met the EPC inclusion criteria. One of the five studies[27] had three associated abstracts from the same study presented at the 2004 ASCO meeting.

Table 3a describes the study types of the included studies and the outcomes reported. Appendix B (Evidence Table 2) reports details from each of the five studies. The literature review identified four clinical trials, of which one was Phase II/III, two Phase II, and one Phase I/II, involving a total of 1022 subjects. An additional 1745 subjects were included in a retrospective review to evaluate the risk of arterial thrombotic events (included subjects with breast, colorectal, and lung cancer, with the number of lung cancer subjects unknown).

Table 3a: Study types and outcomes reported – bevacizumab for lung cancer

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	5	2767[a]	2004-5	4	4	-	-	5
Phase II/III	1 (20%)	842 (30%)	2005	1	1	-	-	1
Phase II	2 (40%)	140 (5%)	2004-5	2	2	-	-	2
Phase I/II	1 (20%)	40 (3%)	2005	1	1	-	-	1
Other[b]	1 (30%)	1745[a] (63%)	2004	-	-	-	-	1
Abstracts	3 (60%)	2628[a] (95%)	2004-5	2	1	-	-	3

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.
[a] Includes an unclear number of subjects with colorectal and breast cancer.
[b] Study of adverse effects.

Peer-reviewed Phase II/III trials. The Phase II/III study was the largest clinical trial in this review.[28] It was presented at the ASCO 2005 meeting and has not yet been published in full text. The study evaluated bevacizumab (15 mg/m^2 q3wks) plus carboplatin (PCB) and paclitaxel *vs* carboplatin and paclitaxel (PC) in the first-line setting. Participants had stage IIIB or IV non-small cell lung cancer (NSCLC); squamous cell NSCLC was excluded. Tumor response, survival, and adverse effects were evaluated. The impact of the interventions on QoL and symptoms was not reported. A total of 842 subjects were randomized, 436 to PCB and 444 to PC. The addition of bevacizumab significantly increased tumor response (27 percent *vs* 10 percent; $p = 0.0001$), progression-free survival (6.4 mo *vs* 4.5 mo; $p < 0.0001$), and overall survival (12.5 mo *vs* 10.2 mo; $p = 0.0075$). Bevacizumab-treated participants had more grade 4/5 neutropenia (24 percent *vs* 16 percent), grade 3/4 thromboembolism (3.8 percent *vs* 3 percent), and hemorrhage (4.1 percent *vs* 1 percent).

Peer-reviewed Phase II and I/II trials. Of the three Phase II and I/II trials, one was randomized.[29] This randomized study by Johnson et al.[29] was published in full-text form in 2004 and provided the background data for the Phase II/III study by Sandler et al.[28] described above. The predominant differences were that a third arm with bevacizumab at 7.5mg/m^2 was included, and patients with squamous cell NSCLC were included. These patients with squamous cell NSCLC were later excluded in the Sandler[28] study due to an increased risk of adverse effects in this sub-population.

Herbst and colleagues evaluated bevacizumab plus erlotinib in a non-randomized Phase I/II study published in 2005.[27] Participants had heavily pre-treated non-squamous NSCLC, and 20 percent partial responses were identified. This combination is undergoing further study. Raefsky and colleagues presented a 2005 ASCO abstract of bevacizumab plus irinotecan, carboplatin, and radiotherapy in limited stage small cell lung cancer (SCLC).[30] This combination was also deemed appropriate for further study.[30]

Compendia Listings

Treatment indication and toxicities. Table 3b summarizes the compendia's discussions of the off-label use of bevacizumab for treatment of lung cancer. Five of the six compendia explicitly stated there was an off-label indication for the drug in the setting of this cancer. All compendia, regardless of whether they discussed an off-label indication for breast cancer or not, discussed toxicities, including severity and frequency of adverse effects, and which organs have been reported to be affected. All but AHFS-DI and Clinical Pharmacology discussed bevacizumab-related toxicities specifically among patients being treated for lung cancer.

Table 3b: Summary of compendia listings – bevacizumab for lung cancer

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
Off-label indication explicitly stated	No	Yes	Yes	Yes	Yes	Yes
Sub-category of indication (accepted or acceptance not established)	-	Accepted	Evidence favors efficacy Recommendation: Adult, Class IIb Strength of Evid: Adult, Category B	NR	Category 2A – lower level evidence and uniform consensus that the recommendation is appropriate	NR
Stage of cancers	-	Non-squamous non small cell lung cancer, advanced/metastatic, first-line treatment	Advanced non-squamous NSCLC	"Non-small cell lung cancer"	Non-squamous NSCLC: no history of hemoptysis, no CNS metastases, no ongoing therapeutic anticoagulation	Advanced and metastatic
Method of treatment (first line or other)	-	First line – in combination	First line – in combination	NR	First line – in combination	NR
Routes of administration	-	IV	NR	IV	NR	IV
Uses of the agent (monotherapy or combination)	-	Combination	Combination	Combination with carboplatin and paclitaxel	Combination	Combination
Comparator discussed (placebo, standard treatment, other agents)	-	None	Same combination, but with placebo instead of bevacizumab	NR	Same combination, but without bevacizumab	Same combination, but placebo instead of bevacizumab
Outcomes mentioned for the off-label use (survival, tumor response, other)	-	Response rates, time to progression, and overall survival	Response rates, time to progression, and overall survival	NR	Response rate Progression-free survival Median survival	Response rate Progression-free survival Median survival
Toxicity reporting	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: Yes Severity: No By organ: Yes Frequency: No	Overall: Yes Indication-specific: Yes Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: Yes Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: Yes Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes
Dose indicated for the off-label use	-	5 mg per kg over 90 min every 14 days	No	No	No	Yes for bevacizumab + paclitaxel + carboplatin

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
Number of evidence citations	-	3	2	1	2	1
Range of years of citations	-	2004-2005	2004-2005	2004	2004-2005	2005
Sources of evidence (abstracts/published articles)	-	2 published article + 1 abstract	1 published article + 1 abstract	1 published article[a]	1 published article + 1 abstract	Abstract
Number of abstracts cited [years]	-	1 [2005]	1 [2005]	0	1 [2005]	1 [2005]
Number of published articles cited [years]	-	2 [2004-2005]	1 [2004]	1 [2004]	1 [2004]	0
Date of last update	1/10/2006	12/06/2005	NR	NR	11/22/05	7/25/2005

[a] Listed erroneously in evaluated version of drug monographs as "package insert."

Studies cited in compendia versus studies identified in EPC review. Only USP-DI, DRUGDEX, and NCCN provided clear references (Table 3b); 2 to 3 references were cited by each compendium. All three compendia cited the Sandler[28] Phase II/III trial and its preliminary study, published by Johnson et al.[29] USP-DI also cited the Herbst Phase I/II study of bevacizumab plus erlotinib.[27] All of the cited references were also identified in the EPC review. Facts & Comparisons erroneously cited the package insert; however, the editor informed us that the indication was based on the preliminary study published by Johnson et al.[29] Clinical Pharmacology was silent regarding references; while AHFS-DI did not include this off-label indication or list references.

A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 3c.

Table 3c: Articles cited by compendia vs. articles identified by EPC – bevacizumab for lung cancer

Reference	EPC	AHFS-DI	USP-DI	DRUGDEX	F & C	NCCN	Clin Pharm
Reviewed by compendia:	-	No	Yes	Yes	Yes	Yes	Yes
Phase II/III							
Sandler 2005[28]	x		x	x		x	x
Phase II							
Raefsky, 2005[30]	x						
Johnson, 2004[29]	x		x	x	x[a]	x	
Phase I/II							
Herbst, 2005[27]	x		x				
Phase I							
(none)							
Other							
Skillings, 2005[24]	x						

[a] Johnson, 2004 was supposed to have been cited, but the package insert was erroneously substituted as the citation in the drug monograph we reviewed.

Recommendations and supporting evidence. USP-DI states that there is acceptable evidence for an off-label indication of bevacizumab for lung cancer in the first-line setting. The profile of the recommended patient population follows that of the Sandler[28] study. The recommended dose is 5 mg per kg over 90 min every 14 days in combination with other chemotherapies, not the 15mg/m^2 every 3 weeks used in the Sandler[28] study.

DRUGDEX provides a recommendation of level IIb based upon evidence strength B. The profile of the recommended patient population follows that of the Sandler[28] study, and it is stated that the agent should be used in combination with other chemotherapies; a dose is not recommended.

Facts & Comparisons provides an off-label indication for NSCLC without further specification about the patient population. It recommends that bevacizumab be used in combination with paclitaxel and carboplatin; a dose is not recommended.

NCCN cites an indication as Category 2A based on lower level evidence and uniform consensus that the recommendation is appropriate. The profile of the recommended patient population follows that of the Sandler[28] study, and it is stated that the agent should be used in combination with other chemotherapies; a dose is not recommended. Toxicity data are provided.

Clinical Pharmacology provides an off-label indication for advanced and metastatic NSCLC without further specification about the patient population. It recommends that bevacizumab be

used in combination with paclitaxel and carboplatin; dosing is specific to this combination.

Summary. Listings of bevacizumab for lung cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Five of the six compendia (all except AHFS-DI) discuss bevacizumab for treatment of NSCLC.
- *Specificity of clinical information:* All five of the compendia listing this recommendation describe use in advanced or metastatic NSCLC. All five recommend combination therapy, although only two describe specific combination regimens (Facts & Comparisons and Clinical Pharmacology). Four of the five (all but Facts & Comparisons) describe outcomes expected to be impacted (similarly listed as response rate, time to progression, and overall survival), and three of the five (DRUGDEX, NCCN, and Clinical Pharmacology) present quantitative estimates of the magnitude of benefit.
- *Evidence rating:* Only two compendia (DRUGDEX and NCCN) provide explicit evidence ratings for the off-label indication of bevacizumab for NSCLC. Evidence is rated in the second tier by both. All five compendia listing this indication cite at least one study; four cite the same Phase III study. None of the five compendia cites more than three studies.
- *Recommendation statements:* USP-DI lists the off-label use under the "Accepted" category. DRUGDEX lists the recommendation as IIb ("Recommended in most cases"), while NCCN describes uniform consensus that the indication is appropriate. Facts & Comparisons and Clinical Pharmacology make no further qualification of the off-label use of bevacizumab in NSCLC.
- *Toxicity:* Toxicities related to bevacizumab are reported in all of the compendia, and four (USP-DI, DRUGDEX, Facts & Comparisons, and NCCN) note toxicities specifically in patients with NSCLC.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice are more consistent for bevacizumab in lung cancer than for the same agent in breast cancer. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it does not include lung cancer as an off-label indication for bevacizumab. It emphasizes well-designed, controlled, published studies, but does not cite the published Phase II/III study identified in the EPC review. The last update was 1/10/06, but 2005 data, including the Phase II/III study, are not cited.
- USP-DI specifies that it includes off-label indications, and it does include lung cancer as an off-label indication for bevacizumab. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff. It cites the one Phase III study identified in the EPC review, as well as two Phase I/II or II studies. The last update was 12/6/05; 2005 data are cited.
- DRUGDEX specifies that it includes off-label indications, and it does include lung cancer as an off-label indication for bevacizumab. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites the one Phase III study and one of the preliminary Phase II studies identified in the EPC review.

The date of the last update was not reported; 2005 data are cited.

- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it includes lung cancer as an off-label indication for bevacizumab. It emphasizes Phase II, III, and IV studies with over 30 subjects, but does not cite any of the clinical trials identified in the EPC review that meet these criteria, including the Phase III study. We were informed by the editors that one Phase II study was supposed to have been cited, but that the package insert was erroneously substituted in the version we reviewed. The date of the last update is not stated, but 2005 data are not cited.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is an off-label indication for bevacizumab in lung cancer as per the guideline. The last update was 11/22/05, and 2005 data are cited.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it includes lung cancer as an off-label indication for bevacizumab. It emphasizes prospective trials, but cites only one of the four clinical trials identified in the EPC review (the 2005 Phase III study), omitting the earlier Phase I/II and Phase II studies. The last update was 7/27/05, and 2005 data are cited.

Oxaliplatin (Eloxatin®) for Breast Cancer

Oxaliplatin is a third-generation platinum analog. Oxaliplatin is a non-cell cycle specific, alkylating chemotherapeutic drug that impairs DNA synthesis by forming platinum-DNA crosslinks that inhibit DNA replication and transcription. Its activity and toxicity profiles differ from both cisplatin and carboplatin, and thus it lacks cross-resistance with these compounds. Unlike cisplatin or carboplatin, oxaliplatin is not associated with significant renal or auditory toxicity, and hematological toxicity is usually mild. Oxaliplatin has a large spectrum of anticancer activity and has been used in combination with many other chemotherapy agents.

Oxaliplatin is FDA approved as a second-line therapy for the treatment of metastatic colorectal cancer; a first-line treatment for advanced colorectal cancer; and an adjuvant treatment for stage III colorectal cancer. It has also been evaluated for off-label use for breast cancer.

Systematic Review by EPC

A total of 44 articles and abstracts were identified through the EPC literature search. Of these, nine met the EPC inclusion criteria. Eight of the nine were abstracted. One Phase II study of oxaliplatin by continuous infusion published in 1990 could not be obtained for abstraction.

Table 4a describes the study types of the included studies and the outcomes reported. Appendix B (Evidence Table 3) reports details from each of the eight studies. The literature review identified eight prospective clinical trials, of which one was a Phase II/III study and seven were Phase II studies. A total of 357 subjects were involved.

Table 4a: Study types and outcomes reported – oxaliplatin for breast cancer

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	8	357	2002-5	8	4	-	4	8
Phase II/III	1 (12%)	137 (38%)	2004	1	1	-	-	1
Phase II	7 (88%)	220 (62%)	2002-5	7	3	-	4	7
Phase I/II	-	-	-	-	-	-	-	-
Other	-	-	-	-	-	-	-	-
No. of above published as abstracts	3 (38%)	198 (55%)	2004-5	3	2	-	2	3

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.

Peer-reviewed Phase II/III trials. One Phase II/III study was identified.[31] This was a randomized study of oxaliplatin plus 5-FU *vs* vinorelbine plus 5-FU in women with previously-treated advanced or metastatic breast cancer. All subjects had received taxane and doxorubicin based chemotherapy in the past. The vinorelbine arm was chosen as an established comparator intervention in this clinical setting. The oxaliplatin dose was 130mg/m^2 every 3 weeks. The study was prematurely closed after accrual of 137 subjects due to recruitment difficulties. Oxaliplatin-based chemotherapy was as efficacious as the vinorelbine-based chemotherapy in terms of tumor response, time to progression, and overall survival. The oxaliplatin-based intervention caused significantly less neutropenia (13 percent *vs* 78 percent; $p < 0.001$), mucositis (12 percent *vs* 32 percent; $p = 0.0043$), and neurosensory changes (0 percent *vs* 7.5 percent; $p = 0.0279$).

Peer-reviewed Phase II trials. Of the seven Phase II trials, none was randomized. Oxaliplatin doses ranged from 85 to 130mg/m^2. Monotherapy demonstrated activity in heavily-pretreated metastatic breast cancer patients; studies of combination therapy with other chemotherapeutics were recommended.[32] Co-interventions studied were capecitabine, 5-FU, and gemcitabine. All studies involved subjects with heavily-pretreated metastatic breast cancer. A non-randomized parallel Phase II study of two different dosing schedules, every 2 or 3 weeks in combination with gemcitabine, showed equal efficacy of both schedules.[33]

Peer-reviewed Phase I and other studies. No studies in these categories were identified.

Compendia Listings

Treatment indication and toxicities. Table 4b summarizes the compendia's discussions of the off-label use of oxaliplatin for treatment of breast cancer. Both Clinical Pharmacology and DRUGDEX explicitly stated an off-label indication for the drug in this cancer. All the compendia, regardless of whether they discussed an off-label indication for breast cancer or not, discussed toxicities, including severity and frequency of adverse effects, and which organs have been reported to be affected. None discussed oxaliplatin-related toxicities specifically among patients being treated for breast cancer.

Table 4b: Summary of compendia listings – oxaliplatin for breast cancer

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
Off-label indication explicitly stated	No	No	Yes	No	No	Yes
Sub-category of indication (accepted or acceptance not established)	-	-	Efficacy: Adult, Evidence is inconclusive Recommendation: Adult, Class III Strength of Evidence: Adult, Category B	-	-	Advanced or metastatic
Stage of cancers	-	-	Prior taxane and anthracycline treatment	-	-	Taxane- and anthracycline-retreated advanced and metastatic breast cancer
Method of treatment (first line or other)	-	-	NR	-	-	NR
Routes of administration	-	-	NR	-	-	IV
Uses of the agent (monotherapy or combination)	-	-	Combination with 5-FU	-	-	Combination with fluorouracil
Comparator discussed (placebo, standard treatment, other agents)	-	-	None	-	-	None
Outcomes mentioned for the off-label use (survival, tumor response, other)	-	-	Response rate	-	-	Time to progression, median survival
Toxicity reporting	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes
Dose indicated for the off-label use	-	-	130 mg/m^2 IV on day 1 plus 5-FU 1000 mg/m^2/d on days 1-4 every 3 weeks	-	-	130mg/m^2 IV on day 1 plus 5- fluorouracil continuous infusion days 1-4) every 3 weeks
Number of evidence	-	-	2	-	-	1

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
citations						
Range of years of citations	-	-	1990-2002	-	-	2002
Sources of evidence (abstracts/published 0rticles)	-	-	Articles	-	-	Article
Number of abstracts cited [years]	-	-	0	-	-	0
Number of published articles cited [years]	-	-	2 (1990-2002)	-	-	1 [2002]
Date of last update	1/10/2006	09/22/2005	NR	NR	12/05/05 [12/05/2005]*	7/13/2005

* Last update of clinical practice guideline.

Studies cited in compendia versus studies identified in EPC review. Only Clinical Pharmacology and DRUGDEX provided any references (Table 4b). The same reference was cited by both.[34] This reference was also identified in the EPC review. DRUGDEX also cited a 1990 Phase I trial that was not identified by the EPC.[35] A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 4c.

Table 4c: Articles cited by compendia vs. articles identified by EPC – oxaliplatin for breast cancer

Reference	EPC	AHFS-DI	USP-DI	DRUGDEX	F & C	NCCN	Clin Pharm
Reviewed by compendia:	-	No	No	Yes	No	No	Yes
Phase II/III							
Delaloge 2004[31]	x						
Phase II							
Cottu 2005[33]	x						
Gebbia 2004[36]	x						
Pectasides 2003[37]	x						
Thuss-Patience 2003[38]	x						
Leonardi 2002[39]	x						
Zelek 2002[34]	x			x			x
Garufi 2001[32]	x						
Phase I/II							
(none)							
Phase I							
Caussanel, 1990[35]				x			
Other							
(none)							

Recommendations and supporting evidence. DRUGDEX lists an off-label indication for oxaliplatin for breast cancer after prior taxane and anthracycline treatment based on inconclusive evidence for efficacy of strength "Category B" (based on data derived from RCTs that involved small numbers of patients or had significant methodological flaws). The recommendation was "Class III" (not recommended).

Clinical Pharmacology provides an off-label indication for oxaliplatin for advanced or metastatic breast cancer after progression despite taxane and anthracycline therapy. It recommended the use of oxaliplatin in combination with 5-FU at a dose of 130mg/m^2 every 3 weeks.

Summary. Listings of oxaliplatin for breast cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Two of the six compendia (DRUGDEX, Clinical Pharmacology) discuss oxaliplatin for treatment of breast cancer.
- *Specificity of clinical information:* The two compendia described a similar role for oxaliplatin in advanced or metastatic breast cancer after failure of taxane and anthracycline treatment. The compendia cite the same Phase II study of combination treatment with 5-FU and provide identical dosing information. Both compendia cite data on response rate, for which observed improvements are quantified; Clinical Pharmacology also mentions time to progression and median survival, for which no quantitative data are presented.
- *Evidence rating:* Only DRUGDEX provides an explicit evidence rating for the off-label indication of oxaliplatin for breast cancer, describing the evidence as category B and inconclusive. Both DRUGDEX and Clinical Pharmacology cite at least one reference.

- *Recommendation statements:* Only DRUGDEX provided an explicit recommendation on the off-label use of oxaliplatin for breast cancer, listing it as "Not recommended."
- *Toxicity:* Toxicities related to oxaliplatin are reported in all of the compendia, but none notes toxicities specifically in patients with breast cancer.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it does not include breast cancer as an off-label indication for oxaliplatin. It emphasizes well-designed, controlled, published studies, but does not cite the published Phase II/III study identified in the EPC review. The last update was 1/10/06, but the 2004 Phase II/III study is not cited.
- USP-DI specifies that it includes off-label indications, but it does not include breast cancer as an off-label indication for oxaliplatin. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff, but it does not cite the Phase II/III study identified in the EPC review. The last update was 9/22/05; the Phase II/III study was presented at ASCO in June 2005.
- DRUGDEX specifies that it includes off-label indications, and it does include breast cancer as an off-label indication for oxaliplatin. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites two studies, but fails to cite additional studies identified in the EPC review, including the single Phase II/III trial (2005). The date of the last update was not reported, but 2005 data are not cited.
- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it does not include breast cancer as an off-label indication for oxaliplatin. It emphasizes Phase II, III, and IV studies with over 30 subjects, but does not cite the four clinical trials identified in the EPC review that meet these criteria. The date of the last update is not stated, but 2005 data are not cited.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is not an off-label indication for oxaliplatin in breast cancer as per the guideline. The last update was 12/5/05, but 2005 data are not cited.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it includes breast cancer as an off-label indication for oxaliplatin. It emphasizes prospective trials, but does not cite any of the eight prospective studies identified in the EPC review. The last update was 7/13/05, but the Phase II/III study presented at ASCO in June 2005 is not cited.

Oxaliplatin (Eloxatin®) for Lung Cancer

As stated above, oxaliplatin is a third-generation platinum analog. Oxaliplatin is a non-cell cycle specific, alkylating chemotherapeutic drug that impairs DNA synthesis by forming

platinum-DNA crosslinks that inhibit DNA replication and transcription. Its activity and toxicity profiles differ from both cisplatin and carboplatin, and thus it lacks cross-resistance with these compounds. Unlike cisplatin or carboplatin, oxaliplatin is not associated with significant renal or auditory toxicity, and hematological toxicity is usually mild. Oxaliplatin has a large spectrum of anticancer activity and has been used in combination with many other chemotherapy agents.

Oxaliplatin is FDA approved as a second-line therapy for the treatment of metastatic colorectal cancer; a first-line treatment for advanced colorectal cancer; and an adjuvant treatment for stage III colorectal cancer. It has also been evaluated for off-label use for lung cancer.

Systematic Review by EPC

A total of 109 articles and abstracts were identified through the EPC literature search. Of these, 20 met the EPC inclusion criteria. Nineteen of the 20 were abstracted. One Phase II study of oxaliplatin by continuous infusion published in 1990 could not be obtained for abstraction.

Table 5a describes the study types of the included studies and the outcomes reported. Appendix B (Evidence Table 4) reports details from each of the 19 studies. The literature review identified 18 prospective clinical trials, of which 12 were Phase II studies, two were Phase I/II, and four were Phase I. A total of 666 subjects were involved.

Table 5a: Study types and outcomes reported – oxaliplatin for lung cancer

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	19	666	1998-2005	16	7	-	11	19
Phase III	-	-	-	-	-	-	-	-
Phase II	12 (63%)	546 (82%)	1998-2005	12	7	-	7	12
Phase I/II	2 (11%)	62 (9%)	2001-2	2	-	-	1	2
Other[a]	5 (26%)	58 (9%)	2001-3	2	-	-	3	5
No. of above published as abstracts	4 (21%)	232 (35%)	2004-5	4	2	-	2	4

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.
[a] Four Phase I studies and 1 case report.

Peer-reviewed Phase III trials. No Phase III studies were identified.

Peer-reviewed Phase II trials. A total of 12 Phase II studies were identified, of which two were randomized.[40,41] All studies evaluated oxaliplatin in the setting of advanced stage III or IV NSCLC; 11 of 12 included patients in the first-line setting. One study evaluated oxaliplatin as monotherapy, and all others included co-interventions. Co-interventions included gemcitabine (n = 7 studies), vinorelbine (n = 1), docetaxel (n = 1), pemetrexed (n = 1), and paclitaxel (n = 1). Oxaliplatin doses ranged from 65 to 130 mg/m^2. All concluded that oxaliplatin has activity in this setting, except an ASCO abstract by Lippe.[42] Generally response rates were felt to be similar to other platinum-containing doublets, with equal or better tolerability. Further investigation was recommended. The data from randomized and non-randomized studies were similar.

Peer-reviewed Phase I/II trials. Oxaliplatin was combined with vinorelbine and

gemcitabine in two Phase I/II studies. Both demonstrated that oxaliplatin could be safely administered and had activity, verifying plans to go on to Phase II studies.

Peer-reviewed Phase I and other studies. The four small Phase I studies and one case report all suggested that the Phase II studies described above were feasible and warranted.

Compendia Listings

Treatment indication and toxicities. Table 5b summarizes the compendia's discussions about the off-label use of oxaliplatin for treatment of lung cancer. Only DRUGDEX lists this as an off-label indication. All compendia discussed toxicities, including severity and frequency of adverse effects, and which organs have been reported to be affected. None discussed oxaliplatin-related toxicities specifically among patients being treated for lung cancer.

Table 5b: Summary of compendia listings – oxaliplatin for lung cancer

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
Off-label indication explicitly stated	No	No	Yes	No	No	No
Sub-category of indication (accepted or acceptance not established)	-	-	Efficacy: Adult, Evidence is inconclusive Recommendation: Adult, Class III Strength of Evidence: Adult, Category B	-	-	-
Stage of cancers	-	-	Stage IV	-	-	-
Method of treatment (first line or other)	-	-	Monotherapy	-	-	-
Routes of administration	-	-	NR	-	-	-
Uses of the agent (monotherapy or combination)	-	-	NR	-	-	-
Comparator discussed (placebo, standard treatment, other agents)	-	-	NR	-	-	-
Outcomes mentioned for the off-label use (survival, tumor response, other)	-	-	Response	-	-	-
Toxicity reporting	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes
Dose indicated for the off-label use	-	-	130 mg/m2 IV as a 2 hr infusion every 21 days	-	-	-
Number of evidence citations	-	-	1 (+1)[a]	-	-	-
Range of years of citations	-	-	1998-2002	-	-	-
Sources of evidence (abstracts/published articles)	-	-	Article	-	-	-
Number of abstracts cited [years]	-	-	0	-	-	-
Number of published articles cited [years]	-	-	2 (1998-2002)	-	-	-
Date of last update	1/10/2006	09/22/2005	NR	NR	03/04/05 [11/22/2005]*	7/13/2005

* Last update of clinical practice guideline.
[a] One article cited; 1 additional article included in the reference list.

Studies cited in compendia versus studies identified in EPC review. Only DRUGDEX provided any references about oxaliplatin for lung cancer treatment (Table 5b). A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 5c.

Table 5c: Articles cited by compendia vs. articles identified by EPC – oxaliplatin for lung cancer

Reference	EPC	AHFS-DI	USP-DI	DRUGDEX	F & C	NCCN	C P
Reviewed by compendia:	-						
Phase III							
(none)							
Phase II							
Bidoli 2005[40]	x						
Broad 2005[43]	x						
Cappuzzo 2005[44]	x						
Kouroussis 2005[45]	x						
Lippe 2005[42]	x						
Santos 2005[46]	x						
Scagliotti 2005[41]	x						
Buosi 2004[47]	x						
Winegarden 2004[48]	x						
Franciosi 2003[49]	x						
Monnet 2002[50]	x			*			
Monnet 1998[51]	x			x			
Phase I/II							
Faivre 2002[52]	x						
Monnet 2001[53]	x						
Phase I							
Bidoli 2004[54]	x						
Doroshow 2003[55]	x						
Kouroussis 2003[56]	x						
Kakolyris 2002[57]	x						
Other							
Santini 2001[58]	x						

* Non-cited reference.

Recommendations and supporting evidence. Only DRUGDEX lists an off-label indication for oxaliplatin for lung cancer. It bases this recommendation on inconclusive evidence for efficacy of strength "Category B" (based on data derived from RCTs that involved small numbers of patients or had significant methodological flaws). The recommendation was "Class III" (Not recommended). None of the other compendia list an off-label indication for this agent-disease combination.

Summary. Listings of oxaliplatin for lung cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Only DRUGDEX discusses oxaliplatin for treatment of lung cancer.
- *Specificity of clinical information:* DRUGDEX lists the indication for stage IV (metastatic) NSCLC. It gives specific dosing information for monotherapy based on two cited studies. DRUGDEX describes specific data on response rate as reported in one referenced study.
- *Evidence rating:* DRUGDEX provides an explicit evidence rating for the off-label indication of oxaliplatin for lung cancer. It rates the evidence as inconclusive, placing the strength of evidence in its second tier. Two studies are cited.

- *Recommendation statements:* DRUGDEX uses the evidence rating of Class III or "Not recommended" for the off-label indication of oxaliplatin for NSCLC.
- *Toxicity:* Toxicities related to oxaliplatin are reported in all of the compendia, but none notes toxicities specifically in patients with NSCLC.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it does not include lung cancer as an off-label indication for oxaliplatin. There is no published Phase III study of oxaliplatin in lung cancer; thus the compendium adheres to its stated methodology, which emphasizes well-designed, controlled, published studies.
- USP-DI specifies that it includes off-label indications, but it does not include lung cancer as an off-label indication for oxaliplatin. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff. No Phase III or IV studies were identified in the EPC review. The last update was 9/22/05, but 2004 and earlier data are not cited.
- DRUGDEX specifies that it includes off-label indications, and it does include lung cancer as an off-label indication for oxaliplatin. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites only one of the 19 studies identified in the EPC review. The single cited reference is consistent with the monotherapy indication listed; however, a second study included in the reference list but not cited describes combined treatment with vinorelbine. The date of the last update was not reported, but 2005 and earlier data are not cited.
- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it does not include lung cancer as an off-label indication for oxaliplatin. It emphasizes Phase II, III, and IV studies with over 30 subjects, but does not cite the seven clinical trials identified in the EPC review that meet these criteria. The date of the last update is not stated, but 2005 and earlier data are not cited.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is not an off-label indication for oxaliplatin in lung cancer as per the guideline. The last update was 3/4/05, but no prior data are cited.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it does not include lung cancer as an off-label indication for oxaliplatin. It emphasizes prospective trials, but does not cite any of the 12 prospective Phase II studies identified in the EPC review. The last update was 7/13/05; published studies available prior to that date are not cited.

Irinotecan (Camptosar®) for Breast Cancer

Irinotecan is an intravenous chemotherapeutic agent. It is a derivative of camptothecin, a cytotoxic plant alkaloid isolated from the Chinese tree *Camptotheca acuminata*. Irinotecan is a potent anticancer drug with activity in a broad range of experimental tumor models. Irinotecan and its metabolite SN-38 work by inhibiting topoisomerase I, a cellular enzyme involved in maintaining the topographic structure of DNA during translation, transcription, and mitosis. By binding with the topoisomerase I-DNA complex, irinotecan or SN-38 prevents the single-strand DNA breaks usually created by this complex. This activity is not in itself cytotoxic, and ongoing DNA synthesis is required to cause lethal cellular damage. Irreversible DNA damage occurs when a DNA replication fork encounters the irinotecan or SN-38/topoisomerase I complexes resulting in double-strand DNA breaks.

Irinotecan is FDA approved for the treatment of metastatic colorectal cancer that has recurred or progressed after therapy with 5-FU and as part of a first-line treatment regimen containing 5-FU and leucovorin for metastatic colorectal cancer. It has also been evaluated for off-label use in breast cancer.

Systematic Review by EPC

A total of 151 articles and abstracts were identified through the EPC literature search. Of these, 10 met the EPC inclusion criteria.

Table 6a describes the study types of the included studies and the outcomes reported. Appendix B (Evidence Table 5) reports details from each of the 10 studies. The literature review identified nine prospective clinical trials, of which five were Phase II and four were Phase I, involving a total of 324 subjects. An additional 20 subjects were included in a retrospective review identifying activity of this agent in this setting.

Table 6a: Study types and outcomes reported – irinotecan for breast cancer

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	10	344	2001-5	8	4	-	7	10
Phase III	-	-	-	-	-	-	-	-
Phase II	5 (50%)	293 (85%)	2003-5	5	3	-	4	5
Phase I	4[a] (40%)	31 (9%)	2004-5	2	-	-	2	4
Other	1 (10%)	20 (6%)	2001	1	1	-	1	1
No. of above published as abstracts	5 (50%)	106 (31%)	2004-5	3	-	-	2	5

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.
[a] Three studies of mixed advanced solid tumor populations.

Peer-reviewed Phase III trials. No Phase III studies were identified.

Peer-reviewed Phase II trials. Of the five Phase II trials, two were randomized – one published by Perez et al in full-text form[59] and one presented by Vukelja et al. at ASCO in

2005.[60] The Perez study evaluated irinotecan monotherapy at 100 mg/m^2 *vs* 240 mg/m^2 in patients with previously treated metastatic breast cancer. Activity was nearly equal between these two doses. The Vukelja study evaluated irinotecan monotherapy at 60 mg/m^2 *vs* 30 mg/m^2 in patients with previously treated advanced breast cancer. The higher dose was somewhat more efficacious.

The other three Phase II studies were non-randomized. Two were published in full-text form.[61,62] Doses ranged from 100 to 300 mg/m^2, and co-interventions were docetaxel and gemcitabine. All studies were in patients with previously treated advanced breast cancer.

Peer-reviewed Phase I and other studies. The five other studies evaluated irinotecan with a variety of co-interventions and doses. Complete information was not always provided, and populations were not necessarily limited to breast cancer. These studies predominantly supported the progression to Phase II trials.

Compendia Listings

Treatment indication and toxicities. Table 6b summarizes the compendia's discussions of the off-label use of irinotecan for treatment of breast cancer. Only DRUGDEX explicitly stated whether there was an off-label indication for the drug in the setting of this cancer. DRUGDEX stated that the evidence was inconclusive and that the recommendation was "level IIb." All other compendia, regardless of whether they discussed an off-label indication for breast cancer or not, discussed toxicities, including severity and frequency of adverse effects, and which organs have been reported to be affected. None discussed irinotecan-related toxicities specifically among patients being treated for breast cancer.

Table 6b: Summary of compendia listings – irinotecan for breast cancer

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
Off-label indication explicitly stated	No	No	Yes (Irinotecan hydrochloride)	No	No	No
Sub-category of indication (accepted or acceptance not established)	-	-	Efficacy: Adult, Evidence is inconclusive Recommendation: Adult, Class IIb * Strength of Evidence: Adult, Category C**	-	-	-
Stage of cancers	-	-	Advanced	-	-	-
Method of treatment (first line or other)	-	-	Other	-	-	-
Routes of administration	-	-	NR	-	-	-
Uses of the agent (monotherapy or combination)	-	-	NR	-	-	-
Comparator discussed (placebo, standard treatment, other agents)	-	-	NR	-	-	-
Outcomes mentioned for the off-label use (survival, tumor response, other)	-	-	Response rate	-	-	-
Toxicity reporting	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: No By organ: Yes Frequency: No	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes/ By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes
Dose indicated for the off-label use	-	-	No	-	-	-
Number of evidence citations	-	-	2	-	-	-
Range of years of citations	-	-	1994-1997	-	-	-
Sources of evidence (abstracts/published articles)	-	-	Journal	-	-	-
Number of abstracts cited [years]	-	-		-	-	-
Number of published articles cited [years]	-	-	2 [1994-1997]	-	-	-
Date of last update	1/10/2006	10/28/2004	NR	NR	12/05/2005	1/30/2006

*Recommended in some cases. The given test or treatment is not generally considered to be useful. It may be indicated in some, but not most, cases.

**Based on data derived from expert opinion or consensus, case reports or case series.

Studies cited in compendia versus studies identified in EPC review. Only DRUGDEX provided any references (Table 6b); two references were cited, published in 1994 and 1997. Neither reference met the EPC criteria for inclusion, as both were narrative reviews. Further, more recent updates were identified by the EPC search. A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 6c.

Table 6c: Articles cited by compendia vs. articles identified by EPC – irinotecan for breast cancer

Reference	EPC	AHFS-DI	USP-DI	DRUGDEX	F & C	NCCN	Clin Pharm
Reviewed by compendia:	-	No	No	Yes	No	No	No
Phase III							
(none)							
Phase II							
Frasci 2005[62]	x						
Moulder 2005[63]	x						
Vukelja 2005[60]	x						
Perez 2004[59]	x						
Agelaki 2003[61]	x						
Phase I/II							
(none)							
Phase I							
Gold 2005[64]	x						
Faivre 2004[65]	x						
Frasci 2004[66]	x						
Verscharaegen 2004[67]	x						
Other							
Shigeoka 2001[68]	x						
Rothenberg, 1997[69]				x*			
Burris, 1994[70]				x*			

*Did not meet EPC inclusion criteria because narrative review.

Recommendations and supporting evidence. DRUGDEX states that there is inconclusive evidence for a clear recommendation of irinotecan for breast cancer, indicating a recommendation of level IIb, evidence category C. Its cited references were narrative reviews from 1994 and 1997, much earlier than the currently available Phase II data. DRUGDEX does not specify whether irinotecan should be used as monotherapy or in combination; advanced breast cancer is the specified setting.

Summary. Listings of irinotecan for breast cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Only DRUGDEX discusses irinotecan for treatment of breast cancer.
- *Specificity of clinical information:* DRUGDEX lists the indication for advanced breast cancer. It does not give specific dosing information, citing two review articles. DRUGDEX mentions response rate, but does not cite specific data.
- *Evidence rating:* DRUGDEX provides an explicit evidence rating for the off-label indication of irinotecan for breast cancer. It rates the evidence as inconclusive, placing the strength of evidence in its lowest tier, corresponding to data derived from expert opinion or consensus, case reports, or case series. Two references are cited, both review articles.
- *Recommendation statements:* DRUGDEX uses the evidence rating of Class IIb, or "Recommended in some cases … not generally considered to be useful … may be

indicated in some, but not most cases."

- *Toxicity:* Toxicities related to irinotecan are reported in all of the compendia, but none notes toxicities specifically in patients with breast cancer.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it does not include breast cancer as an off-label indication for irinotecan. There is no published Phase III study of irinotecan in breast cancer; thus the compendium adheres to its stated methodology, which emphasizes well-designed, controlled, published studies.
- USP-DI specifies that it includes off-label indications, but it does not include breast cancer as an off-label indication for irinotecan. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff; no Phase III or IV studies were identified in the EPC review. The last update was 10/28/04; no relevant data would have been identified during later searches.
- DRUGDEX specifies that it includes off-label indications, and it does include breast cancer as an off-label indication for irinotecan. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites only two old narrative reviews and does not cite any data after 1997. The date of the last update was not reported, but 2005 data are not cited.
- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it does not include breast cancer as an off-label indication for irinotecan. It emphasizes Phase II, III, and IV studies with over 30 subjects, but does not cite the four clinical trials identified in the EPC review that meet these criteria. The date of the last update is not stated, but 2005 data are not cited.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is not an off-label indication for irinotecan in breast cancer as per the guideline. The last update was 12/5/05, but 2005 data are not cited.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it does not include breast cancer as an off-label indication for irinotecan. It emphasizes prospective trials, but does not cite the nine prospective studies identified in the EPC review. The last update was 1/30/06, but 2005 data are not cited.

Docetaxel (Taxotere®) for Esophageal Cancer

Docetaxel is a semisynthetic antimicrotubule chemotherapy agent. It was isolated in 1986 as a result of the National Cancer Institute (NCI) screening program for natural cytotoxic products. Docetaxel promotes the assembly of microtubules and stabilizes their formation by inhibiting depolymerization. These stable microtubules are non-functional, preventing cell division.

Docetaxel is similar to paclitaxel in structure, mechanism of action, and spectrum of antitumor activity. Non-hematologic toxicities differ between docetaxel and paclitaxel; fluid retention and skin lesions are more severe with docetaxel. The efficacy for docetaxel has been explored with myriad solid tumors including breast, colorectal, head and neck, gastrointestinal (GI), lung, and ovarian cancers. It is effective alone or in combination with other agents.

Docetaxel is FDA approved (1) for the treatment of refractory, locally advanced or metastatic breast cancer; (2) as an adjuvant agent (in combination with doxorubicin and cyclophosphamide) in breast cancer patients with lymph node positive disease; (3) for the treatment of advanced or metastatic NSCLC after progression despite platinum-containing chemotherapy; and (4) for the treatment of metastatic, hormone-refractory prostate cancer. It has also been evaluated for off-label use in esophageal cancer.

Systematic Review by EPC

A total of 132 articles and abstracts were identified through the EPC literature search. Of these, 23 met the EPC inclusion criteria.

Table 7a describes the study types of the included studies and the outcomes reported. Appendix B (Evidence Table 6) reports details from each of the 23 studies. The literature review identified 21 prospective clinical trials, of which 13 were Phase II, six Phase I/II, and two Phase I. A total of 721 subjects were involved in the prospective clinical trials.

Table 7a: Study types and outcomes reported – docetaxel for esophageal cancer

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	23	1026	1996-2005	16	11	-	19	20
Phase II	13 (57%)	521 (51%)	1996-2005	11	9	-	11	12
Phase I/II	6 (26%)	163 (16%)	2004-5	4	-	-	6	6
Phase I	2 (9%)	37 (4%)	1998-2004	-	-	-	1	1
Other	2 (9%)	305 (30%)	2000-3	1	2	-	1	1

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.

Peer-reviewed Phase II trials. There were 13 peer-reviewed Phase II trials. Only one was randomized. This was a study of docetaxel plus cisplatin *vs* the same regimen plus 5-FU. Doses of docetaxel used in the Phase II studies ranged from 25 to 100 mg/m^2, except in the neoadjuvant setting (two studies) where doses were 10 to 35 mg/m^2. Four studies evaluated docetaxel as monotherapy. Co-interventions included radiotherapy, vinorelbine, cisplatin, 5-FU, and irinotecan. Patient populations included all stages of disease and treatment settings (first line, post-first line, heavily pretreated) although more studies included patients with advanced disease. All trials included a statement supporting the need for further study of docetaxel in esophageal cancer, although some also included a statement recommending close attention to the toxicities of some of the various docetaxel combinations.

One important limitation of this literature was that the studies often included patients with gastric or gastroesophageal cancer. Often there was not a clear distinction between esophageal,

gastric, and gastroesophageal cancer, consistent with the occasional clinical difficulties with distinguishing these. At least five of the 13 Phase II trials included patients in all three groups.

Compendia Listings

Treatment indication and toxicities. Table 7b summarizes the compendia's discussions of the off-label use of docetaxel for treatment of esophageal cancer. Four of the six compendia had an off-label listing of docetaxel in esophageal cancer. USP-DI characterized this as "Accepted," whereas DRUGDEX, Facts & Comparisons, and NCCN were less emphatic. All the compendia, regardless of whether they discussed an off-label indication for esophageal cancer or not, discussed toxicities, including severity and frequency of adverse effects, and which organs have been reported to be affected. None discussed docetaxel-related toxicities specifically among patients being treated for esophageal cancer.

Table 7b: Summary of compendia listings – docetaxel for esophageal cancer

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
Off-label indication explicitly stated	No	Yes	Yes	Yes	Yes	No
Sub-category of indication (accepted or acceptance not established)	-	Accepted	Efficacy: Adult, Evidence is inconclusive Recommendation: Adult, Class III Strength of Evidence: Adult, Category B	Unlabeled use	2A	-
Stage of cancers	-	Advanced and/or metastatic carcinomas, incl. adenocarcinomas and squamous cell carcinomas	Incurable adenocarcinoma of the esophagus	NR	Recurrent or metastatic disease	-
Method of treatment (first line or other)	-	NR	Other	NR	Other	-
Routes of administration	-	IV	IV	IV	IV	-
Uses of the agent (monotherapy or combination)	-	After failure of platinum-based therapy Monotherapy or combination (gemcitabine, cisplatin, 5-FU, leucovorin) and radiation therapy	Mono	NR	Combination	-
Comparator discussed (placebo, standard treatment, other agents)	-	NR	NR	NR	NR	-
Outcomes mentioned for the off-label use (survival, tumor response, other)	-	NR	Response rate, median survival time, 1-year survival rate, time to disease progression	NR	Response rate, morbidity	-

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
Toxicity reporting	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: No By organ: No Frequency: No	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: No Indication-specific: No Severity: No By organ: No Frequency: No	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes
Dose indicated for the off-label use	-	Combo: 60 to 85 mg/m2, by 1-hr infusion, every 21 to 28 d Mono: 100 mg/m2, by 1-hr infusion, every 21 d	75 mg/m^2 every 3 weeks for a maximum number of 8 cycles	NR	NR	-
Number of evidence citations	-	17	1 (+4)	3	3	-
Range of years of citations	-	1994-2000	2002	2002-2005	2002-2004	-
Sources of evidence (abstracts/published articles)	-	Journal; Abstracts; Other	Journal; Abstracts	Package insert, reference book, textbook	Journals, abstracts	-
Number of abstracts cited [years]	-	8 [2000]	4 [1996-2000]	0	2 [2002-2004]	-
Number of published articles cited [years]	-	8 [1994-2000]	1 [2002]	0	1 [2004]	-
Date of last update	1/10/2006	11/28/2005	NR	NR	1/13/05 (2/7/06]	11/15/2005

Studies cited in compendia versus studies identified in EPC review. USP-DI, DRUGDEX, Facts & Comparisons, and NCCN all provided references. These references were not necessarily specific to esophageal cancer, nor were they all peer-reviewed articles. USP-DI predominantly cited references to studies of gastric cancer patients to support the indication "gastric and esophageal cancer." Facts & Comparisons included three items, none of which was a peer-reviewed article. A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 7c.

Table 7c: Articles cited by compendia vs. articles identified by EPC – docetaxel for esophageal or gastric cancer

Reference	EPC	AHFS	USP-DI	DRUGDEX	F & C	NCCN	Clin Pharm	Notes
Reviewed by compendia:	-	No	Yes	Yes	Yes	Yes	No	-
Phase III								
(none)								
Phase II								
Ajani, 2005[71]	x							
Burtness, 2005[72]	x							
Kajiyama, 2005[73]	x							
Lorenzen, 2005[74]	x							
Lorenzen, 2005[75]	x							
Muro, 2004[76]	x					X		
Posey, 2004[77]	x							
Airoldi, 2003[78]	x							
Govindan, 2003[79]	x							
Lordick, 2003[80]	x							
Schull, 2003[81]	x							
Font, 2002[82]						x***		
Heath, 2002[83]	x			x				
Jatoi, 2002[84]	x							
Ridwelski 2001[85]				x*				
Ajani, 2000[86]			x**	@				Abstract
Eniu, 2000[87]			x*	@*				Abstract
Giuliani, 2000[88]			x*	@*				Abstract
Mauer, 2000[89]			x***	@				
Mavroudis, 2000[90]			x*	@*				
Thuss-Patience, 2000[91]			x*					
Einzig, 1996[92]	x		x	@				
Sulkes, 1994[93]			x*					
Phase I/II								
Pasini, 2005[94]	x							
Tsai, 2005[95]	x							
Yuki, 2005[96]	x							
Bubis, 2004[97]	x							
Enzinger, 2004[98]	x					X		
Roth, 2000[99]			x***					
Roth, 2000[100]	x		x**					
Mauer, 1998[101]	x		x					
Phase I								
Syed, 2005[102]	x							
Poole, 2000[103]			x***					
Puccio, 2000[104]			x***	@				Abstract
Ryan, 2000[105]			x[$]					
Vokes, 1998[106]	x		x					
Other								

Reference	EPC	AHFS	USP-DI	DRUGDEX	F & C	NCCN	Clin Pharm	Notes
Reviewed by compendia:	-	No	Yes	Yes	Yes	Yes	No	-
Esmaeli, 2003[107]	x							
Jani, 2000[108]	x							
Verweij, 1995[109]			x[#]					
Anonymous, 2001[110]			x[#]					
Package insert[111]					x[#,%]			
Textbook[112]					x[#]			
Database[113]					x[#]			

* Gastric cancer, not esophageal.
** Full-text version of article published and cited by EPC.
*** Abstract from prior to 2004 (did not meet EPC criteria).
[$] Unclear if any esophageal cancer patients are included.
[#] Does not meet EPC inclusion criteria because it is a review article or other non-peer reviewed item.
[@] Non-cited reference.
[%] Additional data from editor identified that there was an error in citation; more specific information provided indicating the textbook was the intended citation.

Recommendations and supporting evidence. USP-DI has 17 citations, only three of which met the EPC criteria. Five of these were for gastric cancer specifically and not esophageal cancer. The one DRUGDEX citation was a Phase II trial also identified by the EPC search; additional relevant references were listed in DRUGDEX but were not cited, including four relevant to esophageal cancer and four relevant to gastric cancer. Facts & Comparisons listed three citations, but none of these was peer-reviewed. Of the three NCCN citations, two were cited by the EPC and one was an abstract presented before 2004 and not published in full text since. None of the compendia cited the only randomized study identified by this review.

Summary. Listings of docetaxel for esophageal cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Four of the six compendia (USP-DI, DRUGDEX, Facts & Comparisons, and NCCN) discuss docetaxel for treatment of esophageal cancer.
- *Specificity of clinical information:* To describe the cancer indication, those compendia that discuss the off-label use of docetaxel in esophageal cancer describe various subgroups of patients. USP-DI uses "advanced and/or metastatic including adenocarcinomas and squamous cell carcinomas." DRUGDEX indications are limited to adenocarcinomas. Facts & Comparisons and NCCN are not specific regarding the cell type, although NCCN notes that nearly all evidence is from trials of patients with squamous cell carcinoma. While USP-DI includes mono- or combination-treatment, DRUGDEX lists only monotherapy, and NCCN lists only combination therapy, while Facts & Comparisons does not specify. DRUGDEX and NCCN describe the outcome of response rate, reporting some quantitative data from one study.
- *Evidence rating:* Only DRUGDEX and NCCN provide explicit evidence ratings for the off-label indication of docetaxel for esophageal cancer. DRUGDEX rates the evidence as inconclusive and in its second tier (B), while NCCN rates the evidence in its second tier ("lower" quality), but with uniform consensus. USP-DI includes an extensive list of references, but these are reported only as lists of the available evidence and are not explicitly rated. DRUGDEX and NCCN cite five and three studies, respectively, while Facts & Comparisons cites a textbook and other non-peer reviewed references.
- *Recommendation statements:* Three of the four compendia listing this off-label indication grade the recommendation. DRUGDEX rates it as class III ("Not

recommended") based on inconclusive evidence, while NCCN uses evidence rating 2A, indicating uniform consensus (in the corresponding NCCN guideline, which was updated in 12/20/05, the evidence for this indication is rated as category 3, indicating major disagreement that the indication is appropriate). USP-DI lists the off-label use under the "Accepted" category. Facts & Comparisons does not grade the off-label use of docetaxel in esophageal cancer.

- *Toxicity:* Toxicities related to docetaxel are reported in most of the compendia, but none notes toxicities specifically in patients with esophageal cancer.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it does not include esophageal cancer as an off-label indication for docetaxel. There is no published Phase III study of docetaxel in esophageal cancer; thus the compendium adheres to its stated methodology, which emphasizes well-designed, controlled, published studies.
- USP-DI specifies that it includes off-label indications, and it does include esophageal cancer as an off-label indication for docetaxel. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff. Seventeen citations are listed, of which eight are classified as Phase II; the rest are of lower phases. Only two of the cited Phase II studies met the EPC inclusion criteria. The last update was 1/28/05; the majority of citations identified by the EPC are prior to that date.
- DRUGDEX specifies that it includes off-label indications, and it does include esophageal cancer as an off-label indication for docetaxel. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites only one of the 23 studies identified in the EPC review (eight additional studies are listed in the references, but not cited). The date of the last update was not reported, but data published since 2002 are neither cited nor listed in references.
- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it includes esophageal cancer as an off-label indication for docetaxel. It emphasizes Phase II, III, and IV studies with over 30 subjects, but cites only non-peer-reviewed publications. The date of the last update is not stated, but 2005 data are not cited.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is an off-label indication for docetaxel in esophageal cancer as per the guideline. The last update was 1/13/05, and 2004 data are cited.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it does not include esophageal cancer as an off-label indication for docetaxel. It emphasizes prospective trials, but does not cite the prospective studies identified in the EPC review. The last update was 11/15/05, but earlier 2005 data are not cited.

Docetaxel (Taxotere®) for Gastric Cancer

As stated above, docetaxel is a semisynthetic antimicrotubule chemotherapy agent. It was isolated in 1986 as a result of the NCI screening program for natural cytotoxic products. Docetaxel promotes the assembly of microtubules and stabilizes their formation by inhibiting depolymerization. These stable microtubules are non-functional, preventing cell division. Docetaxel is similar to paclitaxel in structure, mechanism of action, and spectrum of antitumor activity. Non-hematologic toxicities differ between docetaxel and paclitaxel; fluid retention and skin lesions are more severe with docetaxel. The efficacy for docetaxel has been explored with myriad solid tumors including breast, colorectal, head and neck, GI, lung, and ovarian cancers. It is effective alone or in combination with other agents.

Docetaxel is FDA approved (1) for the treatment of refractory, locally advanced or metastatic breast cancer; (2) as an adjuvant agent (in combination with doxorubicin and cyclophosphamide) in breast cancer patients with lymph node positive disease; (3) for the treatment of advanced or metastatic NSCLC after progression despite platinum-containing chemotherapy; and (4) for the treatment of metastatic, hormone-refractory prostate cancer. It has also been evaluated for off-label use in gastric cancer.

Systematic Review by EPC

A total of 132 articles and abstracts were identified through the EPC literature search. Of these, 72 appeared to meet the EPC inclusion criteria.

Appendix B (Evidence Table 7) reports details from each of the 72 studies. Among these 72 articles or abstracts, there were several that presented the same data. We found it impossible to eliminate the duplicate data among the lower phase studies (Phase I and Phase II); therefore, we have limited this analysis to Phase III studies only, for which duplicate publication was not a problem. There were three Phase III studies.[114-116]

Peer-reviewed Phase III trials. The three Phase III studies evaluated docetaxel for gastric cancer, all in the advanced cancer setting. In the study by Fahlke,[115] docetaxel was combined with cisplatin and compared with 5-FU, leucovorin, and cisplatin. Preliminary safety results are available only for the first 162 of a planned 216 subjects. In a study by Elsaid,[114] docetaxel was combined with carboplatin and compared to epirubicin, cisplatin, and 5-FU. The docetaxel combination was superior in terms of response and survival. In the study by Moiseyenko,[116] docetaxel was combined with cisplatin and 5-FU and compared to cisplatin and 5-FU alone. Response rates were better and survival was longer when docetaxel was added.

Compendia Listings

Treatment indication and toxicities. Table 8 summarizes the compendia's discussions of the off-label use of docetaxel for treatment of gastric cancer. Five of the six compendia had an off-label listing of docetaxel in gastric cancer. USP-DI characterized this as "Accepted," whereas DRUGDEX, Facts & Comparisons, NCCN, and Clinical Pharmacology were less emphatic. All the compendia, regardless of whether they discussed an off-label indication for gastric cancer or not, discussed toxicities, including severity and frequency of adverse effects, and which organs have been reported to be affected. DRUGDEX and NCCN discussed docetaxel-related toxicities specifically among patients being treated for gastric cancer.

Table 8: Summary of compendia listings – docetaxel for gastric cancer

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
Off-label indication explicitly stated	No	Yes	Yes	Yes	Yes	Yes
Sub-category of indication (accepted or acceptance not established)		Accepted	Efficacy: Adult, Evidence favors efficacy Recommendation: Adult, Class IIb Strength of Evidence: Adult, Category B	Unlabeled indication	2A	Advanced
Stage of cancers		Advanced and/or metastatic, including adenocarcinomas and squamous cell carcinomas	Metastatic	NR	Unresectable locoregional disease Following a grossly margin positive resection (R2) in medically fit patients with locoregional disease (M0) Recurrent or metastatic disease	Advanced gastric cancer
Method of treatment (first line or other)		Other	NR	NR	First-line and other	First line and other
Routes of administration		IV	IV	IV	IV	IV
Uses of the agent (monotherapy or combination)		Monotherapy or in combination (gemcitabine, cisplatin, 5–FU, leucovorin) and radiation therapy	Combination (cisplatin)	NR	Combination	Monotherapy
Comparator discussed		NR	None	NR	Yes	NR
Outcomes mentioned for the off-label use (survival, tumor		NR	Survival Response Time to progression	NR	NR	Partial response, stable disease

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
response, other)						
Toxicity reporting	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: Yes Severity: Yes By organ: Ys Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: Yes Severity: Yes By organ: Yes Frequency: Yes	Overall: No Indication-specific: No Severity: No By organ: No Frequency: No
Dose indicated for the off-label use		Combo: 60 to 85 mg/m2, by 1-hr infusion, every 21 to 28 days Mono: 100 mg/m^2, by 1-hour infusion, every 21 days	75 mg/ m^2 and cisplatin 75 mg/m^2 every 3 weeks for 6 cycles	NR	Many regimens may be considered in the first-line setting No established second-line	Dosage regimen not established
Number of evidence citations		17	1 (+ 8)[a]	3	4	2
Range of years of citations		1994-2000	2001	2002-2005	1994-2000	2003
Sources of evidence (abstracts/published articles)		Journal; Abstracts; Other	Journals	Package insert, text books	Journals	Published articles
Number of abstracts cited [years]		8 [2000]	4 [2000]	0	0	0
Number of published articles cited [years]		8 [1994-2000]	5 [1996-2001]	0	4 [1994-2000]	2 [2003]
Date of last update	1/10/2006	11/28/2005	NR	NR	1/12/05 (1/11/06)	11/15/2005

[a] 1 article cited; 8 additional articles included in the reference list (4 esophageal cancer and 4 gastric cancer).

Studies cited in compendia versus studies identified in EPC review. Each of the five compendia listing a gastric cancer indication provided some references. These references were not necessarily specific to the gastric cancer indication, nor were all peer-reviewed articles. As noted above, we limited our analysis to the three Phase III trials, all of which were abstracts published in 2005.

Recommendations and supporting evidence. None of the compendia cited any of the three Phase III studies published in 2005, although one (Facts & Comparisons) included a 2005 citation. As noted above, we limited our analysis for this topic to the three Phase III trials.

Summary. Listings of docetaxel for gastric cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Five of the six compendia (all except AHFS-DI) discuss docetaxel for treatment of gastric cancer.
- *Specificity of clinical information:* To describe the cancer indication, those compendia that discuss the off-label use of docetaxel in gastric cancer use different ad hoc nomenclatures (e.g., USP-DI uses "advanced and/or metastatic," while DRUGDEX uses "metastatic" and Clinical Pharmacology uses "advanced"; NCCN describes the cancer indication in more specific terms that conform to standardized staging classification). Three compendia describe combination treatment (USP-DI, DRUGDEX, NCCN), while two list monotherapy (USP-DI, Clinical Pharmacology), including information about dosages; Facts & Comparisons does not describe use as mono- or combination-therapy. Only two compendia describe outcomes affected by treatment: DRUGDEX lists survival, response rate, and time to progression, while Clinical Pharmacology describes partial response and stable disease. No specific quantitative estimates of the magnitude of benefit are reported**.**
- *Evidence rating:* Only two compendia (DRUGDEX and NCCN) provide explicit evidence ratings for the off-label indication of docetaxel for gastric cancer. DRUGDEX describes the evidence as "favors efficacy" and rates it in the second tier. NCCN also places the evidence in its second tier. USP-DI includes the most extensive list of references with 17 citations, but these are reported only as lists of the available evidence. The other compendia cite between two and nine references.
- *Recommendation statements:* NCCN grades the off-label indication as 2A, indicating lower level evidence but uniform consensus about the appropriateness of the indication (in the corresponding NCCN guideline, which was updated in 1/11/06, the evidence for this indication is rated as category 3, indicating major disagreement that the indication is appropriate). DRUGDEX grades its recommendation as "Recommended in some cases" (Class IIb). USP-DI lists the off-label use under the "Accepted" category without further qualification. Facts & Comparisons and Clinical Pharmacology make no further mention on the off-label use of docetaxel in gastric cancer.
- *Toxicity:* Toxicities related to docetaxel are reported in most of the compendia, but only DRUGDEX and NCCN note toxicities specifically in patients with gastric cancer.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of

current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it does not include gastric cancer as an off-label indication for docetaxel. It emphasizes well-designed, controlled, published studies and – consistent with its policy not to include abstracts – does not cite any of the three Phase III studies identified in the EPC review.
- USP-DI specifies that it includes off-label indications, and it does include gastric cancer as an off-label indication for docetaxel. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff. Seventeen citations are listed, of which eight are classified as Phase II; the rest are of lower phases. The last update was 1/28/05, which was prior to the publication of the three Phase III studies identified by the EPC.
- DRUGDEX specifies that it includes off-label indications, and it does include gastric cancer as an off-label indication for docetaxel. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites only one of the studies identified in the EPC review (eight additional studies are included in the references but not cited). The date of the last update was not reported, but data published since 2002 are neither cited nor listed in references.
- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it includes gastric cancer as an off-label indication for docetaxel. It emphasizes Phase II, III, and IV studies with over 30 subjects, but cites only non-peer-reviewed publications. The date of the last update is not stated, but 2005 data are not cited.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is an off-label indication for docetaxel in gastric cancer as per the guideline. The last update was 1/11/06, but data published after 2000 are not cited, including data from the three Phase III studies published in 2005.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it includes gastric cancer as an off-label indication for docetaxel. It emphasizes prospective trials, but does not cite the Phase III studies identified in the EPC review. The date of the last update was 11/15/05, but no data after 2003 are cited.

Docetaxel (Taxotere®) for Ovarian Cancer

As stated above, docetaxel is a semisynthetic antimicrotubule chemotherapy agent. It was isolated in 1986 as a result of the NCI screening program for natural cytotoxic products. Docetaxel promotes the assembly of microtubules and stabilizes their formation by inhibiting depolymerization. These stable microtubules are non-functional, preventing cell division. Docetaxel is similar to paclitaxel in structure, mechanism of action, and spectrum of antitumor activity. Non-hematologic toxicities differ between docetaxel and paclitaxel; fluid retention and skin lesions are more severe with docetaxel. The efficacy for docetaxel has been explored with myriad solid tumors including breast, colorectal, head and neck, GI, lung, and ovarian cancers. It is effective alone or in combination with other agents.

Docetaxel is FDA approved (1) for the treatment of refractory, locally advanced or metastatic breast cancer; (2) as an adjuvant agent (in combination with doxorubicin and cyclophosphamide)

in breast cancer patients with lymph node positive disease; (3) for the treatment of advanced or metastatic NSCLC after progression despite platinum-containing chemotherapy; and (4) for the treatment of metastatic, hormone-refractory prostate cancer. It has also been evaluated for off-label use in ovarian cancer.

Systematic Review by EPC

A total of 143 articles and abstracts were identified through the EPC literature search. For the ovarian cancer topic, we abbreviated our inquiry, because the large number of citations was expected to exceed our capacity. Therefore, we eliminated several steps in our methodology and in our reporting for this topic: (1) we did not search abstracts presented at the 2004 or 2005 American Society of Clinical Oncology (ASCO) annual meeting; (2) we did not abstract each study into evidence tables; and (3) we do not summarize the results of individual trials by research phase below.

Of the 143 citations identified, 57 appeared to meet the EPC inclusion criteria. We evaluated the abstracts of these citations to classify them by study design. Of the 53 with abstracts, there were 28 prospective clinical trials, of which one was Phase III, 16 Phase II, one Phase I/II, and 10 Phase I.

Compendia Listings

Treatment indication and toxicities. Table 9a summarizes the compendia's discussions of the off-label use of docetaxel for treatment of ovarian cancer. Five of the six compendia had an off-label listing of docetaxel in ovarian cancer. USP-DI characterized this as "Accepted"; Facts & Comparisons and Clinical Pharmacology mentioned no qualifiers, while DRUGDEX and NCCN both qualified the indication. None discussed docetaxel-related toxicities specifically among patients being treated for ovarian cancer.

Table 9a: Summary of compendia listings – docetaxel for ovarian cancer

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
Off-label indication explicitly stated	No	Yes	Yes	Yes	Yes	Yes
Sub-category of indication (accepted or acceptance not established)		Accepted	Efficacy: Adult, Evidence is inconclusive Recommendation: Adult, Class IIb Strength of Evidence: Adult, Category B	Unlabeled use	2B (2A for recurrence)	NR
Stage of cancers		Ovarian carcinoma after prior platinum-based therapy has failed	Ovarian cancer, advanced, previously treated	NR	Bulky stage III/IV disease Incompletely staged (stage IA-IB, grade 2-3, stage IC and stage II to IV) patients with no suspected residual or resectable disease Pathologic stage IA-IB (grades 2-3) and stage IC (all grades) Stage II to IV disease with interval debulking Clinical relapse or recurrence	Advanced: previously treated patients
Method of treatment (first line or other)		Other	Other	NR	Primary/adjuvant + palliation	First line and other
Routes of administration		IV	IV	IV	IV	IV
Uses of the agent (monotherapy or combination)		Alone or in combination	Combination	NR	Alone or in combination	Monotherapy
Comparator discussed (placebo, standard treatment, other agents)		NR	NR	NR	Yes	NR
Outcomes mentioned for the off-label use (survival, tumor		NR	Partial responses, progression-free	NR	NR	Response rates, median

	AHFS-DI	USP-DI	DRUGDEX	Facts & Comparisons	NCCN	Clinical Pharmacology
response, other)			survival, survival			progression-free survival, and overall survival
Toxicity reporting	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Indication-specific: No Severity: No By organ: No Frequency: No	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: No Indication-specific: No Severity: No By organ: No Frequency: No	Overall: Yes Indication-specific: No Severity: Yes By organ: Yes Frequency: Yes
Dose indicated for the off-label use		100 mg/m^2 every 3 wks over 1-hr	100 mg/m^2 IV every 3 weeks	NR	60-75 mg/m^2 over 1 hour and carboplatin AUC 5-6 every 3 weeks	100 mg/m^2 IV over 1 hour every 3 weeks
Number of evidence citations		5	9 (+ 4)[a]	3	3	1
Range of years of citations		1994-1997	1992-1998	2002-2005	2004	1997
Sources of evidence (abstracts/published articles)		Journals; Abstracts Other	Journals	Package insert, textbook, reference book	Journal	Article
Number of abstracts cited [years]		2 [1994]	1 [1993]	0	0	0
Number of published articles cited [years]		2 [1994-1995]	8 [1992-1998]	0 [2002-2005]	3 [2003-2004]	1 [1997]
Date of last update	1/10/20006	11/28/2005	NR	NR	1/13/2006 (1/3/06)	11/15/2005

[a] Nine articles cited; four additional articles included in the reference list.

Studies cited in compendia versus studies identified in EPC review. Each of the compendia listing an indication of docetaxel for ovarian cancer provided references. A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 9b.

Table 9b: Articles cited by compendia vs. articles identified by EPC – docetaxel for ovarian cancer

Reference	EPC	AHFS-DI	USP-DI	DRUGDEX	F & C	NCCN	Clin Pharm	Notes
Reviewed by compendia:	-	No	Yes	Yes	Yes	Yes	Yes	-
Phase III								
Vasey, 2004[117]	x					x		
Markman, 2003[118]						x		Paclitaxel
Parmar, 2003[119]						x		Paclitaxel
Phase II								
Polyzos, 2005[120]	x							
Berkenblit, 2004[121]	x							
Dieras, 2004[122]	x							
Markman, 2004[123]	x							
Aravantinos 2003[124]	x							
Markman, 2003[125]	x							
Rose, 2003[126]	x							
Vorobiof, 2003[127]	x							
Laport, 2001[128]	x			@				
Markman, 2001[129]	x							
Katsumata, 2000[130]	x							
Vasey, 1999[131]	x							
Kavanagh, 1996[132]	x							
Kaye, 1995[133]	x							
Piccart, 1995[134]	x		x	x				
Aapro, 1994[135]			x*					Abstract
Fossella, 1994[136]				x				
Francis, 1994[137]	x		x	x				
McGuire, 1989[138]				@				
Phase I/II								
Pfisterer, 2004[139]	x							
Phase I								
Komiyama, 2005[140]	x							
Berkenblit, 2003[141]	x							
de Bree/Romanos 2003[142]	x							
de Bree/Rosing 2003[143]	x							
Morgan, 2003[144]	x							
Oishi, 2003[145]	x							
Terauchi, 2003[146]	x							
O'Neill, 2002[147]	x							
Vasey, 2001[148]	x							
Soulie, 1997[149]	x							
Tomiak, 1994[150]				x				
Huizing, 1993[151]				@				
Pazdur, 1992[152]				x				
Other								
Brown, 2005[153]	x							
Kuribayashi, 2005[154]	x							
Martino, 2005[155]	x							
Montero, 2005[156]	x							
Watanabe, 2005[157]	x							
Brown, 2004[158]	x							
Hsu, 2004[159]	x							
Esmaeli, 2003[107]	x							
Finsterer, 2003[160]	x							

Reference	EPC	AHFS-DI	USP-DI	DRUGDEX	F & C	NCCN	Clin Pharm	Notes
Reviewed by compendia:	-		Yes	Yes	Yes	Yes	Yes	-
Komiyama, 2003[161]	x							
McNally, 2003[162]	x							
Niwa, 2003[163]	x							
Aoki, 2002[164]	x							
Hirai, 2002[165]	x							
Jeyakumar, 2001[166]	x							
Kouroussis, 2000[167]	x							
Lister-Sharp, 2000[168]	x							
Verschraegen, 2000[169]	x							
Benjapibal, 1998[170]	x			x				
Eisenhauer, 1998[171]	x							
Balat, 1997[172]	x							
Behar, 1997[173]	x							
Kaye, 1997[174]	x						x	Review
Eisenhauer, 1996[175]	x							
Sweeten, 1995[176]	x							
Kavanagh, 1994[177]			x*	@				Abstract
Package insert[111]					x#,%			
Textbook[112]					x#			
Database[113]					x#			
Anonymous, 1993[178]				x*				Abstract
Pazdur, 1993[179]				x				Review
Rowinsky, 1992[180]				x				Review
No. of Abstracts	**0**		**2**	**1**				
Abstract Years								

* Abstract from prior to 2004 (did not meet EPC inclusion criteria).
# Does not meet EPC inclusion criteria because it is a review article or other non-peer reviewed item.
@ Non-cited reference.
% Additional data from editor identified that there was an error in citation; more specific information provided indicating the textbook was the intended citation.

Recommendations and supporting evidence. USP-DI has five citations, only three of which met the EPC criteria. Three were Phase II studies, and one was a document described as "Panel consensus on monograph draft of 5/22/97." One abstract was too old to be obtained on the ASCO web site, so we could not assess its design.

DRUGDEX cited nine citations including three Phase II studies, two Phase I studies, one abstract we could not obtain, and two reviews. Facts & Comparisons listed three citations, but none of these was peer-reviewed (textbook, reference database, and package insert). Of the three NCCN citations, all were Phase III trials; two of the trials were of paclitaxel, while one was a study of docetaxel. These references were cited in the NCCN guideline in a statement supporting the use of "taxanes" (docetaxel and paclitaxel). Clinical Pharmacology cited a review of Phase II trials.[174]

Summary. Listings of docetaxel for ovarian cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Five of the six compendia (all except AHFS-DI) discuss docetaxel for treatment of ovarian cancer.
- *Specificity of clinical information:* To describe the cancer indication, those compendia that discuss the off-label use of docetaxel in ovarian cancer use different ad hoc nomenclatures (e.g., USP-DI, DRUGDEX, and Clinical Pharmacology describe the indication as advanced ovarian cancer [or carcinoma]; NCCN provides more specific

indications that conform to a standardized staging classification). Facts & Comparisons does not describe the stage of disease for which treatment is indicated. Combination treatment is described in USP-DI, DRUGDEX, and NCCN, while USP-DI and Clinical Pharmacology list monotherapy; however, NCCN is the only compendium to list specific combination agents and dosages. DRUGDEX and Clinical Pharmacology describe outcomes of response rates, progression-free survival, and overall survival, but none quantify the effects of treatment.

- *Evidence rating:* Only two compendia (DRUGDEX and NCCN) provide explicit evidence ratings for the off-label indication of docetaxel for ovarian cancer. DRUGDEX describes the evidence as "inconclusive" and rates it in the second tier. NCCN also places the evidence in its second tier. Only NCCN cites recent Phase III studies; DRUGDEX and USP-DI cite older Phase II studies, while Facts & Comparisons and Clinical Pharmacology cite only review articles or textbooks.
- *Recommendation statements:* DRUGDEX and NCCN use an evidence rating for the off-label indication. DRUGDEX lists the indication as Class IIb, "Recommended in some cases," while NCCN endorses the indication based on non-uniform agreement with no major disagreement that the indication is appropriate, except for use in recurrent disease, where they note uniform consensus that the indication is appropriate. USP-DI lists the off-label use under the "Accepted" category. Facts & Comparisons and Clinical Pharmacology make no further qualification of the listing.
- *Toxicity:* Toxicities related to docetaxel are reported in most of the compendia, but none notes toxicities specifically in patients with ovarian cancer.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it does not include ovarian cancer as an off-label indication for docetaxel. It emphasizes well-designed, controlled, published studies, but does not cite any of the 19 published Phase II or III studies identified in the EPC review. The last update was 1/10/06, but 2005 and prior data, including three Phase III trials, are not cited.
- USP-DI specifies that it includes off-label indications, and it does include ovarian cancer as an off-label indication for docetaxel. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff. Five citations are listed, of which three are classified as Phase II; the Phase III trial identified in the EPC review is not cited. The last update was 11/28/05; all of the citations identified by the EPC are prior to this date.
- DRUGDEX specifies that it includes off-label indications, and it does include ovarian cancer as an off-label indication for docetaxel. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites nine citations, including Phase I and II trials, a case report, and two reviews. However, it does not cite the Phase III trial identified in the EPC review. The date of the last update was not reported, but 2005 data are not cited.

- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it includes ovarian cancer as an off-label indication for docetaxel. It emphasizes Phase II, III, and IV studies with over 30 subjects, but cites only non-peer-reviewed publications. The date of the last update is not stated, but the most recent study cited was from 1998.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is an off-label indication for docetaxel in ovarian cancer as per the guideline. The last update was 1/13/05, and 2004 data are cited. The listing cites Phase III trials exclusively; however, two of the three trials cited used paclitaxel rather than docetaxel. These were cited in a statement supporting "taxanes"; we interpreted this to be using paclitaxel studies as indirect evidence supporting use of docetaxel.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it includes ovarian cancer as an off-label indication for docetaxel. It emphasizes prospective trials, but cites only a 1997 review of Phase II prospective clinical trials.[174] The last update was 11/15/05; however, none of the Phase II trials published since the 1997 review are cited, nor is the 2004 Phase III trial identified in the EPC review.

Gemcitabine (Gemzar®) for Biliary Tract Cancer

Gemcitabine is a nucleoside analog with therapeutic indications for treatment of metastatic breast cancer (in combination with paclitaxel) after failure of prior anthracycline-containing adjuvant chemotherapy; treatment of locally advanced or metastatic NSCLC (in combination with cisplatin); and treatment of locally advanced or metastatic pancreatic cancer previously treated with 5- fluorouracil. Gemcitabine is also used off-label for treatment of various other cancers including biliary tract or gallbladder cancer.

Systematic Review by EPC

A total of 60 articles and abstracts were identified through the EPC literature search. Of these, 33 met the EPC inclusion criteria.

Table 10a describes the study types of the included studies and the outcomes reported. Appendix B (Evidence Table 8) reports details from each of the 29 articles and four abstracts. The literature includes 23 peer-reviewed Phase II trials (including one RCT and one non-randomized controlled trial) and one Phase I trial. There are no Phase III trials. The peer-reviewed studies included a total of 694 subjects with biliary tract or gallbladder cancer who received gemcitabine. All studies reported tumor response outcomes and adverse effects; almost all reported survival data. Only two case reports reported QoL data and only three reported data on symptom outcomes.

Table 10a: Study types and outcomes reported – gemcitabine for biliary tract cancer

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	29	694	1998-2005	29	25	2	3	28
Phase III	-	-	-	-	-	-	-	-
Phase II	23 (79%)	654 (94%)	1998-2005	23	22	-	2	23
Phase I	1 (3%)	3 (< 1%)	2000	1	-	-	-	1
Other[a]	5 (17%)	37 (5%)	1998-2004	5	3	2	1	4
Abstracts[b]	4	147	2004-5	4	3	-	-	4

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.
[a] Case report or retrospective review or unclear.
[b] Not considered further.

Peer-reviewed Phase III trials. No Phase III trials have been published.

Peer-reviewed Phase II trials. There were two comparative trials (one randomized) and 21 cohort trials that were peer-reviewed Phase II trials. Only the randomized trial compared gemcitabine (2000 mg/m^2 in combination with mitomycin C) to an alternative treatment (capecitabine and mitomycin C). The study concluded that gemcitabine was inferior to capecitabine for response rate, progression-free survival, and overall survival.[181] The study examined patients with ascertained non-resectable biliary tract cancer who had no prior palliative chemotherapy; the treatments were used as first line therapy. The non-randomized comparative trial compared gemcitabine monotherapy to gemcitabine and 5-FU.[182]

In the 23 trials that evaluated gemcitabine (including the non-randomized comparative trial), all of the patients had non-resectable and/or metastatic biliary tract cancer. Sixteen trials described patients who were either chemonaïve or for whom gemcitabine was first line therapy. Doses of gemcitabine used ranged from 800 to 2200 mg/m^2, although 14 studies used 1000 mg/m^2. Nine Phase II trials evaluated gemcitabine as monotherapy. The trials that used combination therapy included 5-FU, capecitabine, cisplatin, and leucovorin as combination agents. In 23 of 25 cohorts of patients, tumor response rates were reported; the highest complete response rate (13 percent) was found in a study of 30 patients.[183] Partial response rates ranged from 0 to 55 percent; stable disease ranged from 7 to 46 percent; and disease progression ranged from 0 to 65 percent. Median overall survival ranged from 4.6 to 15.4 months. Quality of life and symptom relief were rarely reported. All studies discussed adverse effects.

Compendia Listings

Treatment indication and toxicities. Table 10b summarizes the compendia's discussions of the off-label use of gemcitabine for treatment of biliary tract cancer. Only DRUGDEX, Facts & Comparisons and USP-DI explicitly stated an off-label indication for the agent. NCCN discussed the use of gemcitabine for biliary tract cancer, but did not explicitly state whether the agent is indicated for biliary tract cancer. NCCN did not report on toxicities due to gemcitabine. All the compendia, regardless of whether they discussed biliary tract cancer, discussed toxicities related to gemcitabine use in cancer patients; however, none discussed gemcitabine-related toxicities specifically among patients being treated for biliary tract cancer.

Table 10b: Summary of compendia listings – gemcitabine for biliary tract cancer

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Off-label indication explicitly stated	No	No	Yes	Yes	Unclear	Yes
Sub-category of indication (accepted or acceptance not established)	-	-	NR for this indication (available for only gallbladder cancer)	NR	NR	Accepted
Stage of cancers	-	-	"Biliary tract cancer"	"Biliary cancer"	"Cholangiocarcinoma and gallbladder cancer"	"Locally advanced, unresectable, or metastatic biliary tract and gallbladder"
Method of treatment (first line or other)	-	-	NR	NR	Other	NR
Routes of administration	-	-	Intravenous	Intravenous	Intravenous	Intravenous
Uses of the agent (monotherapy or combination)	-	-	NR	NR	Combination	NR
Comparator discussed (placebo, standard treatment, other agents)	-	-	No	No	No	No
Outcomes mentioned for the off-label use (survival, tumor response, other)	-	-	NR	NR	NR	NR
Toxicity reporting	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: No	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: No Cancer-specific: No Severity: By organ: Frequency:	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes
Dose indicated for the off-label use	-	-	No	No	No	No
Number of evidence citations	-	-	3 (+12) [a]	0	2	31
Range of years of citations	-	-	1998-2002		2001; 2004	1993-2002
Sources of evidence (abstracts/published	-	-	Abstracts Published articles		Published article Book update	Abstracts Published articles

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
articles)			Reviews			Reviews Package insert
Number of abstracts cited [years]	-	-	5 [2000-2001] (excluding one incorrect citation)		0	13 [1993-2001]
Number of published articles cited [years]	-	-	6 published articles [1999-2001] 3 Reviews [2000] 1 Reviewer consen sus ballot [2002]		1 published article [2001] 1 book update [2004]	16 published articles [1998-2001] 1 Review [2002] 1 package insert
Date of last update	12/8/2005	11/9/2005	2006	2005	2006	9/14/2005

[a] Three articles cited; 12 additional articles included in the reference list.

Studies cited in compendia versus studies identified in EPC review. Only DRUGDEX and USP-DI provided an extensive list of references, which included primary peer-reviewed articles, abstracts, review articles, and the package insert for gemcitabine. DRUGDEX included only studies that were published prior to 2002 even though their latest update was in 2006. However, only two references were cited in the text for the off-label indication and one other for toxicity; the remainder were not cited but were simply included in the bibliography. USP-DI included four of the five studies found by the EPC's evidence review that were published in 2001 or earlier (the apparent time range of the USP-DI review). Several publications that did not meet the EPC eligibility criteria were referenced, including package inserts, review articles, a book update, and non-English language publications. A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 10c.

Table 10c: Articles cited by compendia vs. articles identified by EPC – gemcitabine for biliary tract cancer

Reference	EPC	AHFS-DI	Clin Pharm	DRUGDEX	F & C	NCCN	USP-DI	Notes
Reviewed by compendia:	-	No	No	Yes	Yes	Yes	Yes	-
Phase III								
(none)								
Phase II								
Alberts, 2005[184]	x							
Cho, 2005[185]	x							
Gelibter, 2005[186]	x							
Knox, 2005[187]	x							
Park, 2005[188]	x							
Thongprasert, 2005[189]	x							
Andre, 2004[190]	x							
Doval, 2004[183]	x							
Eng, 2004[191]	x							
Hsu, 2004[192]	x							
Kornek, 2004[181]	x							
Tsavaris, 2004[193]	x							
Lin, 2003[194]	x							
Malik, 2003[195]	x							
Murad, 2003[196]	x							
Kuhn, 2002[197]	x							
Gallardo, 2001[198]	x							
Gebbia, 2001[182]	x			*			x	
Kubicka, 2001[199]	x			*		x	x	
Penz, 2001[200]	x			*			x	
Raderer, 1999[201]	x			*			x	Same
Valencak, 1999[202]	x			*			x	study
Mezger, 1998[203]	x			x			x	
Phase I/II								
(none)								
Phase I								
Eckel, 2002[204]							x	Mixed population
Zanon, 2000[205]	x						x	
Other								
Knox, 2004[206]	x							
Price, 2001[207]							x	Review
Bokemeyer, 2000[208]							x	German
Gallardo, 2000[209]							x	Spanish[a]
Teufel, 2000[210]	x						x	
Verderame, 2000[211]	x			*			x	
Castro, 1998[212]	x			x			x	

Reference	EPC	AHFS-DI	Clin Pharm	DRUGDEX	F & C	NCCN	USP-DI	Notes
Reviewed by compendia:	-	No	No	Yes	Yes	Yes	Yes	-
Gallardo, 1998[213]	x						x	
Hejna, 1998[214]				x			x	Review
No. of Abstracts	4			5			14 [b]	
Abstract Years	04-05			01-02			93-01	

[a] Reference incorrect in USP-DI.
[b] Several references were abstracts, but were not cited as such.
* Non-cited references.

Recommendations and supporting evidence. DRUGDEX notes that the recommended agent's use in biliary tract cancer does not imply that it has been approved for labeled use by FDA. No other discussion of biliary tract cancer is made.

Facts & Comparisons notes that gemcitabine has an "Unlabeled use" for biliary tract cancer. No other discussion of biliary tract cancer is made. The on-line compendium does not include references.

NCCN discusses gemcitabine in its section on hepatobiliary cancers. Gemcitabine is offered as an option for primary treatment of gallbladder cancer that is either metastatic or unresectable, and for primary treatment of symptomatic, unresectable, or metastatic intrahepatic or extrahepatic cholangiocarcinoma. NCCN grades both recommendations as category 2A: "There is uniform NCCN consensus, based on lower level evidence including clinical experience, that the recommendation is appropriate." However, only a single primary study specific to gemcitabine is referenced in the guideline.

USP-DI included biliary tract cancers in its list of cancers for which treatment is "Accepted." The compendium specifies that it be indicated for specific tumor stages, as noted in Table 10b. Regarding dose, the compendium states, "Because several doses and regimens using gemcitabine are showing activity, no individual dose/regimen is listed." No mention is made regarding whether gemcitabine is indicated for first line treatment or as monotherapy or in combination therapy. The effectiveness of the treatment is also not quantified. Notably, several of the references cited have errors regarding journal or page numbers.

Summary. Listings of gemcitabine for biliary tract cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Four of the six compendia (DRUGDEX, Facts & Comparisons, NCCN, and USP-DI) discuss gemcitabine for treatment of biliary tract cancer.
- *Specificity of clinical information:* To describe the cancer indication, those compendia that discuss the off-label use of gemcitabine in biliary tract cancer use different ad hoc nomenclatures (e.g., Facts & Comparisons uses "biliary cancer"; and USP-DI uses "locally advanced, unresectable, or metastatic biliary tract and gallbladder") instead of using a standardized classification (such as WHO staging of cancers). Only NCCN describes which combinations of treatments are indicated, and none of the compendia describes the doses. In addition, none of the compendia quantifies the effects of treatment with gemcitabine.
- *Evidence rating:* No compendium provides an explicit evidence rating for the off-label indication of gemcitabine for biliary tract cancer, although NCCN uses an overall evidence rating of "lower evidence, including clinical experience" in its section on hepatobiliary cancers. Only DRUGDEX and USP-DI include extensive references, but

these are reported only as lists of the available evidence.

- *Recommendation statements:* Only NCCN uses evidence rating for the off-label indication. It makes a weak recommendation, "options include," based on lower level evidence. USP-DI lists the off-label use under the "Accepted" category and makes a weak recommendation, "indicated." USP-DI also mentions the off-label use through passive discussion using cited references. DRUGDEX and Facts & Comparisons make no further mention on the off-label use of gemcitabine in biliary tract cancer.
- *Toxicity:* Toxicities related to gemcitabine are reported in most of the compendia, but none notes toxicities specifically in patients with biliary tract cancer.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI is silent about the off-label indication. It does not include biliary cancer as an off-label indication for gemcitabine. There is no published Phase III study of gemcitabine in biliary cancer, thus the compendium adheres to its stated methodology which emphasizes well-designed, controlled, published studies.
- USP-DI specifies that it includes off-label indications, and in its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff. It categorizes the off-label indication of gemcitabine for biliary tract cancer as "Accepted" despite a lack of Phase III studies, and cites several Phase II studies and reviews. It does not cite any of the post-2001 Phase II studies identified in the EPC review, although the date of the last update was 9/14/05.
- DRUGDEX specifies that it includes off-label indications, but it does not include biliary tract cancer as an off-label indication for gemcitabine. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites only studies published before 2001, although the last update was in 2006.
- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it includes biliary cancer as an off-label indication for gemcitabine. It emphasizes Phase II, III, and IV studies with over 30 subjects, but does not cite any of the Phase II studies identified in the EPC review. The last update was in 2005, but data from 1998-2005 are not cited.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is an off-label indication for gemcitabine in biliary cancer as per the guideline, although this is not explicitly stated. The last update was in 2006, but 2005 data are not cited.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it does not include biliary cancer as an off-label indication for gemcitabine. It emphasizes prospective trials, but does not cite any of the Phase I or II studies identified in the EPC review. The last update was on 11/09/05, but data from 1998-2005 are not cited.

Gemcitabine (Gemzar®) for Bladder Cancer

As stated above, gemcitabine is a nucleoside analog with therapeutic indications for treatment of metastatic breast cancer (in combination with paclitaxel) after failure of prior anthracycline-containing adjuvant chemotherapy; treatment of locally advanced or metastatic NSCLC (in combination with cisplatin); and treatment of locally advanced or metastatic pancreatic cancer previously treated with 5-FUl. Gemcitabine is also used off-label for treatment of various other cancers including advanced and/or metastatic bladder cancer.

Systematic Review by EPC

A total of 134 articles and abstracts were identified through the EPC literature search. Of these, 61 met the EPC inclusion criteria.

Table 11a describes the study types of the included studies and the outcomes reported. Appendix B (Evidence Table 9) reports details from each of the 46 articles and 15 abstracts. The literature includes one peer-reviewed Phase III article (RCT), 28 peer-reviewed Phase II trials (one RCT, one non-randomized comparative trial, and the remainder cohort studies), two Phase I/II trials, 12 Phase I trials, and three retrospective trials. The peer-reviewed studies included a total of 2484 subjects with bladder cancer who received gemcitabine. The majority of the studies reported tumor response outcomes, survival data, and adverse effects; only a handful reported data on QoL and symptom outcomes.

Table 11a: Study types and outcomes reported – gemcitabine for bladder cancer

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	46	2484	1994-2005	39	35	4	10	42
Phase III	1 (2%)	203 (8%)	2000	1	1	1	1	1
Phase II	28 (61%)	1034 (42%)	1997-2005	27	25	1	7	28
Phase I/II	2 (4%)	88 (4%)	2002-2004	1	2	-	-	1
Phase I	12 (26%)	293 (12%)	1994-2004	9	5	-	-	12
Other[a]	3 (7%)	866 (35%)	2002-5	1	2	2	2	
Abstracts[b]	15	597	2004-5	15	8	-	-	15

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.
[a] Case report or retrospective trials.
[b] Not considered further.

Peer-reviewed Phase III trials. There was one Phase III RCT[215] evaluating the use of gemcitabine chemotherapy for bladder cancer. This trial was published in 2000 and compared first line therapy of gemcitabine (1000 mg/m^2) and cisplatin combination regimen to standard treatment of MVAC. The study included patients with stage IV TCC, and concluded that both treatments had similar survival and tumor response rates. Gemcitabine was more tolerable, less

toxic, and safer than the MVAC regimen. The 5-year followup of the same study[216] reported similar long-term overall survival rates. The study advanced the role of gemcitabine as standard care in patients with locally advanced or metastatic TCC.

Peer-reviewed Phase II trials. There were two comparative Phase II trials. The first trial[217] used gemcitabine in combination regimens with carboplatin and showed improved outcomes. The other was a randomized Phase II trial[218] that used paclitaxel in combination with gemcitabine and cisplatin, and compared outcomes with the gemcitabine-cisplatin regimen. The study concluded that the addition of paclitaxel to the gemcitabine-cisplatin combination regimen increased toxicity among elderly patients 70 years and above.

There were 26 Phase II trials that evaluated gemcitabine use. The majority of the patients had advanced and/or metastatic bladder cancer. Nineteen of the trials described patients who were either chemonaïve or for whom gemcitabine was first line therapy. Doses of gemcitabine used ranged from 750 to 3000 mg/m^2; the majority of the trials used 1000 mg/m^2. Six trials evaluated gemcitabine as monotherapy. The combination therapy was used in 20 trials that included cisplatin, carboplatin, paclitaxel, docetaxel, vinorelbine, epirubicin, and epidoxorubicin. Tumor response was reported in 27 trials; the greatest complete response rate (32 percent) was found in a study of 49 patients that used 800 mg/m^2 of gemcitabine in combination with paclitaxel and carboplatin.[219] Partial response rates ranged from 9 to 47 percent; stable disease ranged from 9 to 42 percent, and disease progression ranged from 3 to 55 percent. The overall one-year survival rates in seven studies that reported this outcome ranged from 26 to 60 percent. Almost all studies reported median overall survival duration that ranged from 5 to 21 months. Quality of life was reported in one study, and seven studies reported symptom relief.

Peer-reviewed Phase I/II and I trials. There were two Phase I/II trials, and 12 Phase I trials that evaluated gemcitabine use. The majority of the patients had advanced and/or metastatic bladder cancer. Seven trials described patients who were either chemonaïve or for whom gemcitabine was first line therapy. Doses of gemcitabine used ranged from 10 to 2500 mg/m^2; six trials used doses higher than 1000 mg/m^2. Only three trials evaluated gemcitabine as monotherapy. The combination therapy was used in 11 trials that included cisplatin, carboplatin, oxaliplatin, paclitaxel, docetaxel, and ifosfamide. Tumor response was reported in 10 trials; the greatest complete response rate (28 percent) was found in a study of 41 patients that used 2500 mg/m^2 of gemcitabine in combination with paclitaxel.[220] Partial response rates were reported in three trials and ranged from 24 to 53 percent; stable disease was reported in one Phase I/II trial as 19 percent; and disease progression from the same trial was three percent. The overall 1-year survival rates in three studies that reported this outcome ranged from 65 to 100 percent. Virtually all studies reported median overall survival duration that ranged from 5 to 21 months. Quality of life was reported in one study, and no studies reported symptom relief.

Compendia Listings

Treatment indication and toxicities. Table 11b summarizes the compendia's discussions of the off-label use of gemcitabine for treatment of bladder cancer. All but one compendia explicitly stated bladder cancer as an off-label indication for the agent. NCCN discussed the use of gemcitabine for advanced and/or metastatic bladder cancer, but did not explicitly state whether the agent is indicated as an off-label use. NCCN did not report on toxicities due to gemcitabine. All the compendia discussed toxicities associated with gemcitabine chemotherapy, including severity of adverse effects, and which organs were affected. Only Clinical

Pharmacology discussed frequency of adverse effects; AHFS-DI, Clinical Pharmacology, and DRUGDEX reported gemcitabine-related toxicities specifically among patients being treated for advanced and/or metastatic bladder cancer. AHFS-DI and Facts & Comparisons did not explicitly discuss the dose indicated for the off-label use of gemcitabine for bladder cancer.

Table 11b: Summary of compendia listings – gemcitabine for bladder cancer

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Off-label indication explicitly stated	Yes	Yes	Yes	Yes	Unclear	Yes
Sub-category of indication (accepted or acceptance not established)	NR	NR	Efficacy: Adult, Evidence favors efficacy Recommendation: Adult, Class IIb Strength of Evidence: Adult, Category B	NR	Category 2A – lower level evidence and uniform consensus that the recommendation is appropriate "Considered" for gemcitabine + cisplatin "Investigational" for gemcitabine + paclitaxel	Accepted
Stage of cancers	"Advanced or metastatic cancer"	"Locally advanced or metastatic bladder cancer"	"Transitional cell carcinoma of bladder"	NR	"Locally advanced disease or limited metastatic recurrence"	"Metastatic bladder (urothelial) cancer"
Method of treatment (first line or other)	Other	NR	NR	NR	First line for gemcitabine + cisplatin Other for gemcitabine + paclitaxel	NR
Routes of administration	Intravenous	NR	Intravenous	IV	Intravenous	Intravenous
Uses of the agent (monotherapy or combination)	Monotherapy and combination	Combination	Combination	NR	Combination	NR
Comparator discussed (placebo, standard treatment, other agents)	Yes Standard treatment	Yes Standard treatment	Yes Standard treatment	No	Yes	No
Outcomes mentioned for the off-label use (survival, tumor response, adverse effects)	Median time to progressive disease Complete response rate Partial response	Survival time Time to disease progression Time to treatment failure Response ratio	Overall Survival Time to disease progression Time to treatment failure Response ratio	NR	Survival response for gemcitabine + cisplatin Relapse or Noncomplete response as an	Complete response Partial response

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
	rate Symptomatic improvement	compared with standard treatment	compared with standard treatment		indication for gemcitabine + paclitaxel	
Toxicity of the agents	Overall: Yes Cancer-specific: Yes Severity: Yes By organ: Yes Frequency: No	Overall: Yes Cancer-specific: Yes Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: Yes Severity: Yes By organ: Yes Frequency: No	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: No	Overall: No Cancer-specific: No Severity: By organ: Frequency:	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: No
Dose indicated for the off-label use (yes/no)	Not explicitly	Yes	Yes	No	Yes for gemcitabine + cisplatin No for gemcitabine + paclitaxel	Yes
Number of evidence citations	8	1	2 (+1)[a]	0	2 for gemcitabine + cisplatin 0 for gemcitabine + paclitaxel	6
Range of years of citations	1994-2000	2000	1994-2000		2000	1994-1998
Sources of evidence (abstracts/published articles)	Abstracts Published journal articles Reviews	Published journal article	Abstracts Published journal articles		Published journal articles	Abstracts Published journal articles Panel responses Package insert
Number of abstracts cited [years]	1 [1996]	0	1 [1995]		0	1 [1995]
Number of published articles cited [years]	5 journal articles [1994-2000] 2 reviews [2000; 1 NR]	1 journal article for Gemcitabine + cisplatin [2000]	1 journal article for Gemcitabine + cisplatin [2000] 1 Phase I trial [1994]		2 journal articles for gemcitabine + cisplatin [2000]	3 journal articles [1994-1997] 1 panel responses to ballot [1998] 1 package insert Lily-U.S. [1996; 1998]
Date of last update	12/8/2005	11/9/2005	2006	2005	2006	9/14/2005

[a] One abstract and one article cited; one additional article included in the reference list.

Studies cited in compendia versus studies identified in EPC review. Among the compendia that reported off-label use of gemcitabine for treatment of advanced and/or metastatic bladder cancer, only one (Facts & Comparisons) did not provide any reference lists. The other five provided up to eight references, which included primary peer-reviewed articles, abstracts, review articles, and the package insert for gemcitabine. For the peer-reviewed articles, AHFS-DI included five, Clinical Pharmacology included one, DRUGDEX included two, NCCN included one, and USP-DI included three of the 43 studies found by the EPC's evidence review that were published between 1994 and 2004. There was only one[215] common Phase III trial referenced across the four compendia – AHFS-DI, DRUGDEX, NCCN, and Clinical Pharmacology. Several publications that did not meet the EPC eligibility criteria were referenced, including package inserts and review articles. A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 11c.

Table 11c: Articles cited by compendia vs. articles identified by EPC – gemcitabine for bladder cancer

Reference	EPC	AHFS-DI	Clin Pharm	DRUGDEX	F & C	NCCN	USP-DI	Notes
Reviewed by compendia:		Yes	Yes	Yes	Yes	Yes	Yes	
Phase III								
von der Maase, 2005[216]	x							
von der Maase, 2000[215]	x	x	x	x		x		
Phase II								
Ardavanis, 2005[221]	x							
Artz, 2005[222]	x							
Hainsworth, 2005[223]	x							
Li, 2005[224]	x							
Lorusso, 2005[218]	x							
Srinivas, 2005[225]	x							
Castagneto, 2004[226]	x							
Hoshi, 2004[217]	x							
Kaufman, 2004[227]	x							
Linardou, 2004[228]	x							
Gitlitz, 2003[229]	x							
Mallick, 2003[230]	x							
Turkolmez, 2003[231]	x							
Albers, 2002[232]	x							
Neri, 2002[233]	x							
Pectasides, 2002[234]	x							
Ricci, 2002[235]	x							
Hussain, 2001[219]	x							
Meluch, 2001[236]	x							
Carles, 2000[237]	x							
Delord, 2000[238]	x							
Khaled, 2000[239]	x							
Lorusso, 2000[240]	x					x		
Moore, 1999[241]	x							
Lorusso, 1998[242]	x							
Moore, 1997[243]	x	x					x	
Stadler, 1997[244]	x	x					x	
Phase I/II								
Hussain, 2004[245]	x							
Bellmunt, 2002[246]	x							
Phase I								
Sangar, 2005[247]	x							
Herman, 2004[248]	x							
Kent, 2004[249]	x							
Caffo, 2003[250]	x							
Culine, 2003[251]	x							

Reference	EPC	AHFS-DI	Clin Pharm	DRUGDEX	F & C	NCCN	USP-DI	Notes
Reviewed by compendia:		Yes	Yes	Yes	Yes	Yes	Yes	
DiPaola, 2003[252]	x							
Meliani, 2003[253]	x							
Bellmunt, 2001[254]	x							
Bhargava, 2001[255]	x							
Millikan, 2001[256]	x							
Sternberg, 2001[220]	x							
Pollera, 1994[257]	x	x		*			x	
Other								
Bamias, 2005[258]	x							
Roychowdhury, 2003[259]	x							
Stadler, 2002[260]	x							
Anonymous, 2000[261]		x						Review
Roth, 1996[262]		x						Review
No. of Abstracts	15	1	0	1	0	0	1	
Abstract Years	04-05	96		95			95	

* Non-cited reference.

Recommendations and supporting evidence. AHFS-DI states that "gemcitabine is an active agent that is used alone or in combination therapy for the treatment of advanced or metastatic bladder cancer" among its list of off-label uses in cancer. No explicit mention is made regarding the indicated dose and line of treatment. The effectiveness of the treatment is discussed and compared with standard treatment for the cancer. The compendium does not explicitly make any recommendation on the off-label use of gemcitabine in bladder cancer.

Clinical Pharmacology describes one Phase III trial that used gemcitabine for an off-label and post-first line use in combination regimen "for the treatment of locally advanced or metastatic bladder cancer." The dose and effectiveness of the treatment used data from the cited study.

DRUGDEX reports combination therapy use of gemcitabine in "transitional cell carcinoma of bladder" and discusses one Phase III trial to support the indicated off-label use. The compendium indicates gemcitabine use as combination therapy; no mention is made regarding whether gemcitabine is indicated for first line or post-first line treatment. It specifies that the "evidence favors efficacy" for the indicated use.

Facts & Comparisons notes that gemcitabine has an "unlabeled use" for "bladder cancer." No other discussion of gemcitabine use in bladder cancer is made. The on-line compendium does not include references.

NCCN discusses gemcitabine in its section on bladder cancers. The combination therapy of gemcitabine-cisplatin is "considered" as "standard first line choice" for most patients with recurrent metastatic or locally advanced bladder cancer, and the combination therapy of gemcitabine-paclitaxel is "considered" as "investigational." It grades both recommendations as category 2A: "There is uniform NCCN consensus, based on lower level evidence including clinical experience, that the recommendation is appropriate." The compendium "advises" gemcitabine for salvage therapy and for use as monotherapy among patients who do not tolerate a cisplatin-based regimen. Regarding dose, the compendium mentions 1000 mg/m^2 once a week for 4 weeks. The effectiveness of the treatment is discussed for both combination regimens and two primary studies specific to gemcitabine use are cited.

USP-DI includes "metastatic bladder (urothelial) carcinoma" among its list of cancers for which the modality of treatment with gemcitabine is "accepted." Regarding dose, the

compendium recommends 1000 to 1200 mg/m^2 once a week for 3 weeks. The compendium does not indicate gemcitabine use as monotherapy or combination therapy; no mention is made regarding whether gemcitabine is indicated for first line or post-first line treatment. The effectiveness of the treatment is discussed for tumor response rates. No evidence rating for the indicated use is reported, whereas the rating was used in ovarian cancer.

Summary. Listings of gemcitabine for bladder cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* All six compendia discuss gemcitabine for treatment of advanced and/or metastatic bladder cancer.
- *Specificity of clinical information:* To describe the cancer indication, the compendia use different ad hoc nomenclatures (e.g., AHFS-DI uses "advanced or metastatic bladder cancer," and NCCN uses "locally advanced disease or limited metastatic recurrence") instead of using a standardized classification (such as WHO staging of cancers). Only NCCN describes explicitly which combinations and modalities of treatments are indicated. Only three of the compendia (DRUGDEX, NCCN, and USP-DI) describe doses. In addition, the quantification of the effectiveness of treatment with gemcitabine varied across the compendia.
- *Evidence rating:* Only two compendia (DRUGDEX and NCCN) provide explicit evidence ratings for the off-label use of gemcitabine for bladder cancer; NCCN, however, uses an overall evidence rating as "lower level evidence, including clinical experience" in its section on bladder cancers. No compendium cites trials published after 2000, and only four (AHFS-DI, Clinical Pharmacology, DRUGDEX, and NCCN) cite the Phase III trial published in 2000.
- *Recommendation statement:* DRUGDEX makes a recommendation rating of class IIb, "treatment may be useful and is indicated in some, but not most cases," based on the strength of evidence category B, for the off-label use. NCCN makes a weak recommendation – i.e., "consider" and "advise" – based on lower level evidence. AHFS-DI, USP-DI, and Clinical Pharmacology mention the off-label use through passive discussion using cited references. Only Facts & Comparisons does not describe details regarding the off-label use of gemcitabine in bladder cancer.
- *Toxicity:* Toxicities related to gemcitabine are reported in most of the compendia, and AHFS-DI, Clinical Pharmacology, and DRUGDEX note toxicities specifically in patients with bladder cancer.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it includes bladder cancer as an off-label indication for gemcitabine. It emphasizes well-designed, controlled, published studies, but does not cite the published Phase III study identified in the EPC review. The last update was 12/8/05, but 2005 data, including the Phase III study, are not cited.
- USP-DI specifies that it includes off-label indications, and it does include bladder cancer

as an off-label indication for gemcitabine. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff; it does not cite the Phase III study identified in the EPC review. The last update was 9/14/05, but data published in 2000 and 2005 are not cited.

- DRUGDEX specifies that it includes off-label indications, and it does include bladder cancer as an off-label indication for gemcitabine. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites only an old narrative review and does not cite the Phase III study identified in the EPC review. The date of the last update was 2006, but 2005 data are not cited.
- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it includes bladder cancer as an off-label indication for gemcitabine. It emphasizes Phase II, III, and IV studies with over 30 subjects, but does not cite the several clinical trials identified in the EPC review that meet these criteria, including two Phase III studies. The date of the last update is not stated, but 2005 data are not cited.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. As per the guideline, there is not an explicit mention of an off-label indication for gemcitabine in bladder cancer. Instead, the NCCN documents use the terms "considered" for gemcitabine plus cisplatin, and "investigational" for gemcitabine plus paclitaxel. The last update was in 2006, but 2005 data are not cited.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it includes bladder cancer as an off-label indication for gemcitabine. It emphasizes prospective trials, but does not cite several trials identified in the EPC review, including one of two Phase III studies. The last update was 11/9/05, but early 2005 data are not cited.

Gemcitabine (Gemzar®) for Ovarian Cancer

As stated above, gemcitabine is a nucleoside analog with therapeutic indications for treatment of metastatic breast cancer (in combination with paclitaxel) after failure of prior anthracycline-containing adjuvant chemotherapy; treatment of locally advanced or metastatic NSCLC (in combination with cisplatin); and treatment of locally advanced or metastatic pancreatic cancer previously treated with 5-FU. Gemcitabine is also used off-label for treatment of various other cancers including advanced and/or metastatic ovarian cancer.

Systematic Review by EPC

A total of 414 articles and abstracts were identified through the EPC literature search. Of these, 48 met the EPC inclusion criteria.

Table 12a describes the study types of the included studies and the outcomes reported. Appendix B (Evidence Table 10) reports details from each of the 42 articles and six abstracts. The literature includes two peer-reviewed Phase III articles (both randomized controlled trials), 21 peer-reviewed Phase II trials (all cohort studies), three Phase I/II trials, and 10 Phase I trials. The peer-reviewed studies included a total of 1948 subjects with ovarian cancer who received gemcitabine. All studies reported tumor response outcomes and adverse effects; almost all reported survival data. Only two Phase III trials and three Phase II trials reported quality-of-life

data and only two (both Phase III trials) reported data on symptom outcomes.

Table 12a: Study types and outcomes reported – gemcitabine for ovarian cancer

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	42	1948	1998-2006	42	29	5	2	39
Phase III	2 (5%)	266 (14%)	2005-2006	2	2	2	2	2
Phase II	22 (52%)	986 (51%)	1994-2005	22	17	3	-	21
Phase I	13 (31%)	345 (18%)	1994-2004	13	7	-	-	13
Other	5 (12%)	351 (18%)	1997-2004	5	3	-	-	3
Abstracts[a]	6	129	2004-2005	6	5	-	-	6

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.
[a] Not considered further.

Peer-reviewed Phase III trials. There were two Phase III RCTs evaluating the use of gemcitabine chemotherapy for ovarian cancer. The first Phase III trial[263] was published in 2005 and compared post-first line therapy of gemcitabine (1000 mg/m^2 in combination with carboplatin) to the alternative monotherapy of carboplatin. The study included patients with all stages of ovarian cancers including advanced ovarian cancer. The study concluded that gemcitabine in combination had better progression-free survival, higher response rate, improved symptoms with improved QoL, and an acceptable level of hematological toxicity compared to carboplatin monotherapy. The second study was a multicenter trial from Europe published in early 2006 that compared the sequential schedule of single-agent carboplatin followed by docetaxel only *vs* a docetaxel-gemcitabine combination as first line therapy. The study used different dosages (850 to 1250 mg/m^2) of gemcitabine in two of the three arms in combination with docetaxel. This study had higher rates of dyspnea in gemcitabine arms and failed feasibility completion rates.

Peer-reviewed Phase II trials. There were 22 Phase II trials (all cohort studies) that evaluated gemcitabine. The majority of the trials included patients with advanced and/or metastatic ovarian cancer. Five of the trials described patients who were either chemonaïve or for whom gemcitabine was first line therapy. Doses of gemcitabine ranged from 800 to 1250 mg/m^2; eight studies used 800 mg/m^2 and eight used 1000 mg/m^2. Eight trials evaluated gemcitabine as monotherapy. Combination therapy was used in 14 trials and included cisplatin, carboplatin, paclitaxel, doxorubicin, and topotecan. Tumor response was reported in 21 trials; the greatest complete response rate (60 percent) was found in a study of 20 patients that used 800 mg/m^2 of gemcitabine in combination with paclitaxel and carboplatin.[264] Partial response rates ranged from 5 to 50 percent; stable disease ranged from 3 to 52 percent; and disease progression ranged from 0 to 50 percent. The overall 1-year survival rates ranged from 40 to 81 percent in seven studies that reported. Median overall survival ranged from 6 to 44 months. QoL was reported in three studies, and no studies reported symptom relief.

Peer-reviewed Phase I/II or I trials. There were 13 Phase I/II trials or Phase I trials that evaluated gemcitabine use in advanced and/or metastatic ovarian cancer. Three of the trials described patients who were either chemonaïve or for whom gemcitabine was first line therapy.

Doses of gemcitabine ranged from 200 to 1250 mg/m^2; eight studies used 800 mg/m^2 and eight used 1000 mg/m^2. Only one trial evaluated gemcitabine as monotherapy. Combination therapy was used in 14 trials and included cisplatin, carboplatin, paclitaxel, docetaxel, doxorubicin, rubitecan, and topotecan. Tumor response was reported in 12 trials; the greatest complete response rate (85 percent) was found in a study of 57 patients that used 800 mg/m^2 of gemcitabine in combination with paclitaxel and carboplatin.[265] Partial response rates ranged from 6 to 41 percent; stable disease ranged from 6 to 38 percent; and disease progression ranged from 6 to 57 percent. The overall 1-year survival rates ranged from 61 to 92 percent in two studies that reported the data. Median overall survival ranged from 6 to 44 months. No studies reported QoL or symptom relief.

Compendia Listings

Treatment indication and toxicities. Table 12b summarizes the compendia's discussions of the off-label use of gemcitabine for treatment of advanced and/or metastatic ovarian cancer. Only AHFS-DI, Clinical Pharmacology, DRUGDEX, Facts & Comparisons, and USP-DI explicitly stated an off-label indication for the agent. NCCN discussed the use of gemcitabine for advanced and/or metastatic ovarian cancer but did not explicitly state whether the agent is indicated as an off-label use. NCCN did not report on toxicities due to gemcitabine. All other compendia discussed toxicities associated with gemcitabine chemotherapy, including severity of adverse effects, and which organs were affected; however, only Clinical Pharmacology, DRUGDEX, and Facts & Comparisons state the frequency of adverse effects and gemcitabine-related toxicities specifically among patients treated for advanced and/or metastatic ovarian cancer. Only USP-DI indicated the dose for the off-label use of gemcitabine for this cancer.

Table 12b: Summary of compendia listings – gemcitabine for ovarian cancer

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Off-label indication explicitly stated	Yes	Yes	Yes	Yes	Unclear	Yes [a]
Sub-category of indication (accepted or acceptance not established)	Investigational	NR	Efficacy: Adult, Evidence is inconclusive Recommendation: Adult, Class III Strength of Evidence: Adult, Category B	NR	Accepted	Accepted
Stage of cancers	"Advanced epithelial ovarian cancer"	"Ovarian cancer"	"Ovarian cancer"	"Ovarian cancer"	"Recurrent ovarian cancer"	"Advanced or relapsed epithelial ovarian carcinoma"
Method of treatment (first line or other)	Other	Other	Other	NR	Other	Unclear
Routes of administration	Intravenous	Intravenous	Intravenous	Intravenous	NR	Intravenous
Uses of the agent (monotherapy or combination)	Monotherapy	Combination	Monotherapy or combination with other agents	NR	Combination	Monotherapy or combination with other agents
Comparator discussed (placebo, standard treatment, other agents)	No	No	No	No	No	No
Outcomes mentioned for the off-label use (survival, tumor response, other)	Objective responses	Complete responses Partial responses Median survival Median progression-free survival	Response rate	NR	Response rate	NR
Toxicity reporting	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: No	Overall: Yes Cancer-specific: Yes Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: Yes Severity: Yes By organ: Yes Frequency: No	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: No Cancer-specific: No Severity: No By organ: No Frequency: No	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: No
Dose indicated for the off-label use	No	"Not established"	Yes	No	No	Yes
Number of evidence citations	6	4	3 (+1)[b]	0	2	13
Range of years of	1994-2001	2003-2004	1996-2000		1994; 2005	1994-1999

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
citations						
Sources of evidence (abstracts/published articles)	Published articles Review Cancer database	Published articles	Published articles Abstracts Review		Published articles	Published articles Package insert Abstracts Review Manufacturer's comment
Number of abstracts cited [years]	0	0	1 [1996]		0	6 [1998-1999]
Number of published articles cited [years]	4 published articles [1994-1999] 1 Review [2000] 1Cancer database [2001]	4 published articles [2003-2004]	3 reviews [1997-2000]		2 published articles [1994; 2005]	4 published articles [1994-1998] 1 package insert [1996-1998] Abstracts [1998-1999] Review [1999] Manufacturer's comment [1999]
Date of last update	12/8/2005	11/9/2005	2006	2005	2006	9/14/2005

[a] Evidence rating IIID
[b] Three articles cited; one additional review article included in the reference list.

Studies cited in compendia versus studies identified in EPC review. Among all compendia that reported the off-label use of gemcitabine for treatment of advanced and/or metastatic ovarian cancer, only Facts & Comparisons did not provide any reference lists. The other five compendia provided up to 13 references, which included primary peer-reviewed articles, abstracts, review articles, and the package insert for gemcitabine. For the peer-reviewed articles, AHFS-DI included four, Clinical Pharmacology included three, DRUGDEX included two, NCCN included one, and USP-DI included three of the 42 studies found by the EPC's evidence review that were published between 1994 and 2004, with only one[266] common reference across the three compendia (AHFS-DI, NCCN, and USP-DI). Several publications that did not meet the EPC eligibility criteria were referenced, including package inserts, review articles, and database review. A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 12c.

Table 12c: Articles cited by compendia vs. articles identified by EPC – gemcitabine for ovarian cancer

Reference	EPC	AHFS-DI	Clin Pharm	DRUGDEX	F & C	NCCN	USP-DI	Notes
Reviewed by compendia:	-	Yes	Yes	Yes	Yes	Yes	Yes	-
Phase III								
Vasey, 2006[267]	x							
Pfisterer, 2005[263]	x							
Phase II								
du Bois, 2005[268]	x							
Ferrandina, 2005[269]	x							
Gupta, 2005[270]	x							
Kose, 2005[271]	x							
Garcia, 2004[272]	x							
Harries, 2004[273]	x							
Liu, 2004[264]	x							
Papadimitriou, 2004[274]	x							
Bauknecht, 2003[275]	x							
Belpomme, 2003[276]	x		x					
D'Agostino, 2003[277]	x							
D'Agostino, 2003[278]	x		x					
Markman, 2003[279]	x							
Nagourney, 2003[280]	x							
Nogue, 2002[281]	x							
Sehouli, 2002[282]	x							
Underhill, 2001[283]	x							
Silver, 1999[284]	x							
von Minckwitz, 1999[285]	x	x						
Friedlander, 1998[286]	x	x					x	
Lund, 1995[287]	x							
Lund, 1994[266]	x	x				x	x	
Phase I/II								
Barlow, 2004[288]	x							
Sabbatini, 2004[289]	x							
Greggi, 2001[290]	x							
Phase I								
Look, 2004[291]	x							
Micha, 2004[265]	x							
Berkenblit, 2003[141]	x							
Sehouli, 2003[292]	x							
D'Agostino, 2002[293]								
Fracasso, 2002[294]	x							
du Bois. 2001[295]	x							
Iaffaioli, 2000[296]	x							
Pignata, 2000[297]	x							

Reference	EPC	AHFS-DI	Clin Pharm	DRUGDEX	F & C	NCCN	USP-DI	Notes
Reviewed by compendia:	-	Yes	Yes	Yes	Yes	Yes	Yes	-
Shapiro, 1996[298]	x	x					x	
Other								
Rose, 2005[299]						x		Review
Geisler, 2004[300]	x		x					
Markman, 2004[123]	x							
Prasad, 2004[301]	x							
Tewari, 2004[302]	x							
Villella, 2004[303]	x							
Bilgin, 2003[304]			x					Not available
CancerNet/PDQ, 2001[305]		x						Database
Anonymous, 2000[261]		x						Review
Gerson, 2000[306]				*				Review
Eisenhauer, 1997[307]	x							
Kaufmann, 1997[308]				x				Review
Pedersen, 1997[309]				x				Review
Martin, 1996[310]							x	Review
No. of Abstracts	6	0	0	1	0	0	6	
Abstract Years	04-05			96			98-99	

* Non-cited reference.

Recommendations and supporting evidence. AHFS-DI states that "gemcitabine is an active agent in ovarian cancer and currently is being investigated for use in the treatment of advanced epithelial ovarian cancer." The compendium cites Phase II trials for gemcitabine use as monotherapy and for post-first line treatment; no mention is made regarding the indicated dose. The effectiveness of the treatment is discussed, and the compendium identifies the need for further studies to establish the role of gemcitabine in ovarian cancer treatment.

Clinical Pharmacology evaluates gemcitabine use for off-label and post-first line use in ovarian cancer. The compendium discusses gemcitabine use in combination therapy for the treatment of ovarian cancer, with dose for the treatment as "not established." The effectiveness of the treatment is discussed from cited studies.

DRUGDEX includes "ovarian cancer" among its list of cancers for the off-label use of gemcitabine. It specifies that the "evidence for efficacy is inconclusive" for the indicated use. While the compendium indicates gemcitabine use as monotherapy or in combination therapy, no mention is made regarding the indicated dose and whether gemcitabine is used for first line or post-first line treatment.

Facts & Comparisons notes gemcitabine as an "Unlabeled use" for the treatment of "ovarian cancer." No other discussion of gemcitabine use in ovarian cancer is made. The on-line compendium does not include references.

NCCN discusses gemcitabine use in its section on ovarian cancers. It is offered as an "acceptable" modality for treatment of recurrent epithelial ovarian cancer that is either platinum-sensitive or resistant. It grades both recommendations as category 2A: "There is uniform NCCN consensus, based on lower level evidence including clinical experience, that the recommendation is appropriate." The effectiveness of the treatment cited a response rate of 19 percent from a single primary study specific to gemcitabine use.

USP-DI included "advanced and/or relapsed epithelial ovarian carcinoma" among its list of cancers for which the use of gemcitabine is "Accepted." It specifies the indicated use as "reasonable medical therapy at some point in the management of patients with advanced or relapsed epithelial ovarian carcinoma." Regarding dose, the compendium describes 800 to 1250

mg/m^2 once a week for 2 or 3 weeks. While the compendium indicates gemcitabine use as monotherapy or in combination therapy, no mention is made regarding whether gemcitabine is used for first line or post-first line treatment. The effectiveness of the treatment is also not discussed. Notably, the evidence rating for the indicated use is IIID.

Summary. Listings of gemcitabine for ovarian cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* All six compendia discuss gemcitabine for treatment of advanced and/or metastatic epithelial ovarian cancer.
- *Specificity of clinical information:* To describe the cancer indication for which the agent is indicated as an off-label use, the compendia that discuss gemcitabine use different ad hoc nomenclatures rather than a standardized classification (such as WHO staging of cancers). Only DRUGDEX, NCCN, and Clinical Pharmacology describe which combinations of treatments are indicated, and only USP-DI describes appropriate doses. In addition, the description of the effectiveness of treatment with gemcitabine varies across the compendia.
- *Evidence rating:* Only two compendia (DRUGDEX and USP-DI) provide explicit evidence ratings for the off-label use of gemcitabine for ovarian cancer. DRUGDEX rates the evidence as category B, while USP-DI rates it as IIID. Only USP-DI lists more than 10 references.
- *Recommendation statements:* DRUGDEX makes a class III recommendation, "treatment is not useful and should be avoided," for the off-label indication. NCCN uses an evidence rating for the off-label indication and makes a weak recommendation, "options," based on lower level evidence. AHFS-DI and Clinical Pharmacology mention the off-label use through passive discussion using cited references. Facts & Comparisons does not describe in any detail the off-label use of gemcitabine in ovarian cancer.
- *Toxicity:* Toxicities related to gemcitabine are reported in most of the compendia, but only DRUGDEX and Clinical Pharmacology note toxicities specifically in patients with ovarian cancer.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it includes ovarian cancer as an off-label indication for gemcitabine. It emphasizes well-designed, controlled, published studies, but does not cite the 2005 Phase III study identified in the EPC review. The last update was 12/08/05, but 2005 data, including the Phase III study, are not cited.
- USP-DI specifies that it includes off-label indications, and it does include ovarian cancer as an off-label indication for gemcitabine. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff. It does not cite the 2005 Phase III study identified in the EPC review. The last update was 9/14/05, but the Phase III study published earlier that year is not cited.
- DRUGDEX specifies that it includes off-label indications, and it does include ovarian

cancer as an off-label indication for gemcitabine. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites only old narrative reviews and does not cite the 2005 Phase III study identified in the EPC review. The date of the last update was 2006, but 2005 data are not cited.

- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it includes ovarian cancer as an off-label indication for gemcitabine. It emphasizes Phase II, III, and IV studies with over 30 subjects, but does not cite the Phase III study identified in the EPC review. The date of the last update is not stated, but 2005 data are not cited.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is no explicit off-label indication for gemcitabine in ovarian cancer as per the guideline. The last update was in 2006, but 2005 data are not cited.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it includes ovarian cancer as an off-label indication for gemcitabine. It emphasizes prospective trials, but does not cite the one Phase III study identified in the EPC review. The date of the last update was 11/9/05, but early 2005 data are not cited.

Rituximab (Rituxan®) for Chronic Lymphocytic Leukemia

Rituximab is a monoclonal antibody with therapeutic indications for treatment of relapsed or refractory low-grade or follicular CD20-positive, B-cell non-Hodgkin's lymphoma. Rituximab has also been evaluated for treatment of chronic lymphocytic leukemia (CLL).

Systematic Review by EPC

A total of 164 articles and abstracts were identified through the EPC literature search. Of these, 43 met the EPC inclusion criteria.

Table 13a describes the study types of the included studies and the outcomes reported. Appendix B (Evidence Table 11) reports details from each of the 33 articles and 10 abstracts. The peer-reviewed literature includes 13 Phase II trials (one randomized and one non-randomized trial); five Phase I/II trials; and six Phase I trials (one non-randomized comparative trial). There were no Phase III trials. The 33 peer-reviewed studies included a total of 974 subjects with CLL who received rituximab. Tumor response, survival, and adverse effects data were reported in at least 85 percent of the trials and case reports. One trial and five case reports included symptom outcomes data, and no studies reported on quality of life.

Table 13a: Study types and outcomes reported – rituximab for chronic lymphocytic leukemia

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	33	974	1999-2005	30	28		6	29
Phase III	-	-	-	-	-	-	-	-
Phase II	13 (39%)	373[a] (38%)	1999-2005	13	11	-	-	12
Phase I/II	5 (15%)	467 (48%)	2001-2005	5	4	-	1	5
Phase I	5 (15%)	110 (11%)	1999-2004	5	4	-		5
Other[b]	10 (30%)	24 (2%)	1999-2005	7	10	-	5	7
Abstracts[c]	10	212	2004-2005	9	5	-		9

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.
[a] Includes an unknown percentage of 13 patients who received rituximab in one study.
[b] Case reports or retrospective case series.
[c] Not considered further.

Peer-reviewed Phase III trials. No Phase III trials have been published.

Peer-reviewed Phase II trials. There were two comparative trials (one randomized) and 11 cohort studies that were peer-reviewed Phase II trials. The randomized trial consisted of concurrent therapies of rituximab and fludarabine *vs* sequential treatment of fludarabine followed by rituximab for patients with no prior treatment for CLL.[311] Both arms had rituximab consolidation therapy, and similar toxicities were reported. The arm with concurrent therapies had an overall response rate of 90 percent. The non-randomized study included 27 patients with non-Hodgkin's lymphomas who were undergoing autologous stem cell transplantation. It was not reported which of the 13 with CLL received rituximab with high-dose chemotherapy or high-dose chemotherapy alone.[312] All studies used the dosage of 375 mg/m^2. Six of the cohort trials evaluated rituximab as monotherapy. Three trials described patients who were chemonaïve or for whom rituximab was first line therapy, and two trials enrolled patients with a varied history of treatment. In 10 of 13 cohort studies that reported complete response rates, the greatest complete response rate (78 percent) was found in a study of 65 patients.[313] Partial response ranged from 0 to 55 percent; stable disease ranged from 0 to 83 percent; and disease progression ranged from 0 to 32 percent.

Peer-reviewed Phase I/II trials. There were five cohort trials including a three-arm study that were peer-reviewed Phase I/II trials. Four studies reported dosages of 375 mg/m^2 and two studies reported escalating dosages of rituximab from 125 to 250, and 375 mg/m^2, and from 375 to 500 mg/m^2. The three-arm study dosing was 250 or 375 mg/m^2 with no co-intervention. One of the cohort trials evaluated rituximab as monotherapy. One study enrolled patients who were chemonaïve and another study reported over half of the patients with a prior history of chemotherapy. Complete response was reported in all five trials ranging from less than four to 70 percent in one study of 224 patients.[314] Quality of life and symptom relief were not reported. All studies discussed adverse effects.

Peer-reviewed Phase I trials. There were six peer-reviewed Phase I trials including one non-randomized comparison and one retrospective three-arm cohort. Five of the cohort trials evaluated rituximab as monotherapy. All of the studies except for the retrospective study included patients who had prior chemotherapy and also reported response and survival data.

Complete response data was generally not given except in one study and as part of overall response in another. Partial response ranged from 9 to 38 percent. Quality of life and symptom relief were not reported.

Compendia Listings

Treatment indication and toxicities. Table 13b summarizes the compendia's discussions of the off-label use of rituximab for treatment of chronic lymphocytic leukemia. Three compendia (DRUGDEX, Clinical Pharmacology and USP-DI) explicitly stated CLL as an off-label indication for the agent. NCCN discussed the use of rituximab for CLL and small lymphocytic lymphoma (SLL), but did not explicitly state whether the agent is indicated as an off-label use. NCCN did not report on toxicities due to rituximab. All other compendia discussed toxicities associated with rituximab chemotherapy, including severity of adverse effects, and which organs were affected. All compendia, except for NCCN and USP-DI, discussed frequency of adverse effects; AHFS-DI, DRUGDEX, USP-DI, and Facts & Comparisons reported rituximab-related toxicities specifically among patients being treated for CLL. Only Clinical Pharmacology discussed the dose indicated for the off-label use of rituximab for CLL.

Table 13b: Summary of compendia listings – rituximab for chronic lymphocytic leukemia

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Off-label indication explicitly stated	No	Yes	Yes	No	Unclear	Yes
Sub-category of indication (accepted or acceptance not established)	-	Implies experimental	Efficacy: Adult, Evidence favors efficacy Recommendation: Adult, Class III Strength of Evidence: Adult, Category B	-	NCCN Category 2A[a]	Accepted
Stage of cancers	-	NR	"Chronic lymphoid leukemia"	-	All (categorized by stage)	NR
Method of treatment (first line or other)	-	Unclear	First line	-	First line and Second line	1st line and relapsed/refractory
Routes of administration	-	Intravenous	Intravenous	-	Intravenous	"Consult the medical literature and/or experts"
Uses of the agent (monotherapy or combination)	-	Monotherapy Combination therapy	Combination	-	Combination	Combination (1st line) Unclear (relapsed/ refractory)
Comparator discussed	-	No	No	-	No	No
Outcomes mentioned for the off-label use (survival, tumor response, other)	-	Overall response rate Complete response rate	Overall response rate	-	NR	Overall response rate Complete response rate
Toxicity reporting	Overall: Yes Cancer-specific: Yes Severity: Yes By organ: Yes (Death for CLL) Frequency: Yes	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: Yes Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: Yes Severity: Yes By organ: Yes (Death for CLL) Frequency: Yes	Overall: No Cancer-specific: No Severity: By organ: Frequency:	Overall: Yes Cancer-specific: Yes Severity: No By organ: Yes (Death for CLL) Frequency: No
Dose indicated for off-label use	-	Yes	No	-	No	No
Number of evidence citations	1	2	12 (+6)[b]	1 [c]	1	29
Range of years of	2004	2000-2001	1999-2001	2001	2003	1999-2005 [d]

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
citations						
Sources of evidence (abstracts/published articles)	Prescribing information	Published article Abstract	Published articles Abstracts Case reports Review articles	Prescribing information	Published article	Published articles Abstracts Case reports Review articles Package insert
Number of abstracts cited[years]	-	1 [2000]	8 [2000-2001]	-	0	9 [2000-2001]
Number of published articles cited [years]	-	1 [2001]	4 (+6 non-cited) [1999-2001]	-	1 [2003]	15 (+4 reviews) [1999-2005]
Date of last update	12/8/2005	7/7/2004	2006	2005	12/19/2005	12/5/2005

[a] There is uniform NCCN consensus, based on lower level evidence including clinical experience, that the recommendation is appropriate.
[b] 12 abstracts and articles cited; 6 additional articles included in the reference list.
[c] For CLL-specific adverse effect.
[d] Not including Insert

Studies cited in compendia versus studies identified in EPC review. Only DRUGDEX and USP-DI provided an extensive list of references, which included primary peer-reviewed articles, abstracts, case reports, review articles, and the package insert for rituximab. DRUGDEX includes 18 references relevant to the agent's use in CLL but discusses its use from only two citations and toxicities from two other citations. USP-DI includes seven of the 33 studies found in the EPC review that were published between 1999 and 2005. Several publications that did not meet the EPC eligibility criteria were referenced, including package inserts, review articles, and a book update. A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 13c.

Table 13c: Articles cited by compendia vs. articles identified by EPC – rituximab for chronic lymphocytic leukemia

Reference	EPC	AHFS-DI	Clin Pharm	DRUGDEX	F & C	NCCN	USP-DI	Notes
Reviewed by compendia:	-	No	Yes	Yes	No	Yes	Yes	-
Phase III								
(none)								
Phase II								
Del Poeta, 2005[313]	x							
Khouri, 2004[315]	x							
Tsiara, 2004[316]	x							
Byrd, 2003[311]	x					x	x	
Hainsworth, 2003[317]	x							
Tothova, 2003[312]	x							
Tsimberidou, 2003[318]	x							
Itala, 2002[319]	x			*				
Schulz, 2002[320]	x						x	
Huhn, 2001[321]	x			*			x	
Hainsworth, 2000[322]	x							
Ladetto, 2000[323]	x			*			x	
Nguyen, 1999[324]	x						x	
Phase I/II								
Keating, 2005[314]	x						x	
Wierda, 2005[325]	x							
Weide, 2004[326]	x							
Savage, 2003[327]	x							
Byrd, 2001[328]	x			x			x	
Winkler, 1999[329]	x						x	
Phase I								
Perz, 2002[330]	x							
O'Brien, 2001[331]	x						x	
Keating, 2000[332]	x		x	x			x	
Other								
Narayan, 2005[333]	x							
Robak, 2005[334]	x							
Watanabe, 2005[335]	x							
Nabhan, 2004[336]	x							
Jilani, 2003[337]	x							
Cohen, 2002[338]	x							
Kanelli, 2001[339]	x							
Seipelt, 2001[340]	x						x	
Syrigos, 2001[341]							x	Review
Weiss, 2001[342]				*			x	Review
Herold, 2000[343]	x			*			x	
Schulz, 2000[344]				*			x	Not available
Byrd, 1999[345]	x						x	
Lim, 1999[346]	x			x			x	
Yang, 1999[347]	x			x			x	

Reference	EPC	AHFS-DI	Clin Pharm	DRUGDEX	F & C	NCCN	USP-DI	Notes
Reviewed by compendia:	-	No	Yes	Yes	No	Yes	Yes	-
No. of Abstracts	10		1	8		0	9	
Abstract Years	04-05		01	00-01			00-01	

* Non-cited reference.

Recommendations and supporting evidence. DRUGDEX discusses the off-label use of rituximab in its section on CLL. It specifies that the "evidence for efficacy is favorable" for the indicated use. While the compendium indicates rituximab use as a combination therapy in untreated CLL, no mention is made regarding the indicated dose. USP-DI included CLL among its list of cancers for which treatment is "Accepted." There are no data on stage of disease for rituximab use, nor is any information provided. However, rituximab is indicated for first line treatment in combination therapy as well as for relapsed or refractory indications. Treatment effectiveness is quantified.

NCCN discusses rituximab in its section on CLL and small lymphocytic lymphoma. It is offered as an option with other chemotherapeutic agents for secondary treatment of any stage of CLL/SLL. NCCN grades the recommendation as category 2A: "There is uniform NCCN consensus, based on lower level evidence including clinical experience, that the recommendation is appropriate."

Clinical Pharmacology evaluates rituximab use for an off-label and post-first line use in CLL. The compendium reported rituximab in monotherapy and combination therapy. The dose and effectiveness of the treatment are quantified.

Summary. Listings of rituximab for CLL in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Four of the six compendia (Clinical Pharmacology, DRUGDEX, NCCN, and USP-DI) discuss rituximab for treatment of CLL.
- *Specificity of clinical information:* The four compendia that discuss rituximab indicate different types of cancer for which the agent should be used, in addition to the combinations of treatments. Clinical Pharmacology discusses appropriate doses. None of the compendia describes the effects of treatment with rituximab. Only DRUGDEX, USP-DI, and Clinical Pharmacology report response data.
- *Evidence rating:* DRUGDEX and USP-DI include extensive lists of references, although these are reported only as lists of the available evidence.
- *Recommendation statements:* DRUGDEX makes a class III recommendation, "treatment is not useful and should be avoided," for the off-label indication based on the strength of evidence category B. NCCN makes a weak recommendation, "option" and "suggested," based on lower level evidence. USP-DI and Clinical Pharmacology mention the off-label use through passive discussion using cited references. AHFS-DI and Facts & Comparisons did not describe the off-label use of rituximab in CLL.
- *Toxicity:* Toxicities related to rituximab are reported in most of the compendia, and four (AHFS-DI, DRUGDEX, Facts & Comparisons, and USP-DI) note toxicities specifically in patients with CLL.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it does not include CLL as an off-label indication for gemcitabine. There is no published Phase III study of rituximab in CLL; thus the compendium adheres to its stated methodology, which emphasizes well-designed, controlled, published studies.
- USP-DI specifies that it includes off-label indications, and it does include CLL as an off-label indication for rituximab. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff. It cites several Phase II studies in support of the off-label indication, including five of the 13 Phase II studies identified in the EPC review. The last update was 12/5/05, but some 2003-5 data are not cited.
- DRUGDEX specifies that it includes off-label indications, and it does include CLL as an off-label indication for rituximab. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It cites only studies published before 2003, although the date of the last update was 2006.
- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it does not include CLL as an off-label indication for rituximab. It emphasizes Phase II, III, and IV studies with over 30 subjects, but does not cite any of the Phase II studies identified in the EPC review. The last update was in 2005, but data from 1999-2005 were not cited.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is no explicit off-label indication for rituximab in CLL as per the guideline. The last update was in 2005, but early 2005 data are not cited.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it includes CLL as an off-label indication for rituximab. It emphasizes prospective trials, but cites only one Phase I study of rituximab in CLL published in 2000; it fails to cite 13 Phase II, 6 Phase I/II, and 2 other Phase I studies identified in the EPC review. The last update was 7/7/04, but data from 1999-2004 were not cited.

Erlotinib (Tarceva®) for Head and Neck Cancer

Erlotinib is an inhibitor of human epidermal growth factor receptor tyrosine kinase with therapeutic indications for treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Erlotinib has also been evaluated for treatment of head and neck cancer.

Systematic Review by EPC

A total of 18 articles and abstracts were identified through the EPC literature search. Of these, three met the EPC inclusion criteria.

Table 14a describes the study types of the included studies and the outcomes reported. Appendix B reports details from each of the three articles and abstracts. The literature includes only a single peer-reviewed study, a Phase II trial in 115 patients that reported tumor response, survival data, and adverse effect data.

Table 14a: Study types and outcomes reported – erlotinib for head and neck cancer

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	1	115	2004	1	1	-	-	1
Phase III	-	-	-	-	-	-	-	-
Phase II	1 (100%)	115 (100%)	2004	1	1	-	-	1
Phase I	-	-	-	-	-	-	-	-
Other	-	-	-	-	-	-	-	-
Abstracts[a]	2	20	2005	2	-	-	1	2

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.
[a] Not considered further.

Peer-reviewed Phase III trials. No Phase III trials have been published.

Peer-reviewed Phase II trials. Only one study of 115 patients with locally recurrent of metastatic head and neck cancer previously treated with other anti-neoplastic agents has been peer-reviewed. The study reported partial response of four percent and overall survival of 6 months. Adverse effect data were also reported, but quality of life and symptom relief data were not reported.

Compendia Listings

Treatment indication and toxicities. Table 14b summarizes the compendia's discussions of the off-label use of erlotinib for treatment of head and neck cancer. Clinical Pharmacology, DRUGDEX, and Facts & Comparisons explicitly stated an off-label indication for the agent. NCCN mentions the development of newer tyrosine kinase inhibitors, including erlotinib, to attenuate the overexpression of epidermal growth factor receptor (EGFR) and/or common ligands that has been observed in greater than 90 percent of squamous cell carcinomas of head and neck cancer. The other compendia, regardless of whether they mentioned head and neck cancer, discussed toxicities, including severity and frequency of adverse effects, and which organs were affected. Only DRUGDEX discussed erlotinib-related toxicities specifically among patients being treated for head and neck cancer.

Table 14b: Summary of compendia listings – erlotinib for head and neck cancer

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Off-label indication explicitly stated	No	Yes	Yes	Yes	No	No
Sub-category of indication (accepted or acceptance not established)	-	NR	Efficacy: Adult, Evidence is inconclusive Recommendation: Adult, Class III Strength of Evidence: Adult, Category B	NR	-	-
Stage of cancers	-	"Metastatic or recurrent squamous cell carcinoma"	"Head and neck cancer"	NR	-	
Method of treatment (first line or other)	-	NR	Other	NR	-	-
Routes of administration	-	Oral	Oral	Oral	-	-
Uses of the agent (monotherapy or combination)	-	Monotherapy	Monotherapy	NR for this indication	-	-
Comparator discussed (placebo, standard treatment, other agents)	-	No	No	NR for this indication	-	-
Outcomes mentioned for the off-label use (survival, tumor response, other)	-	Overall response rate Median progression-free survival Median overall survival	Overall response rate Median overall survival	NR	-	-
Toxicity reporting	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: Yes Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: No Cancer-specific: No Severity: By organ: Frequency:	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes
Dose indicated for the off-label use	-	Yes	No	No	-	-

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Number of evidence citations	-	1	3	None cited for this indication	-	-
Range of years of citations	-	2004	2001	-	-	-
Sources of evidence (abstracts/published articles)	-	Published study	Abstracts Published study	-	-	-
Number of abstracts cited [years]	-	0	1 [2000]	-	-	-
Number of published articles cited [years]	-	1 [2004]	2 Reviews [2001]	-	-	-
Date of last update	12/8/2005	11/9/2005	2006	2005	12/19/2005	11/14/2005

Studies cited in compendia versus studies identified in EPC review. Only Clinical Pharmacology referenced the single peer-reviewed study. A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 14c.

Table 14c: Articles cited by compendia vs. articles identified by EPC – erlotinib for head and neck cancer

Reference	EPC	AHFS-DI	Clin Pharm	DRUGDEX	F & C	NCCN	USP-DI	Notes
Reviewed by compendia:	-	No	Yes	Yes	Yes	No	No	-
Phase III (none)								
Phase II Soulieres, 2004[348]	x		x					
Phase I/II (none)								
Phase I (none)								
Other Adjei, 2001[349]				x				Not MEDLINE
Ciardiello, 2001[350]				x				Review
No. of Abstracts	2		0	1	0			
Abstract Years	04-05			00				

Recommendations and supporting evidence. Clinical Pharmacology included evaluation of erlotinib for treatment of head and neck cancer. The compendium referenced the single peer-reviewed study and stated that there is an indication for the treatment of head and neck cancer, specifically metastatic or recurrent squamous cell carcinoma. The dose used in the study was cited. DRUGDEX included evaluation of erlotinib for treatment of head and neck cancer. The dose used in one review is cited. Facts & Comparisons did not include any citation relevant to this indication.

Summary. Listings of erlotinib for head and neck cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Three of the six compendia (Clinical Pharmacology, DRUGDEX, and Facts & Comparisons) discuss erlotinib for treatment of head and neck cancer.
- *Specificity of clinical information:* Clinical Pharmacology describes the cancer indication as "head and neck cancer, specifically metastatic or recurrent squamous cell carcinoma," with reference to the single peer-reviewed study. DRUGDEX references one abstract and one review and describes the off-label indication as for the treatment of head and neck cancer.
- *Evidence rating:* Only DRUGDEX provides an explicit evidence rating for the off-label use of erlotinib for head and neck cancer. It assigns the evidence the rating category IIb and also notes that the evidence for efficacy is inconclusive.
- *Recommendation statements:* Clinical Pharmacology mentions the off-label use through passive discussion using cited references. DRUGDEX makes class III recommendation, "treatment is not useful and should be avoided."
- *Toxicity:* Toxicities related to erlotinib are reported in most of the compendia, but only DRUGDEX notes toxicities specifically in patients with head and neck cancer.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it does not include head and neck cancer as an off-label indication for erlotinib. There is no published Phase III study of erlotinib in head and neck cancer; thus the compendium adheres to its stated methodology, which emphasizes well-designed, controlled, published studies.
- USP-DI does not include head and neck cancer as an off-label indication for erlotinib. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff. The last update was 11/14/05, but the single Phase II study from 2004 that was identified in the EPC review is not cited.
- DRUGDEX specifies that it includes off-label indications, and it does include head and neck cancer as an off-label indication for erlotinib. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It does not cite the Phase II study identified in the EPC review. The date of the last update was 2006, but 2004 data are not cited.
- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it includes head and neck cancer as an off-label indication for erlotinib. It emphasizes Phase II, III, and IV studies with over 30 subjects, but does not cite the Phase II study (2004) identified in the EPC review. The date of the last update is not stated, but 2004 data are not cited.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is no off-label indication for erlotinib in head and neck cancer as per the guideline. The last update was 12/19/05, but the 2004 Phase II study is not cited.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it includes head and neck cancer as an off-label indication for erlotinib. It emphasizes prospective trials, and includes the Phase II trial published in 2004.

Erlotinib (Tarceva®) for Pancreatic Cancer

As stated above, erlotinib is an inhibitor of human epidermal growth factor receptor tyrosine kinase with therapeutic indications for treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Erlotinib has also been evaluated for treatment of pancreatic cancer.

Systematic Review by EPC

A total of 22 articles and abstracts were identified through the EPC literature search. Of these, 5 met the EPC inclusion criteria.

Table 15a describes the study types of the included studies and the outcomes reported. The literature includes only a single peer-reviewed study, a Phase I trial in 17 patients which reported tumor response, survival data, and adverse effect data.

Table 15a: Study types and outcomes reported – erlotinib for pancreatic cancer

Study type	No. of studies	No. of subjects	Publication years	Outcomes Reported				
				TR	Survival	QoL	Sx	AEs
Peer-reviewed studies (total)	1	17	2005	1	1	-	-	1
Phase III	-	-	-	-	-	-	-	-
Phase II	-	-	-	-	-	-	-	-
Phase I	1 (100%)	17 (100%)	2005	1	1	-	-	1
Other	-	-	-	-	-	-	-	-
Abstracts[a]	4	620[b]	2004-5	1	2	-	-	4

Abbreviations: AEs = adverse effects; No. = number; QoL = quality of life; Sx = symptoms; TR = tumor response.
[a] Not considered further.
[b] Includes subjects who received placebo.

Peer-reviewed Phase III trials. No Phase III trials have been published.

Peer-reviewed Phase II trials. No Phase II trials have been published.

Peer-reviewed Phase I trials. Only one study of 17 patients with pancreatic cancer previously treated with other anti-neoplastic agents has been peer-reviewed. The study reported partial response of 35 percent and a 14 month median survival. Adverse effect data were also reported, but quality of life and symptom relief data were not reported.

Compendia Listings

Treatment indication and toxicities. Table 15b summarizes the compendia's discussions of the off-label use of erlotinib for treatment of pancreatic cancer. Only DRUGDEX, USP-DI, and Clinical Pharmacology explicitly stated an off-label indication for the agent. NCCN discussed the Phase III trial data (referencing a review article), but did not include erlotinib in any of its algorithms for treatment of pancreatic cancer. All other compendia, regardless of whether they discussed pancreatic cancer, discussed toxicities, including severity and frequency of adverse effects, and which organs were affected. Only Clinical Pharmacology discussed erlotinib-related toxicities specifically among patients being treated for pancreatic cancer.

Table 15b: Summary of compendia listings – erlotinib for pancreatic cancer

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
Off-label indication explicitly stated	No	Unclear [a]	Yes	No	No (but a trial is discussed)	Unclear [b]
Sub-category of indication (accepted or acceptance not established)	-	NR	Efficacy: Adult, Evidence is inconclusive Recommendation: Adult, Class III Strength of Evidence: Adult, Category B	-	Not discussed	Accepted
Stage of cancers	-	"Locally advanced, unresectable or metastatic"	"Carcinoma of pancreas"	-	"Advanced or metastatic"	"Locally advanced, unresectable or metastatic"
Method of treatment (first line or other)	-	First line	First line	-	NR	First line
Routes of administration	-	Oral	Oral	-	NR	Oral
Uses of the agent (monotherapy or combination)	-	Combination	Combination	-	Combination	Combination
Comparator discussed (placebo, standard treatment, other agents)	-	No	Yes (gemcitabine alone)	-	Yes (gemcitabine alone)	No
Outcomes mentioned for the off-label use (survival, tumor response, other)	-	NR	Overall survival	-	Median survival 1-year survival	NR
Toxicity reporting	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: Yes Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes	Overall: No Cancer-specific: No Severity: By organ: Frequency:	Overall: Yes Cancer-specific: No Severity: Yes By organ: Yes Frequency: Yes
Dose indicated for off-label use	-	Yes	No	-	No	Yes
Number of evidence citations	-	(1 [c])	1	-	1	1
Range of years of	-	NR	2005	-	2004	2005

	AHFS-DI	Clinical Pharmacology	DRUGDEX	Facts & Comparisons	NCCN	USP-DI
citations						
Sources of evidence (abstracts/published articles)	-	0	Abstract	-	Review	Product Information
Number of abstracts cited [years]	-	0	1 [2005]	-	0	0
Number of published articles cited [years]	-	0	0	-	-	0
Date of last update	12/8/2005	11/9/2005	2006	2005	6/28/2005	11/14/2005

[a] The dagger sign was not used for the indication
[b]. The brackets were not used for this indication
[c]. One study of 259 patients discussed regarding adverse effects for erlotinib use with gemcitabine, but reference was not provided. No studies cited for effect.

Studies cited in compendia versus studies identified in EPC review. No compendium referenced any primary peer-reviewed articles or abstracts. A comparison of references identified in the EPC review versus those cited by the compendia is presented in Table 15c.

Table 15c: Articles cited by compendia vs. articles identified by EPC – erlotinib for pancreatic cancer

Reference	EPC	AHFS-DI	Clin Pharm	DRUGDEX	F & C	NCCN	USP-DI	Notes
Reviewed by compendia:	-	No	Yes	Yes	No	Yes	Yes	-
Phase III (none)								
Phase II (none)								
Phase I/II (none)								
Phase I Iannitti, 2005[351]	x							
Other McBride, 2004[352]						x		Review
Unknown			[a]					
No. of Abstracts	4			1				
Abstract Years	2004-05			2005				

[a] Discussed a study of 259 subjects, but did not cite a reference.

Recommendations and supporting evidence. Clinical Pharmacology states that there is an indication for erlotinib for the first-line treatment of locally advanced, unresectable, or metastatic pancreatic cancer in combination with gemcitabine. A specific dose is listed, with a reference to the compendium's gemcitabine monograph. Under the section on adverse reactions, there is a discussion of a study of 259 patients with pancreatic cancer who received erlotinib 100 mg with gemcitabine, but no reference is cited.

DRUGDEX notes the off-label indication for erlotinib for the first line treatment of locally advanced, metastatic pancreatic cancer in combination with gemcitabine. The compendium cites one abstract, and the dose used in the study is mentioned. The effectiveness of the treatment is described as "evidence is inconclusive."

As noted above, NCCN discussed the Phase III trial data, but did not include erlotinib in any of its algorithms for treatment of pancreatic cancer.

USP-DI includes pancreatic cancer in its list of cancers for which treatment is "Accepted" when used in combination with gemcitabine for first line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer. It references the "Product Information" for this information. Referencing the same source, the compendium recommends a specific dose. The effectiveness of the treatment is not discussed.

Summary. Listings of erlotinib for pancreatic cancer in the compendia reviewed here may be summarized as follows:

- *Inclusion of off-label indication:* Three of the six compendia (Clinical Pharmacology, DRUGDEX and USP-DI) discuss erlotinib for treatment of pancreatic cancer.
- *Specificity of clinical information:* Clinical Pharmacology and USP-DI both recommend the same dose of erlotinib for pancreatic cancer, to be used in combination with gemcitabine. NCCN discusses erlotinib, but without including it in its algorithms for treatment of pancreatic cancer.

- *Evidence rating:* Clinical Pharmacology, DRUGDEX, and USP-DI all include erlotinib for the treatment for pancreatic cancer without citing available, peer-reviewed references. Only DRUGDEX provides an explicit evidence rating for the off-label indication of erlotinib for pancreatic cancer ("evidence is inconclusive").
- *Recommendation statements:* Clinical Pharmacology mentions the use through passive discussion using cited references. DRUGDEX makes class III recommendation, "treatment is not useful and should be avoided."
- *Toxicity:* Toxicities related to erlotinib are reported in most of the compendia, but only Clinical Pharmacology notes toxicities specifically in patients with pancreatic cancer.

Analysis of Compendia Listings vs. Stated Methodologies

Comparing the compendia listings with their self-described methodologies for dealing with off-label indications, we find that the methodologies and actual practice diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations. Results may be summarized as follows:

- AHFS-DI specifies that it includes off-label indications when they are supported by evidence and current practice; it does not include head and neck cancer as an off-label indication for erlotinib. It emphasizes well-designed, controlled, published studies. No such studies were identified in the EPC review.
- USP-DI discusses the role of erlotinib in pancreatic cancer, even though it does not explicitly state erlotinib as an off-label indication. In its methodology it emphasizes Phase III and IV studies, with lower level evidence to be included at the discretion of its staff. No Phase III or IV studies were identified in the EPC review.
- DRUGDEX specifies that it includes off-label indications, and it does include pancreatic cancer as an off-label indication for erlotinib. In its methodology it emphasizes a comprehensive review of available evidence, including case reports. It does not cite the single Phase I study identified in the EPC review. The date of the last update was 2006, but 2005 data are not cited.
- Facts & Comparisons specifies that it includes off-label indications when legitimate and appropriate; it does not include pancreatic cancer as an off-label indication for erlotinib. It emphasizes Phase II, III, and IV studies with over 30 subjects; no such studies were identified in the EPC review.
- NCCN specifies that it includes off-label indications when they are included in its clinical practice guidelines. There is an off-label indication for erlotinib in pancreatic cancer as per the guideline. The single Phase I study (2005) identified in the EPC review is not cited. The last update was 6/28/05.
- Clinical Pharmacology specifies that it includes an off-label indication when it is in current clinical practice and the dose is available; it includes pancreatic cancer as an off-label indication for erlotinib. It emphasizes prospective trials, but does not cite the Phase I trial published in 2005. The date of the last update was 11/9/05, but 2005 data are not cited.

Discussion

Compendia claim to use evidence-based methods in their evaluation of therapeutic agents. While the compendia describe general approaches to identifying literature, evaluating studies, and formulating recommendations, we noted important discrepancies between a complete and systematic enumeration of relevant supporting clinicals studies and the literature cited in the compendia. Since the first step in a critical appraisal of literature is the systematic search and identification of relevant studies, the problems we have identified in reporting of references indicate a potential problem with the compendia. Cited literature was often neither the most recent nor the most valid in terms of study design. While it may not be necessary for compendia to provide a thorough enumeration of literature considered, the lack of transparency makes it difficult to determine whether omitted references had been identified but excluded (e.g., due to poor quality or lack of relevance) or never identified and considered. This is particularly problematic when compendia do not include a listing for a particular off-label indication, as a discussion of evidence or a rationale for no listing is seldom provided (we refer to this as "silence" on a particular indication). All the compendia are less transparent in their methods than published systematic reviews, or they do not adhere to standards for reporting of systematic reviews.[12,353]

Drug compendia are primarily organized according to individual drugs or biologics, or sometimes according to drug classes. They are not organized – as clinical practice guidelines are – according to a clinical presentation or disease for the purpose of disease management. Thus, compendia typically do not provide a comparison between different therapeutic choices for a particular condition. However, some have added indexing by condition (e.g., Facts & Comparisons), and some have made evaluation of therapeutic alternatives a standard part of the editorial process (e.g., AHFS-DI).

We noted important differences between various versions of the same compendium. Most significant were differences between print media editions and electronic media editions. Electronic media editions were typically updated more quickly and contained more information, particularly citations. However, several compendia published multiple electronic media editions, with differences in update schedules and content; this creates the potential for confusion. For example, DRUGDEX, which provides a detailed description of drugs and includes citations, may be confused with a similar product from the same publisher, DrugPoints, which provides only summary information without references. Differences in updates appear to have caused discrepancies between print and electronic editions on listing of non-approved indications.

We also noted important differences between the compendia in their citation of evidence. Each of the editors noted in interviews that they had made, or planned to make, changes in their editorial policies to become more transparent in regard to how evidence was used in their evaluations. However, several characteristics of the compendia may be obstacles to greater transparency:

- Space limitations of the print medium; electronic media have been utilized by several publishers to overcome space limitations and provide citations.
- Purpose-designed to be concise and easy to use; additional detail on evidence may be at odds with this goal.
- Scope of the task of keeping broad listings current; each compendium has mechanisms for prioritizing topics for updates and managing limited staff resources.

Among the 14 agent-cancer combinations we examined, there was a great deal of variability

in whether compendia listed a non-approved indication (Table 16). DRUGDEX was the only compendium that discussed all 14 of the agent-cancer combinations evaluated. Only the indications of gemcitabine for bladder and ovarian cancer were discussed by all six compendia. These indications were the only two of the 14 indications we examined that were discussed by AHFS-DI. Clinical Pharmacology, NCCN, and USP-DI each discussed nine of the 14 combinations, though they differed in which combinations were omitted.

Table 16: Discussion of agent-cancer combinations by compendia

	AHFS-DI	Clin Pharm	DRUGDEX	F & C	NCCN	USP-DI	No. of Com-pendia
Bevacizumab – breast	No	No	Yes	No	Yes	No	2
Bevacizumab – lung	No	Yes	Yes	Yes	Yes	Yes	5
Oxaliplatin – breast	No	Yes	Yes	No	No	No	2
Oxaliplatin – lung	No	No	Yes	No	No	No	1
Irinotecan – breast	No	No	Yes	No	No	No	1
Docetaxel – esophageal	No	No	Yes	Yes	Yes	Yes	4
Docetaxel – gastric	No	Yes	Yes	Yes	Yes	Yes	5
Docetaxel – ovarian	No	Yes	Yes	Yes	Yes	Yes	5
Gemcitabine – biliary tract	No	No	Yes	Yes	Yes	Yes	4
Gemcitabine – bladder	Yes	Yes	Yes	Yes	Yes	Yes	6
Gemcitabine – ovary	Yes	Yes	Yes	Yes	Yes	Yes	6
Rituximab – CLL	No	Yes	Yes	No	Yes	Yes	4
Erlotinib – head & neck	No	Yes	Yes	Yes	No	No	3
Erlotinib – pancreas	No	Yes	Yes	No	No [a]	Yes	3
No. of agent-cancer combinations	2	9	14	8	9	9	

[a] But a trial is discussed.

Some patterns emerge by compendium. DRUGDEX more often than the other compendia listed off-label indications, while AHFS-DI did so less often than the other compendia. Since the compendia rarely describe evidence in the absence of a listing, it is impossible to determine the reasons for silence, and thus is difficult to determine with certainty the reasons for the variability.

The compendia differed in the terminology used to state whether agents were indicated for specific cancers. Several of the compendia also used different terminology or approaches for different agent-cancer combinations. Uniquely, NCCN categorized its recommendations by cancer, as opposed to by agent. Also uniquely, NCCN consistently used explicit "Categories of Consensus," where all recommendations were category 2A ("There is uniform NCCN consensus, based on lower level evidence including clinical experience, that the recommendation is appropriate.") unless otherwise indicated. USP-DI categorized cancers into those for which use of the agent was "Accepted" or "Acceptance not established." USP-DI also explicitly indicated whether agents were included in U.S. product labeling. Only for ovarian cancer did USP-DI state that the indication for gemcitabine has an evidence rating of IIID (although this was not defined within the document). AHFS-DI generally does not make explicit recommendations, but instead makes broader comments such as that an agent "is used for" or "is an active agent against" specific cancers. Similarly, Clinical Pharmacology describes several studies for each agent-cancer combination without explicitly stating whether the agent is indicated; although for each agent, it discusses cancers only when use of the agent represents current practice and a dosage regimen has been established and documented. DRUGDEX makes explicit

recommendation ratings (class II to III) for each of the 14 agent-cancer off label indications. Facts & Comparisons only categorizes indications as FDA labeled or unlabeled uses for each agent. Examples of the different wording of recommendations and related statements follow:

- AHFS-DI: "Gemcitabine is an active agent that is used alone [3 references] or in combination therapy [2 references] for the treatment of advanced or metastatic bladder cancer...."
- Clinical Pharmacology: "Adults: Doses not established. As a single agent, gemcitabine... was evaluated in patients with recurrent epithelial ovarian cancer. Of the 22 patients treated, 2 complete responses (9.1 percent) ... were reported …[1 reference]."
- DRUGDEX: "For the indicated use of gemcitabine in transitional cell carcinoma of bladder … evidence favors efficacy." "Recommendation: Adult, Class IIb. Strength of Evidence: Adult, Category B."
- Facts & Comparisons: "Unlabeled uses: Bladder cancer; biliary cancer; ... ovarian cancer."
- NCCN: For gemcitabine and cisplatin for bladder cancer: "This combination is considered a standard first-line choice for most patients. [category 2A]" and "For salvage therapy, paclitaxel..., gemcitabine, or ifosfamide is advised depending upon the patient's current status."
- USP-DI: Under "Accepted" category: "Rituximab is indicated for the treatment of relapsed/refractory chronic lymphocytic leukemia (CLL) [25 references]," and "Gemcitabine is indicated, alone or in combination with other chemotherapeutic agents, as reasonable medical therapy at some point in the management of patients with advanced or relapsed epithelial ovarian carcinoma (Evidence rating: IIID) [1 reference]."

Facts & Comparisons provided only basic information about whether the agents were indicated, about dosing, administration, contraindications, adverse effects, and drug interactions. The evidence was not discussed or cited. In contrast, USP-DI and DRUGDEX generally provided an extensive set of references, although many of the references were of abstracts or review articles. In general, USP-DI did not attempt to discuss or summarize the evidence, but instead simply provided references after statements such as that the agent is indicated for the cancer; however, the proportion of the available evidence that was cited varied substantially across indications. Both for gemcitabine for biliary cancer and rituximab for CLL approximately half of the studies identified in the EPC review were cited, while for gemcitabine for both bladder and ovarian cancer less than 10 percent of the available evidence was cited. Similarly, AHFS-DI cited fewer than 10 percent of the available studies, but discussed them in greater detail than USP-DI. In at least four of the agent-cancer combinations, several (or a majority) of the citations provided by DRUGDEX were not linked to the text, but were simply included in reference lists. (Our count of these additional references may be an underestimate, since we relied only on the titles in the reference lists to determine potential eligibility.) Clinical Pharmacology and NCCN generally referenced at most one or two studies, focusing on Phase III or other specific trials.

Among the 14 examples, there was a great deal of variability in how up-to-date the cited literature was between topics and between compendia. For example, there were three important Phase III studies of bevacizumab published last year, two in breast cancer and one in lung cancer. Of these, one was published in full-text form (breast cancer), and the others were presented as abstracts only. The fully published breast cancer trial (bevacizumab combined with capecitabine) showed improvement in tumor response, but not for progression-free survival (the

primary end-point) or overall survival. The Phase III trial abstract (bevacizumab combined with paclitaxel) reported an improvement in tumor response, progression-free, and overall survival. None of the compendia cited either study, including the two compendia that listed this non-approved indication (DRUGDEX and NCCN). However, for lung cancer, five of the compendia listed an off-label indication for bevacizumab, and three of the five cite the recent Phase III trial. This Phase III trial was presented only in abstract form as well. Bevacizumab combined with carboplatin and paclitaxel significantly improved tumor response and progression-free and overall survival. It may be that the lung cancer abstract was identified because it was presented at the ASCO 2005 meeting, a venue that receives close scrutiny and from which many citations are listed. However, it is unclear why the breast cancer trials, one published in full in early 2005 and the other also presented at ASCO, were missed by all of the compendia studied. Similarly, a Phase III trial for gemcitabine for bladder cancer was not mentioned in three of six compendia despite being published over 5 years ago. Finally, we note that often when abstracts are cited as evidence supporting a non-labeled indication, these citations are infrequently revised to reflect subsequent publication of the same study in full.

It was difficult for us to ascertain the reason for cases in which the cited evidence did not seem current; revision dates for drug monographs are not always provided, and even when they are provided, they do not clearly indicate what content was revised. For example, a recent revision date might reflect a change in adverse effect information, but off-label indications may not have been reviewed, or the literature search updated.

The primary area of uniformity across compendia, with the exception of NCCN, is in discussions about adverse effects. The compendia mostly fully report on adverse effects and toxicities for each agent, generally as provided by packaging inserts. NCCN, which divided its discussions by cancer instead of by agent, does not discuss adverse effects. However, the compendia varied by whether they discussed cancer-specific toxicities. DRUGDEX discussed cancer specific toxicities from articles cited for all of the agent-cancer combinations. AHFS-DI discussed toxicities of gemcitabine when used for bladder cancer and of rituximab when used for CLL (although CLL was not discussed as an indication for rituximab), but not toxicities of other agents used for specific other cancers. Likewise Clinical Pharmacology discussed cancer-specific toxicities for only three of the 14 agent-cancer combinations (gemcitabine-bladder, gemcitabine ovary, and erlotinib-pancreas), and Facts & Comparisons discusses rituximab-related deaths in CLL.

Our assessment of the off-label indications for anticancer agents listed by various compendia had several limitations; we will describe the three most important. First, we assessed only a limited number of combinations of agents and cancers. While we attempted to select representative examples (older and newer agents, rare and common cancers, well-studied and poorly studied areas), nevertheless there are many more indications and drugs that we did not evaluate. However, given that variability is one of the key findings we observed among the 14 examples we evaluated, additional examples would be unlikely to lead to a different conclusion.

Second, although we probably identified most available published data on the 14 example indications, we did not thoroughly evaluate the studies in terms of the magnitude of effects and the methodological quality of the studies. In particular, we did not specify a definition *a priori* for equivocal evidence or identify among the examples situations for which we believed the evidence to be equivocal. Our approach of stratifying studies by research design adjusts in a gross way for study quality; however, a more detailed evaluation of study quality might lead to modified conclusions. While the compendia do perform a careful assessment of the studies they

identify, they cite few of the available studies. We were also not able to ascertain whether the relatively small number of available studies that were referenced by the compendia accurately reflect the amount of evidence on which the recommendations and discussions were based; however, differences in interpretation of the evidence are more likely to reflect what evidence was considered rather than how the evidence was evaluated.

Finally, we evaluated only the most current listings; each of the compendia is an evolving resource that changes as new information becomes available. Off-label listings may be added or removed over time, as new drugs or new evidence becomes available and practice patterns change. Our methods did not permit us to ascertain whether silence for certain indications reflected a withdrawn off-label indication listing, or one that had never been listed.

In conclusion, our assessment found little agreement between our independent identification of evidence on 14 example off-label indications and the evidence cited in drug compendia. Furthermore, the compendia we examined were discordant in which combinations of agents and cancers were discussed, how they stated whether an agent is indicated for a specific cancer, the level of detail regarding its use, and how the evidence was discussed and referenced. In general, a small percentage of the available evidence was explicitly cited. There was little agreement in the evidence regarding efficacy cited between drug compendia, and although adverse effects are generally fully described, the compendia are discordant on whether they discuss adverse effects among patients with specific cancers. When compendia did not include an off-label indication, it was impossible for us to ascertain whether silence reflected a conscious editorial decision after evaluation of available evidence, or a case where available evidence was not identified and evaluated.

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