9-27-2010

The FDA Black Box Warning System: The Utmost in Drug and Patient Safety?

Andrew T. Georgi
Yale University

The FDA Black Box Warning System: The Utmost in Drug and Patient Safety?

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Andrew Georgi
2010

Abstract:

THE FDA BLACK BOX WARNING SYSTEM: THE UTMOST IN DRUG AND PATIENT SAFETY? Andrew Georgi (Sponsored by Paul Barash, MD, and Loreta Grecu, MD). Department of Anesthesiology, Yale University School of Medicine, New Haven, CT.

Of the 7856[Ψ] pharmaceutical products under the purview of the Food and Drug Administration (FDA), over six hundred have a black box warning (BBW). As the FDA's highest level of warning included on drug package inserts, this notation is reserved for those drugs that pose significant risks leading to "death or serious injury". However, the types of warnings that warrant this distinction have not been clearly identified and are not always readily justifiable. In addition, great variability exists among the drugs resources charged with transmitting this critical information to healthcare professionals and the public.

The objective of this paper is to establish the most comprehensive list of drugs with a BBW, classify their content according to organ systems, and in doing so evaluate the consistency of information presented by these widely-used drug resources. This was accomplished by cross-referencing and analyzing the drug BBW information from four resources: DailyMed, Micromedex, Facts & Comparisons, and BlackBoxRx.

Six hundred and thirty-five drug/drug combinations were identified as having a BBW. The most frequently affected organ systems were cardiovascular and pulmonary with 200/635 and 144/635 drug BBWs, respectively. DailyMed was the most comprehensive list with 551/635 drugs, still a shortfall of 13%. The four lists were in complete agreement for 416/635 (65%) of the drugs listed. This highlights the FDA's need to review the black box warning system and determine how best to communicate this drug information accurately and efficiently to the healthcare community.

[Ψ] Refers to the number of distinct clinical drugs and packs (both generic and branded) contained in the NLM website dailymed.nlm.nih.gov. Provided on 4/13/10 by Dr. Stuart Nelson, Head of Medical Subject Headings at the National Library of Medicine.

Acknowledgements:

A great deal of gratitude is owed to Dr. Paul Barash and Dr. Loreta Grecu for their near infinite patience, enthusiasm, and guidance with this work. Thank you for letting me make mistakes and learn from the process. Dr. Stuart Nelson is also recognized for his help in accessing black box warning information from DailyMed, without which this work would not have been possible.

Table of Contents

Introduction:

Understanding the purpose and station of the black box warning (BBW) first requires an exploration of its origins and the organization responsible for its development: The Food and Drug Administration (FDA).

Although the Food and Drug Act was not signed into law until 1906, the FDA's birth can be dated back to 1862 when Abraham Lincoln appointed a single individual, Charles Wetherell, to the Department of Chemistry. This modest beginning stands in stark contrast to the sizeable organization into which the FDA has grown. A subsidiary of the Department of Health and Human Services, the Food and Drug Administration has more than 11,000 employees and an annual working budget of over $2.5 billion. (1) Its regulatory responsibilities include governing "the safety and purity" of products that range from the U.S. food supply, nutritional supplements, and cosmetics to vaccines, medical devices, blood products, and pharmaceuticals. This equates to oversight of over $1 trillion worth of products each year, or 25 cents of every dollar spent by American consumers. (2,3) The Center for Drug Evaluation and Research (CDER) is a subdivision of the FDA with over 2200 employees, mostly physicians and scientists, whose chief responsibility it is to regulate the pharmaceutical industry and act as "America's consumer watchdog for medicines." (4)

FDA approval of pharmaceuticals is a complicated and lengthy endeavor requiring intensive animal studies on toxicity and pharmacologic activity which the FDA must review before a drug can even be considered for initial study in humans. From there it must successfully navigate three phases of clinical trials used to assess adverse reactions, safe dosing, drug kinetics, and later its efficacy in target populations with

selected indication(s) for which the drug seeks approval. The FDA in turn must evaluate whether or not these collected data demonstrate that the drug is safe and effective for its intended use and that adequate and appropriate directions and precautions are portrayed in the drug's labeling. In certain instances, such as when a new drug class is introduced or a drug seeking approval carries significant safety risks, an Advisory Committee of outside experts may be convened to establish the conditions of approval and any accompanying special labeling. (4)

All FDA approved drugs require labeling which can be found on the product container, packaging, and an accompanying document referred to as the "package insert" or "product information". It is noteworthy to point out that this drug labeling is written by the pharmaceutical companies, but must undergo negotiation and approval by the FDA. The drug labeling should be "a summary of essential scientific information needed for safe and effective use of the drug. It should be informative, accurate, and neither promotional in tone nor false or misleading, and should be based on data derived from human experience whenever possible." (4) This involves incorporating all clinically relevant information pertaining to that drug including any contraindications, adverse reactions, warnings, or precautions. The information contained within the package insert can also be found in prescribing texts such as the Physicians' Desk Reference (PDR), PDA & smartphone software programs, and online resources, some of which will be described later. In fact, the FDA now requires that pharmaceutical companies file all prescription labels electronically. (5)

The first drug label appeared with isoproterenol, which in 1968 consisted of a two line warning on the inhaler package. (3) Over the years the product label has become

much more extensive and complex, making its navigation by clinicians and patients much too difficult and time-consuming to be of real value. This led the FDA to revisit how these inserts were formatted and establish a more concise and orderly way of presenting the information in 2006, a format to which all newly approved drugs must adhere. (3) The purpose of the new format was to not only make the information more readable and accessible, but also to highlight the most critical clinical information in an appropriate manner. Each package insert is divided into three major sections:

1. The Highlights of Prescribing Information
2. Full Prescribing Information Table of Contents
3. The Full Prescribing Information

As all drugs are associated with a variety of adverse effects, a description of these effects is an essential component of the drug label so that the individual clinician and patient can weigh the potential benefits against these risks. In each section, risks associated with a drug are presented in descending order of importance and severity. (6) As the FDA's utmost cautionary statement, the black box warning appears at the very beginning of the package insert in the "Highlights of Prescribing Information" just below the drug name and year of approval. It appears again at the beginning of the "Full Prescribing Information" section. Aptly named, the BBW must also be bolded with a heading in all caps, and a solid black line on all four sides constituting the box. (3) It is issued only for "the most serious warnings necessary to ensure the continued safe use of the product", (7) and is the highest level of five possible warnings that the FDA can require in the package insert. (8) While the pharmaceutical company writes the contents of the drug labeling, it cannot unilaterally decide to include a BBW. The ability to issue a

BBW is reserved by the FDA. (7) Following the 2007 FDA Amendments Act (FDAAA), the FDA also has the power to mandate labeling changes, including BBWs. (9)

Despite its initial appearance in the PDR with Choramphenicol fifteen years earlier, the "boxed warning" or "black box warning" was not introduced as an official part of the package insert in 1979. (3,9) The Code of Federal Regulations stipulated that "special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data." (7) However, exactly how these "special problems" were identified or specifically what level of proof was necessary remained unclear. In 1998 to address this, Beach et al. published their own research reviewing 206 drugs with BBWs in an attempt to identify what situations resulted in the FDA mandating a BBW. (6) They concluded that six such situations existed:

1. "early detection of a side effect by physicians may result in intervention that may reverse the adverse reaction;
2. a well-defined subset of patients are at higher risk for the treatment;
3. the risk from the treatment of the particular drug may outweigh the benefits in particular circumstances;
4. the dosing or drug interaction is pivotal to the risk;
5. the training of the physician or the setting is crucial; and
6. there are other special requirements for administering the drug"

Eight years later, the FDA subsequently issued general guidelines, still in effect, that identify three situations which require a BBW:

1."There is an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug. This includes potentially life threatening or permanently disabling adverse reactions.

2. There is a serious reaction that can be prevented or reduced in frequency or severity by patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patient in a specific manner, or avoiding use in a specific clinical situation.

3. The FDA approved the drug with restrictions on use and distribution to assure safe use." (1)

These guidelines, however, still fail to delineate a standardized approach or formulaic manner by which a drug is labeled with a BBW. This has lead many clinicians to question the accuracy and utility of the FDA's most stringent warning. Indeed, physician compliance to prescribing recommendations found in BBWs can be highly variable. (10)

Notwithstanding this uncertainty that surrounds the BBW, its effects are felt at all levels of the healthcare totem from the pharmaceutical manufacturer, to clinician, pharmacist, and on to the patient; and despite its black hue, it can often have the effect of a "scarlet letter". For example, the package insert is not the only material required to display the BBW. The pharmaceutical company must include it in all promotional items such as magazine/TV/radio advertisements, exhibits, booklets, literature, or any other material that describes the drug's use by medical professionals. (7) This restricted

advertising and arguably negative publicity can affect sales as both practitioners and patients may be less inclined to use the drug. Physicians potentially bear the brunt of lawsuits from patients who do experience adverse reactions set forth in the BBW as some courts have ruled these warning adequately advise the physician of the drug's associated risks, thus protecting the pharmaceutical company from product liability. (6) This may cause physicians to turn to drugs with which they are less familiar, which carry their own side effect profile, and perhaps are more costly, thus adversely affecting the patient. (7) This indeed was the case with droperidol which will be discussed later. Issuance of a BBW may even result in patient noncompliance to the therapy. (11)

Despite its potential and realized shortcomings, the BBW may still represent the hereto best method to summarize the most severe adverse reactions pursuant to patient safety. It has been referred to as the "FDA's primary instrument to protect the public from potentially dangerous effects of medicines". (10) While only 635/7856[α] drugs have a BBW, they still make-up a considerable amount of prescriptions filled. Looking at a sample population of nearly one million patients, Wagner et al. concluded that over 40% of ambulatory care patients had been prescribed at least one BBW medication during the 30-month study period. (10) Because these warnings are, as a rule, reserved for only the most serious reactions that often can be prevented or reduced with appropriate drug use, failed awareness or respect for their content can be costly. The Institute of Medicine reports 400,000 in-hospital adverse drug reactions per year at a cost of $3.5 billion. (3) It can be extrapolated that misuse of drugs with BBWs may account for a significant portion of these though no actual data exists that can verify this.

[α] See methods for definition of how drugs with a BBW were quantified

Since the majority of BBWs are introduced following post-marketing surveillance (e.g. MedWatch), clear, timely, and effective communication of these and other adverse reactions to clinicians is of paramount importance. (7) However, efforts to do so have not always been effective. (10) With the enormous repository, steady influx, and continuous modifications of medications, physicians face a daunting challenge of keeping pace. In this digital age, fewer patients and healthcare providers actually refer to the package inserts themselves to obtain detailed drug information and instead seek out electronic resources. Numerous resources, publicly and privately funded, free and fee-based, percolate the internet or come packaged in software for PDAs and smartphones. Web-based drug databases such as Micromedex (12), Facts & Comparisons (13), and DailyMed (14) endeavor to supply comprehensive and updated drug information.[β] However, even DailyMed, a multimillion dollar federally funded project and storehouse for the FDA mandated electronic product labels, has the disclaimer that it "does not contain a *complete* listing of labels for approved prescription drugs." (15)

This begs the following questions: If the FDA does not profess to house the entirety of records for the pharmaceutical products it regulates, in particular those products that carry its most severe warning, where can these be found? Also, with increasing time constraints and demands in clinical practice and the overwhelming amount of information presented even in these black box warnings, how can the practitioner stay readily informed of the multifaceted effects these cautionary statements forewarn for their patients?

[β] A more detailed description of these three web-based drug resources which were used along with a fourth resource, BlackBoxRx, for the BBW drug information presented in this thesis research will be provided later.

Statement of Purpose:

The purpose of this paper is to identify all drugs that contain a black box warning and classify these warnings in tabulated form by organ systems. Warnings that did not fall under this umbrella, including drug interactions, administration instructions, and cautionary statements for specific targeted populations, were also classified on the table, accordingly. The data gathered were also used to identify the frequency of the warning classifications found in the BBW drugs. In addition, the resources utilized in compilation of the BBW table were evaluated for relative comprehensiveness and consistency with respect to each other and the collective BBW list they were used to create.

Methods:

A literature search was performed from July 2009-February 2010 via PubMed using the terms “black box warning”, “boxed warning”, and “warning classification” to identify any previous publications of black box warnings classified in the manner. No such articles were identified.

For the purpose of this paper, online drug resources were selected based on ease of access to black box warning information, perceived use by physicians and pharmacists, and availability to the general public. Four web-based drug databases were identified: DailyMed (14), Micromedex (12), Facts & Comparisons (13), and BlackBoxRx (16) (formerly FormWeb). An illustration of the format in which black box warning information was presented in each of these resources is included. (Figures 1-4) (17,18,19,20) A more detailed discussion of the perceived strengths and weaknesses of each database will be discussed later.

First, a collective list of all drugs with BBW labels as found in these four resources was compiled. This combined list will be referred to as the “collective BBW list”. Three of the electronic drug resources provided a separate distinct list of all drugs that contained a black box warning in their respective databases.(16,21,22) Of the four, DailyMed was the only resource which had no such list available; as such, assistance was proved by Dr. Stuart Nelson, Head of Medical Subject Headings at the National Library of Medicine (NLM), to analyze the downloadable XML-based Structured Product Labeling (SPL) found in DailyMed. The SPL content was utilized to create a distinct BBW list in spreadsheet format for DailyMed. (23) Each drug SPL in DailyMed that contained a tag for a black box warning was included on this list. These four lists of drugs

with black box warnings corresponding to the four drug databases will be referred to as the databases' "individual BBW lists". (Figure 5) Of note, combination drugs, including those where one or multiple identifiable components were responsible for the black box warning, were included on the collective BBW list.

In compiling this collective BBW list, it is important to note that disparities existed between the individual BBW lists with regards to which drugs contained a black box warning. Any drug listed as having a black box warning on at least one of the individual BBW lists was included on the collective BBW list. This included drugs in which only certain dose(s) or route(s) possessed a corresponding BBW. In the case of DailyMed where multiple SPLs existed for particular drugs, some with a BBW, some without, only one SPL with a BBW was required to be included on the collective BBW list. (Figure 6)

Drugs were listed alphabetically by generic name including combination drugs which were in addition alphabetized according to their component drugs. An effort was made to identify identical drugs listed in duplicate due to minor variations in the drugs' names among the various drug databases. In these instances, the drug was listed under one name with the alternate name(s) in parentheses. For example, epoetin alfa and ethacrynate were listed with erythropoietin and ethacrynic acid in parentheses, respectively.

From this collective BBW list, each drug specific BBW was analyzed. As a federally funded and sponsored website with manufacturer package inserts uploaded electronically, DailyMed was used as the primary resource from which BBW information was extracted. When discrepancies existed between the BBWs from the various

databases, the BBW from DailyMed was used to create the table. (Figures 7&8) If a drug on the collective BBW list did not contain a BBW in DailyMed, then the BBW found in Micromedex was used. (Figure 9) When neither DailyMed nor Micromedex contained BBW information on a drug, the warning found in Facts & Comparisons was utilized. (Figure 10) BlackBoxRx's BBW was used to create the table information when it was the sole resource for a drug BBW. (Figure 11) When BBW content discrepancies existed within a drug database for same formulation due to different dosing, routes, or SPLs from different manufacturers, the most complete or detailed BBW was used. (Figure 12)

The BBW content gathered and analyzed in this fashion was used to create the "BBW table". In order to maintain a succinct and manageable table, warnings were classified broadly by systems (e.g. torsade de pointe and myocardial infarction under cardiovascular; depression and suicidal thinking under psychiatric). Many cautionary statements contained in the black box warning did not pertain to the aforementioned classifications. These included cautions of drugs that should be *reserved for* or *avoided in* select patient populations, indications, or situations; had specific administration instructions; required or recommended monitoring of patients before/during/after use of the drug; alerted about concurrent medication/substance use; and/or forewarned of potential abuse and overdose. Examples of how various warnings within the BBWs were categorized on the BBW table can be seen in Table 1.

Only warning information mentioned specifically within the BBW was included in the creation of the BBW table. When the BBW message referred the reader to other sections of the product label for additional warnings and instructions, this information was not analyzed nor included in the table. Also, any warning or cautionary symptoms

(e.g. rash, nausea, cough) mentioned in the BBW separately or as part of a clinical syndrome were presumed relevant and categorized on the BBW table. As an example, antipsychotics warn of "increased risk of death" and go on to specify that most were "either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature". (Figure 13) Since "pneumonia" is listed as a specific example of cause of death, the "pulmonary" classification in addition to "cardiovascular" and "infectious diseases" are included for antipsychotics that carry this black box warning label. Symptoms typically associated with a system (e.g. "headache" with "neurologic"; "abdominal pain" with "gastrointestinal") were categorized accordingly.

When a *risk* was identified as pertaining distinctly to or being greater in a select population because of comorbid illness or concurrent medication, only the actual *risk* was classified on the table. In addition to this, the BBW categories for "Caution Select Circumstances" or "Concurrent Item Restriction" would be marked to indicate that a comorbid illness or concomitant medication, respectively, played a role in the BBW. For instance, metformin/repaglinide lists a warning for "lactic acidosis" and states that the "risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure." (Figure 14) From this BBW statement, only the "Metabolic/Electrolyte Disturbance", "Caution Select Circumstances", and "Concurrent Item Restriction" categories were marked on the BBW table.

The total number of BBWs with content pertaining to each classification on the table was also calculated. When multiple distinct warnings relevant to a common classification were found within a single BBW, that category was marked only once on

the BBW table and counted only once for the total number of classifications. For example, muronomab-CD3 contains a warning for "central nervous reactions" in addition to "seizures, coma, cerebral edema, cerebral herniation, … and paralysis." (24) All of these warnings are classified under "neurologic" and counted as one "neurologic" BBW in the calculation. In addition, certain warning content could potentially belong to multiple classifications. As an example, methoxsalen warns of risk of "melanoma". (25) Both the "dermatologic" and "oncologic" classifications were marked and counted towards the frequency of each category (one "dermatologic" BBW and one "oncologic" BBW) based on this risk.

As mentioned previously, discrepancies existed between the drug databases; hence, the relative comprehensiveness of each was evaluated. This was achieved by identifying the presence or absence of a drug's BBW in each database as compared to the collective BBW derived from all four resources as described above. Drugs not present on a database's individual BBW list were searched for independently by generic and trade names using the database's search function. Drug BBWs found in this manner were considered present even though not listed on the database's individual BBW list. (Figure 15)

In some cases, the warnings were present as a BBW in one database but only as a bolded warning[γ] in others. These bolded warnings were identifiable in BlackBoxRx and DailyMed. When a warning was identified as a BBW in at least one database, it was not counted as present in the other databases that identified it as a bolded warning. The number of instances where this occurred was also calculated.

[γ] Bolded warnings do not carry the same level of risk as BBWs. Similar to BBWs, they appear at the beginning of the package insert and are emphasized by bolded text but are not further accentuated with a black box.

BlackBoxRx's individual BBW list did not include many combination drugs. When formerly listed under the name of Formweb, BlackBoxRx included a statement (since removed) notifying its users that combination drugs in which a separate black box warning was already listed under the responsible component drug(s) name(s) would not be included separately on its BBW list. Thus the omission of these combination drugs was considered *intentional* by BlackBoxRx. Any combination drug where its component drug(s) and BBW(s) were listed in BlackBoxRx and collectively contained the *same* warnings as found in the combination drugs was considered present for the purpose of determining the relative comprehensiveness of BlackBoxRx. In cases where the individual BBWs of components contained different information from the combination drug, the combination drug was considered missing from BlackBoxRx unless the combination drug was separately included on the individual BBW list. However, the other three drug databases did include combination drugs on their individual BBW lists even in cases where identifiable component drugs were responsible for the warning and were listed separately. Thus, combination drugs not listed on the other three resources were presumed to be *unintentional* and counted as missing even if their components were listed. The number of combination drugs counted as present in this manner was calculated for each database.

Also, for all combination drugs on the collective BBW list, the responsible component(s) with a BBW were identified when possible. In some cases, the component drug would be explicitly mentioned in the BBW; otherwise, the combination drug warning was compared with the warning(s) of its component drugs to determine if it was the same for one or more of its constituents. In some instances the BBW pertained to that

specific combination drug and differed from its component drug warnings; in others, it was unclear which component(s) were responsible. These drugs were also identified.

Results:

A total of 635 drugs/drug combinations with black box warnings were collectively identified using the four aforementioned resources. (Table 2) Of these, 101 were combination drugs. Combination drugs that carry BBW(s) identical to their component(s) are identified in the table by displaying the component drug(s) to which a BBW pertains in bold type. For example, the combination drug "abacavir sulfate/lamivudine/zidovudine" is presented on the table in all bolded font indicating that all three component drugs contribute to its BBW. For combination drugs where it is not discernible to which component(s) the BBW pertains, no part of the combination drug is bolded. This is seen a farther down the table with "acetaminophen/hydrocodone bitartrate".

The classifications for each drug's black box warning are also displayed on Table 2. It should be noted on the table that erlotinib hydrochloride is listed, but has no classification of its black box warning. This is due to the fact that while erlotinib hydrochloride is listed on the DailyMed individual BBW list, when referring to its SPL the BBW is an empty box. (Figure 16) (26) Also, Sodium Polystyrene Sulfonate shows no categorization in the table as its BBW simply states "cation-exchange resin". (Figure 17) (27)

Table 3 depicts the frequency of BBWs on the collective BBW list that fall into each classification. The majority of warnings contained cautionary statements geared toward select patient populations or indications (66%) as well as administration and monitoring precautions (63%). Of organ systems, cardiovascular was the most affected with 200/635 (31%) BBWs, followed by pulmonary (144/635 or 23%), and

hematologic/bleeding (143/635 or 23%). Warnings pertaining to the eye (12/635 or 1.9%), ears-nose-throat (ENT) (9/635 or 1.4%), endocrine system (8/635 or 1.3%), and autoimmunity (8/635 or 1.3%) were relatively infrequent.

In order to determine the relative comprehensiveness of each drug resource, a comparison of the number of BBW drugs found in each of the four drug databases as compared to the collective BBW list is presented on Table 4. DailyMed contained the most drugs with a black box warning with 551/635. It was followed in succession by BlackBoxRx (536/635), Micromedex (514/635), and Facts & Comparisons (500/635). The number of combination drugs contributing to each database's total is also presented on Table 4. The frequency of these combination drugs found in each database followed the same trend as the database's total drugs. This last statement holds true provided that BlackBoxRx's component drugs are added to its combination drug totals. As described in the methods, these 63 combination drugs, intentionally excluded from BlackBoxRx, had their component drug(s) that were responsible for the BBW listed in BlackBoxRx's database.

The number of BBW drugs found on the collective BBW list but missing from each individual drug database is tallied in the lower section of Table 4 along with the database's method of exclusion. Three methods were identified: 1) The warning was present in the drug label as a bolded warning but was not listed as a black box warning. BlackBoxRx and DailyMed identified drugs with bolded warnings; BlackBoxRx listed seven drugs, DailyMed eight, that were listed as BBWs in at least one of the other databases. 2) The drug was listed in the database; however, it was not associated with a BBW. Despite specifically searching each database for drugs from the collective BBW

list, often these drugs were found not to contain a BBW in several of the databases. 3) The drug itself was not listed within the database. This last method was most frequent with BlackBoxRx as its database exclusively lists drugs with BBWs and bolded warnings. The only two listed for BlackBoxRx refer to "metoprolol tartrate" and "hydrochlorothiazide/metoprolol tartarte". Metoprolol tartrate carries a more extensive BBW than metoprolol succinate. Metoprolol tartrate's BBW contains additional precautions for patients with bronchospastic diseases, diabetes/hypoglycemia, pheochromocytoma, or undergoing major surgery. It also cautions of precipitation of thyroid storm with withdrawal of metoprolol tartrate in patients with thyrotoxicosis. (28) As BlackBoxRx lists only "metoprolol" in its database and the BBW does not include the extra precautions found in that for metoprolol tartarte, metoprolol tartrate and the combination drug hydrochlorothiazide/metoprolol are considered missing from the BlackBoxRx BBW list.

Since no established gold standard resource for BBW drugs exists and omissions as well as add-ons existed within each database, the reliability of each was measured with respect to the others by looking at the consistency between the databases' BBW lists. (Table 5) The four lists shared 416 BBW drug/drug combinations among all of them. BlackBoxRx maintained the highest consistency with the other databases, having both the most BBW drugs shared with two other databases (80/536) as well as with one (35/536). It also had the least number of BBW drugs where it was the sole source (5/536) and least number of BBW drugs missing from its list that were found on the other three lists (7/99). DailyMed had the most BBW drugs where it was the only resource listing them (55/551). Some examples of these "drugs" not found in the other three databases include

compounds such as allergy testing solutions (see boxelder maple pollen, cat hair/pelt, etc. on table), a “sterile water” preparation to be used “only with automated compounding devices”, and a drug (erlotinib hydrochloride) with an empty black box warning as mentioned above. (Figure 16) Facts & Comparisons had the second most number of BBW drugs only found in its database (17/500), four of which were listed only as bolded warning on two other lists. The actual package inserts of drugs such as these were not examined to determine whether or not the drugs in fact deserved a BBW.

Discussion:

No previous publication identifying and classifying all black box warnings was found through web searches or a literature review in PubMed. The BBW table developed for this thesis research constitutes the first record of any effort to classify and quantify data related to drug BBWs. The table provides an overview of which drugs the FDA designates as BBW compounds and categorizes their BBWs by affected systems relevant to their prescribing. As such, it can be used as an initial resource in identifying which drugs have serious adverse reactions requiring a BBW and what areas are of principle concern. It also serves as a valuable cue to recall specifics of black box warnings once these have been reviewed by the healthcare professional.

The types of precautions and concerns that the FDA deems an important element in these black box warnings have also been identified. As seen in Table 3, 416/635 BBW drugs (or 66%) contain information warning of increased risk associated with a specific patient population, indication, or clinical scenario. Many times the warning is relevant only to these circumstances. Nearly as frequent are specific instructions warning of routes of administration, experience/expertise required for prescribing, monitoring practices, and prerequisites for dispensing facilities (found in 402/635 BBW drugs). It should come as no surprise that the cardiovascular and pulmonary systems are the most frequently affected organ systems.

These results also draw attention to the significant variability even among reputable resources in the drug information that is presented. The number of BBW drugs missing from each database ranged from 85 to 135. This constitutes a deficiency of between 13-21% when compared to the collective BBW list. The complete concurrence

in BBW lists between all four resources was only 65%. Ten percent of the drugs listed in DailyMed were not on any of the other three databases' individual BBW lists. This brings into question the accuracy and efficiency with which black box warning information is conveyed. This is in addition to the questions that remain about the validity and utility of the black box warning itself: [1] How clinically relevant is the black box warning? [2] What is the best resource for accessing black box warning information? There has been much concern with regards to the first question which can be illustrated by the case of droperidol. (1)

Droperidol

Droperidol (Inapsine), is a member of the butyrophenone class of antipsychotic medications and was developed in the 1960's by a Belgium company Janssen Pharmaceutica. Although used by psychiatrists and oncologists, in 1970 it received FDA approval as an injectable antiemetic and adjuvant to general anesthesia. (29) Despite the recommended starting dose of 2.5mg (IV) on the package insert, anesthesiologists as the drug's chief prescribers would typically use a dose of 0.625mg to 1.25mg (IV) to achieve the desired effect. Over the next 30 years, these "off-label" low-dose regimens became a widely accepted first-line therapy for prophylaxis and treatment of post-operative nausea and vomiting (PONV) and by 2001 droperidol boasted roughly a 30% market share for antiemetics. (29,30,31,32,33)

In the UK, droperidol *was* also available in an oral preparation (Droleptan) used at much higher doses in the chronic management of psychiatric patients. In the beginning of 2001, the Medicines Control Agency (UK's equivalent of the FDA) raised concerns regarding evidence of QT prolongation in psychiatric patients on chronic oral doses (>25

mg) of droperidol. (34,35) The proprietary maker of droperidol, Janssen-Cilag Ltd., decided to voluntarily withdraw all preparations from the UK market citing inadequate pricing and volume to justify the continued production of solely the parenteral formulation of droperidol used for PONV. (29,34,36)

Still marketed in the U.S., the parenteral formulation of droperidol in turn that year received a BBW based on a review of 273 case reports the FDA had gathered over the preceding 4 years. (37,38) An Advisory Committee for the FDA had concluded from these case reports that there was enough evidence and concern for QT prolongation and/or torsades de pointes, in some cases resulting in death, that a BBW was warranted. The warning not only underscores these concerns but also extends the recommendation that droperidol be "*reserved for* use in the treatment of patients who fail to show an acceptable response to other adequate treatments" and stipulates that "ECG monitoring should be performed prior to treatment and continued for *2-3h after* completing treatment". (39) This action by the FDA created a commotion within the anesthesia community and many cried foul as to the merit and reasons behind their decision. (37,40)

Of the 273 case reports, 127 were considered "serious adverse outcomes", 74% of which were reports that came from outside the U.S. (37) Seventy-four of the 127 had evidence of a cardiac component, but only 17 (12 according to White PF (29)) of these occurred at doses ≤2.5 mg, 10 of which were ≤1.25 mg, the doses typically used for PONV. (37,40) A total of 89 deaths were reported, only 2 of which were in patients who received ≤2.5 mg, while the majority had received much larger doses (25-250 mg) that were typically used in psychiatric patients as mentioned previously. (37) Dr.'s Habib and Gan examined more closely the 10 cases involving doses of droperidol ≤1.25 mg and

found that none had demonstrated a cause-and-effect relationship, as many were subject to confounding factors including co-administration of other medications with known proarrhythmic effects. (40)

Droperidol's manufacturers were almost immediately affected by the FDA's introduction of a BBW. In the year that followed, droperidol sales fell 10-fold and it disappeared off of many hospital formularies. (29,41) By 2007, a survey of approximately 300 anesthesiologists showed that use of droperidol as a first-line agent for both prophylaxis and treatment of PONV decreased from 47% & 38% to 5% & 8% respectively. (38) Of those not using droperidol, 39% cited so because of "medicolegal reasons" surrounding the BBW, 30% due to its nonavailablility; only 1.5% did so because they believed droperidol to be dangerous. In the same survey, 92% also responded that they did not feel the BBW was justified and 60% stated that they would use droperidol as their first line agent for PONV prophylaxis if the BBW was removed. (38)

The resulting increase in the use of other drugs such as promethazine, actually resulted in a concomitant increase in overall adverse events. (42,43) The 5-HT_3 antagonists (ondansetron, dolasetron, granisetron) that largely filled the gap in managing PONV left by droperidol's spectacular decline had their own set of unique and not so unique problems. When the BBW was issued, generic droperidol was substantially less expensive: approximately 1/10 to 1/30 the cost of its replacement 5-HT_3 antagonists (ondansetron, dolasetron, granisetron). (29) Ironically, the 5-HT3 antagonists too are associated with QTc prolongation and cardiac arrhythmias, resulting in Health Canada (the Canadian equivalent of the FDA) issuing a BBW for dolasetron. (41) Even in a study

done by its own manufacturer, ondansetron did not demonstrate any safety or efficacy advantages over low-dose droperidol. (29) Studies have even been performed to investigate another well-known butyrophenone, haloperidol, as a treatment for PONV as it does not contain a BBW for torsades de pointes and thus does not carry the same "medicolegal" repercussions or burdensome monitoring. (41,43)

A number of studies involving droperidol at these lower doses have failed to demonstrate any cardiovascular adverse events such as arrhythmias, including torsades de pointes, or sudden death. (41,31,44,45) While it is true that even low-dose droperidol exhibits dose-dependent QTc prolongation, it is modest and short-lived. (41)

Despite the mounting evidence as to the safety of low-dose droperidol for PONV, the BBW inclusion of "doses at *or below* recommended doses" persists. (39) During the 2003 Advisory Committee meeting, the FDA medical office that spearheaded the BBW labeling for droperidol clarified that the BBW does not pertain to doses <2.5 mg, as these doses are off-label and lack sufficient evidence to linking them with a significant risk of QT prolongation and torsases de pointes. (43) It further emphasized that "clinicians should exercise medical judgements and use drugs according to their own medical judgment, [the FDA] really [doesn't] regulate off-label use of drugs." (43) This clarification has not changed how many health care providers and agencies view droperidol's use. (43) The FDA did request that the then generic manufacturer Akorn Pharmaceuticals, perform a study or literature review to establish droperidol's safety at these lower doses in order to receive separate labeling; however, Akorn declined, stating that this would not be economically feasible. (41,43) Even while advocating droperidol's BBW, Ludwin et al. suggest that it needs to be modified to more appropriately state

"Doses of Inapsine below 2.5 mg are considered off-label. The FDA has no position on the safety or efficacy of doses below 2.5 mg." (43)

It is appropriate that the FDA has brought attention to the adverse cardiac events that can occur with the use of droperidol and that it continue to raise awareness for adverse reactions from other drugs as they percolate in via MedWatch, the new Sentinel system, and other post-marketing surveillance systems; however, care must be taken that the FDA issue its highest warning only when the situation warrants it, or risk indifference and inertia on the part of healthcare providers.

Resources for Black Box Warning Information:

DailyMed, as the federally funded repository for all mandated electronic drug labeling, was the most highly scrutinized and held to the highest standard. It is a website run by the National Library of Medicine (NLM) that provides "a standard, comprehensive, up-to-date, look-up and download resource of medication content and labeling as found in medication package inserts" and "high quality information about marketed drugs". (15) Despite these statements, on the very same introductory webpage DailyMed acknowledges "[DailyMed] *does not* contain a complete listing of labels for approved prescription drugs" and that "the drug labeling has been reformatted to make it easier to read but its content has not been altered *or verified* by FDA or National Library of Medicine". (italics added)

DailyMed did provide the most BBW drugs out of the four resources; however, 10% of these were not found in any of the other resources and it was still missing 13% of the drugs found on the collective BBW list. DailyMed also appeared to provide the most detailed and accurate drug information as each individual drug package insert could be

viewed in its entirety. DailyMed also provides a "Drug Label Sections" menu at the beginning of the package insert that links to the various sections of the product label. (Figure 1) Drugs can be searched for individually by generic and/or trade names. Also as a free website it is readily available to any interested party. However, in practice its use is much more cumbersome than the other resources and despite boasting the most complete database in terms of the number of BBW drugs, finding accurate drug labeling was not always possible as will be illustrated.

As DailyMed does not provide a distinct list of BBW drugs, the user is forced to search for each drug individually unless he/she possesses the technological savvy to extract this information from the downloadable XML files. Even if this is accomplished, navigating through the list is not so simple as many drugs are not listed once, but numerous times accounted for by each separate SPL for each manufacturer and formulation. Still more concerning, the content of these SPLs do not always provide the same information. This is best illustrated by looking at metformin hydrochloride as an example.

A search for "metformin" using DailyMed yields 63 results. (Figure 18) Forty-five of these are various formulations of metformin hydrochloride (tablet; tablet, film coated; tablet, extended release; etc.) while eighteen are combination drugs containing metformin. The vast majority contain the BBW seen in Figure 19. However, of the forty-five individual metformin SPLs, five did not contain a BBW and one contained a highly inadequate BBW. (Figure 20 & Figure 21) Even among the 18 metformin combination drugs, five had abridged BBWs, three had no BBW, and one had a BBW pertaining to the

other constituent drug but not metformin (Figure 22). This supports the notion that the content found in DailyMed indeed needs to be *verified* by the FDA and NLM.

Micromedex has the third most BBW drugs listed and was the second most consistent between the various databases. Micromedex[θ] is a private, fee-based, drug resource used in many hospitals, pharmacies, and clinics. It gives access to and pools from the drug information found in the Physicians' Desk Reference (PDR) and Drugdex[θ] among other sources. Drug information, including black box warnings, are presented in drug "summary documents" which primarily draw upon Drugdex and link to this source when additional information is desired. Unlike DailyMed, Micromedex provides a distinct list of all drugs within its database that contain a BBW (Figure 5) When a drug is accessed from this BBW list, the user is taken to the black box warning section of the drug summary document. (Figure 2) The black box warning information in this section contains the same language as the official drug product labeling albeit at times abridged. It also clearly states the routes to which the BBW pertains and differences in the BBW for these if they exist. Similar to the "Drug Label Sections" menu in DailyMed, Micromedex contains a table of contents at the left hand margin which links the user to the various sections of the drug prescribing information. Above the summary document's black box warning section is a link titled "(see details in DRUGDEX®)" which takes the user to the full BBW label as found in DailyMed. (Figures 1&2) The BBWs found in the "summary document" page as well as the Drugdex link were the primary source for BBW information gathered from Micromedex. Similar to DailyMed, it also has a search function which includes the ability to look for drugs by trade names and contains full

[θ] Micromedex as well as Drugdex are products offered by Thomson Reuters Healthcare Division.

drug labeling information in addition to the BBW. However, unlike DailyMed, it requires a paid subscription for access.

Facts & Comparisons was another drug resource utilized and is a subsidiary of Wolters Kluwer Health. Similar to Micromedex, it too provides a distinct BBW list. As compared to DailyMed and the Drugdex section of Micromedex, it does not usually include the exact wording of a BBW but in most cases a truncated rearrangement with pertinent details (Figures 3 & 5). Unlike the other two, however, it does allow BBW searches by therapeutic classes and includes these therapeutic classes on its BBW list. A unique feature of Facts & Comparisons when compared to the other three is its search function which has an auto fill feature to help the user with his/her query. (Figure 23)

Of the four resources, Facts & Comparisons had the least number of drugs on its individual BBW list. This is despite the fact that 29 of the drugs included were *not actually on* their BBW list (Figures 5 & 19) but were found to have a BBW by using its search function to individually look for BBW drugs that were found on other lists. (Figure 15) It also had at least four instances where it likely listed a black box warning inappropriately for drugs containing a bolded warning. It, too, requires a paid subscription.

BlackBoxRx.com, as the name implies, is a web-based list of only those medications that carry a black box warning[Ψ]. It is published and updated by Dr. Joyce Generali, Director of the Drug Information Center at the University of Kansas Hospital. BlackBoxRx provides an alphabetized list of BBW drugs by generic drug name. (Figure 5) Similar to Facts & Comparisons, drugs can also be searched for by therapeutic class.

[Ψ] BlackBoxRx also lists drugs with a bolded warning connoted by a "*" next to the name.

The black box warnings typically contain key information in the same language as used in the actual product labels (SPLs in DailyMed) though in bullet format and often truncated to remove seemingly repetitive information. (Figure 24) Information on when the BBW was last updated is clearly displayed and the user is able to sign up for email notification of any future updates.

BlackBoxRx had the second most BBW drugs listed as well as the greatest degree of concordance with the other databases. However, unlike the other three, it does fail to provide an individual drug search function including the ability to search for drugs by trade name, does not include drug label information in addition to the BBW nor a web link to this, and does not disclose what resources were utilized to compile its BBW list. BlackBoxRx also does not specifically include many combination drugs and does not list many specific formulations (e.g. metoporolol tartrate and metoprolol succinate) though often in these latter cases it will identify the route of administration which is often formulation specific (e.g. it does not list olanzapine and olanzapine palmoate separately but does list olanzapine "oral and injectable formulations"). The best features of this website arguably are its concise presentation and free access, providing useful information to clinicians and patients alike.

Limitations

There are a number of limitations with the data presented in this paper. Only four of the numerous resources for black box warnings available to the practitioner or patient were utilized in identifying drugs that contained a BBW. Doing so may not have accounted for all the drugs that contain a BBW and resulted in an incomplete table. Likewise, it is also possible that some of the drugs presently included in the BBW table

may have erroneously been included as the actual package inserts were not examined to confirm. Also, drugs were included on the list even if the BBW was found in only one of the resources and/or if the BBW pertained only to one or several of many specific preparation(s), dose(s), or route(s), making each drug inclusion only as reliable as the source where it was listed. No distinction was made in the table with regards to which database was utilized for which drug or which dose(s) or route(s) carry the black box warning.

In addition, the BBW information analyzed in order to categorize each warning was taken only from one resource as described in the methods. Many times it was found to not contain the *exact same* BBW information present in other databases. In comparing each database to the others, it was only verified that a BBW was present/absent for each drug, not that the information was identical.

An attempt was made to include all content from the black box warning in the table, even if the included symptom or event was not perceived to be "life threatening or permanently disabling" itself, per se. A BBW that specifically included "nausea" would receive a gastrointestinal categorization on the table and be indistinguishable from a drug that warned of "ischemic colitis" by looking at the table. Thus, classifications marked on the table do not always reflect on what may be perceived as the primary reason for the BBW, but highlight what systems/symptoms are affected and thus what areas deserve special attention.

The categories were selected by the author to best describe in a concise and displayable manner the exceptionally varied BBWs, and only gives the reader a *general* idea of affected organ systems or other general precautions included in the BBW. They

fail to give the complete details of each BBW as well as other pertinent information including other adverse effects, contraindications, precautions, prescribing information, and precautionary actions to be taken for these as described both inside the BBW and elsewhere in the package labeling.

Also, the information contained in this paper is only as current as when the data were evaluated and does not reflect any additional changes made to current drugs nor to drugs that have since been added or removed. The author attempted to describe as specifically as possible the manner in which the BBW table and other results were derived to allow the reader the ability to determine how best to use this information for himself/herself.

Conclusion:

While the FDA has already taken great strides towards fulfilling the initiatives set forth in the Food and Drug Administration Amendments Act of 2007, a great deal of ground has yet to be covered. (46) For health care providers' confidence to be restored and maintained in the black box warning system, such warnings need to be founded on sound clinical evidence with clear and timely distribution to the practitioner. A more focused and organized BBW could help with physician and patient adherence. Many of the black box warnings contain a redundancy of precautions that would be more forceful if stated concisely. BBWs that explicitly state the contraindications or cautionary actions to be taken do have better physician compliance than those that do not. (10) As the organization of the package insert has become more clearly defined, so should the black box warning itself with a succinct statement of risks, the population or circumstance to which these risks apply, and what actions should be taken; this before a more detailed

explanation of risks and reference to supporting evidence is made. Supporting evidence is critical to ensure that the same mistakes are not made as were seen with droperidol. Referring to paucity of proof used in their decision to place the black box warning, Dr. Chang, the FDA medical officer in charge of droperidol labeling, stated, "Unfortunately, this is not atypical. We see a lot of cases like this where the information is just simply incomplete." (43) Dr. Chang's comments not only highlight this regrettable reality but also the need to effect its change.

The FDA's most stern warning is only as effective as the medium in which it is communicated. Inconsistencies seen with the black box warnings raise questions as to the accuracy of other product label information being presented to the healthcare community and public at large. As "America's consumer watchdog for medicines" and sole sovereign over the issuance and content of BBWs, the FDA is in the best position to act as the preeminent resource for black box warning information. Whether or not they elect to do so remains to be seen.

Tables and Figures:

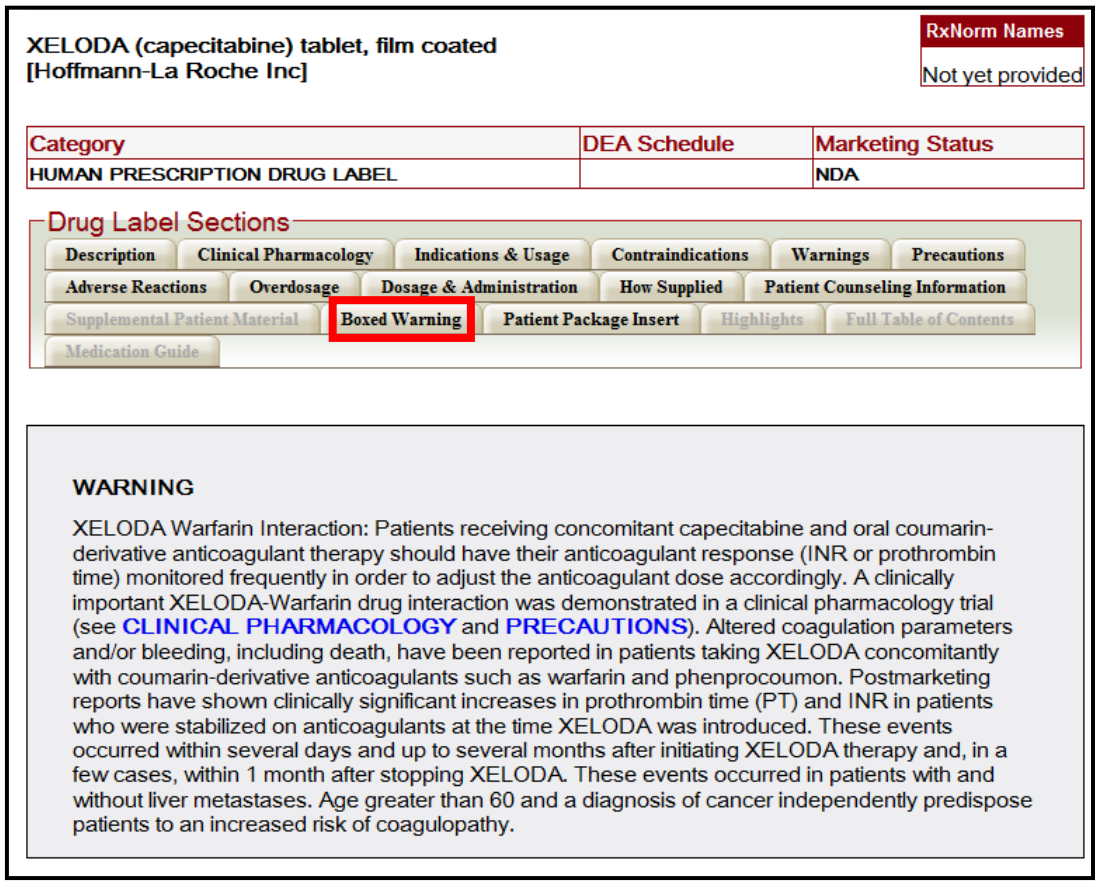


Figure 1: Capecitabine as example black box warning from DailyMed.

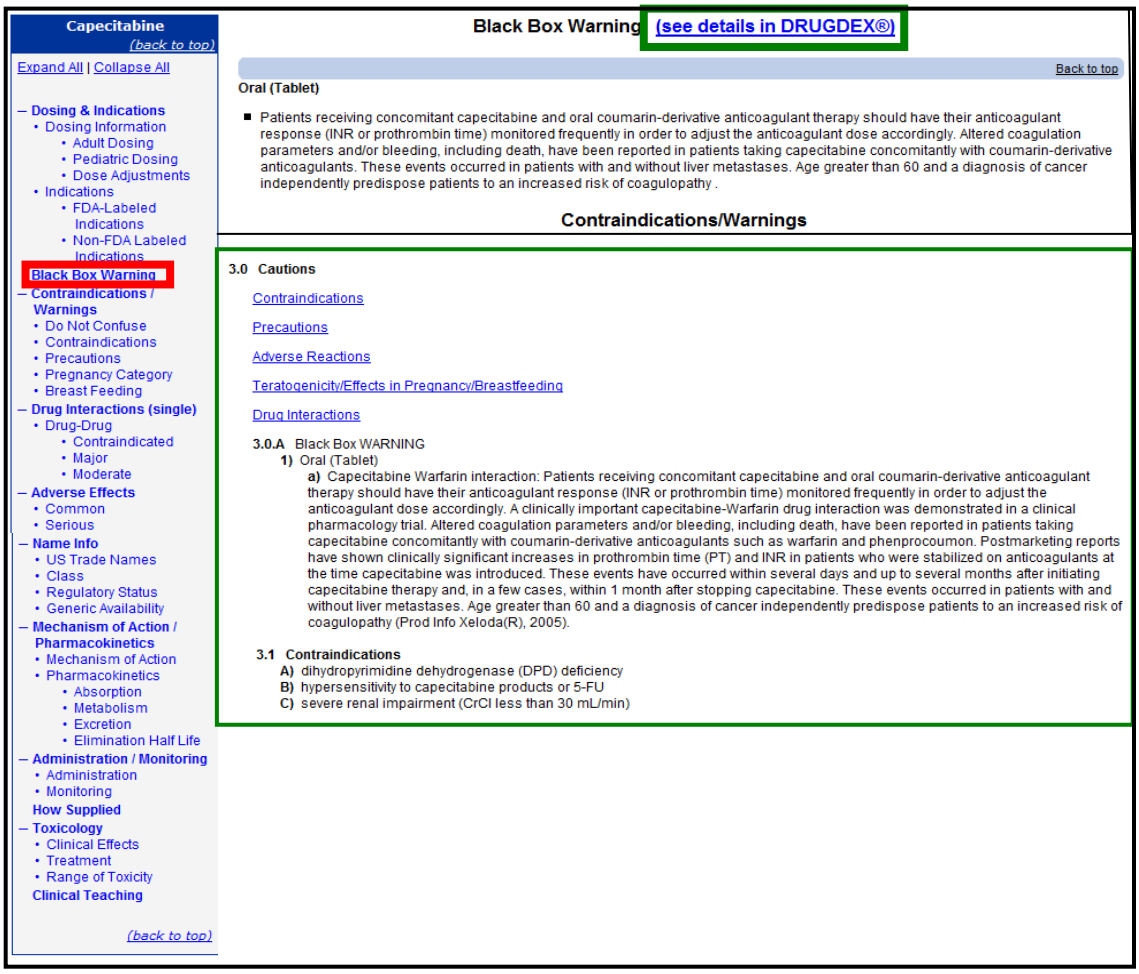


Figure 2: Capecitabine as example black box warning from Micromedex. Red box highlights black box warning link in side bar table of contents that takes the user to the black box warning section of the drug's "summary document". Further information is available by clicking on the Drugdex link (thick green box) which takes the user to the black box warning section of Drugdex (thin green box).

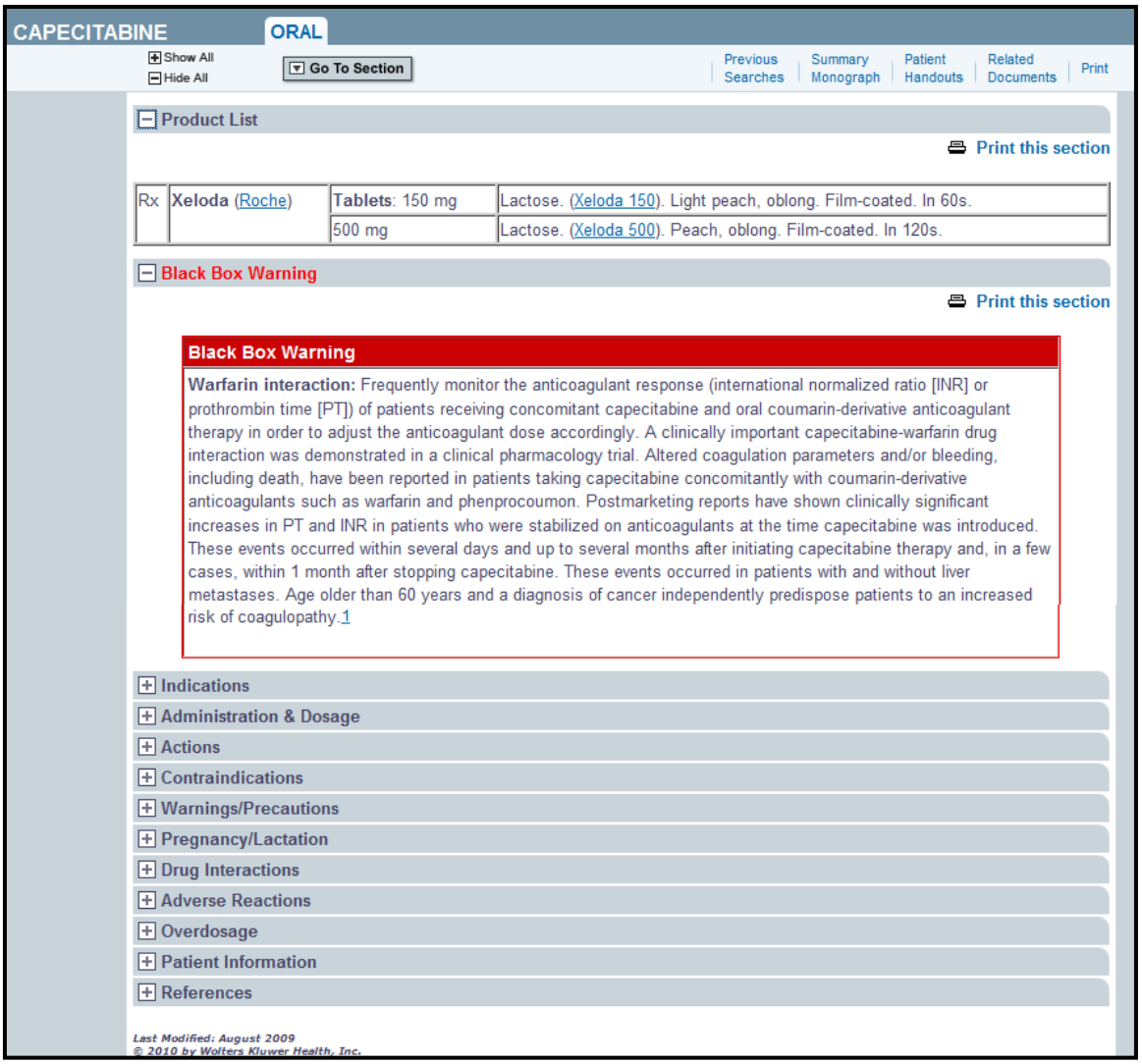


Figure 3: Capecitabine as example black box warning from Facts & Comparisons.

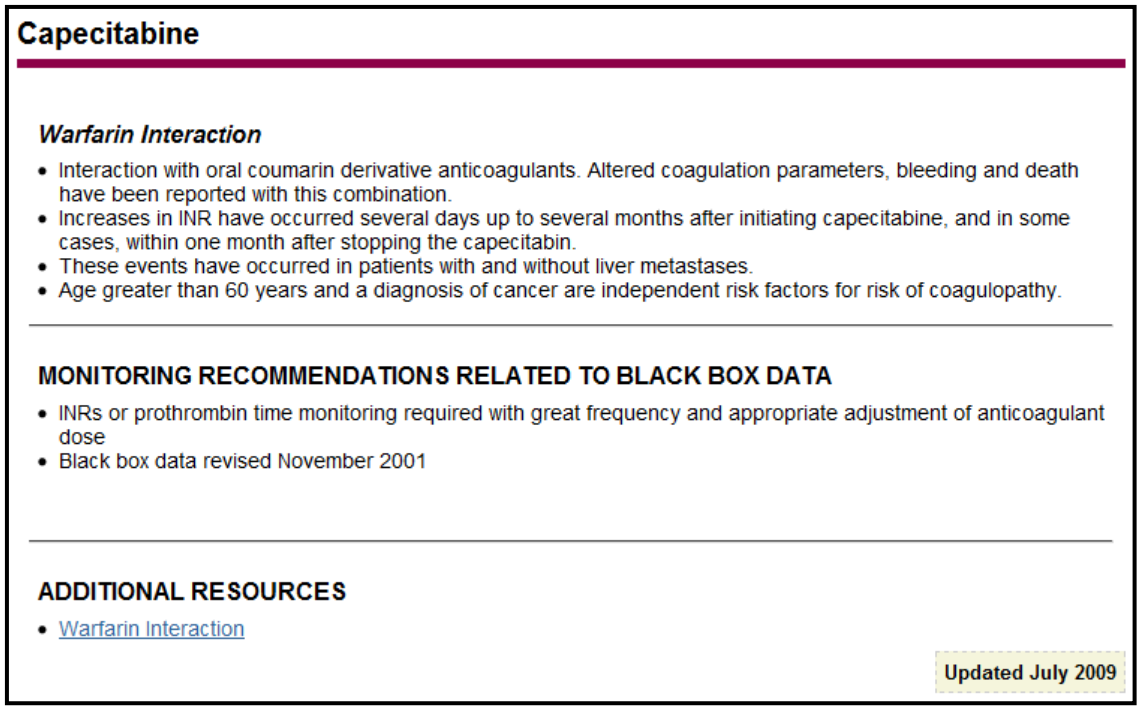


Figure 4: Capecitabine as example black box warning from BlackBoxRx.

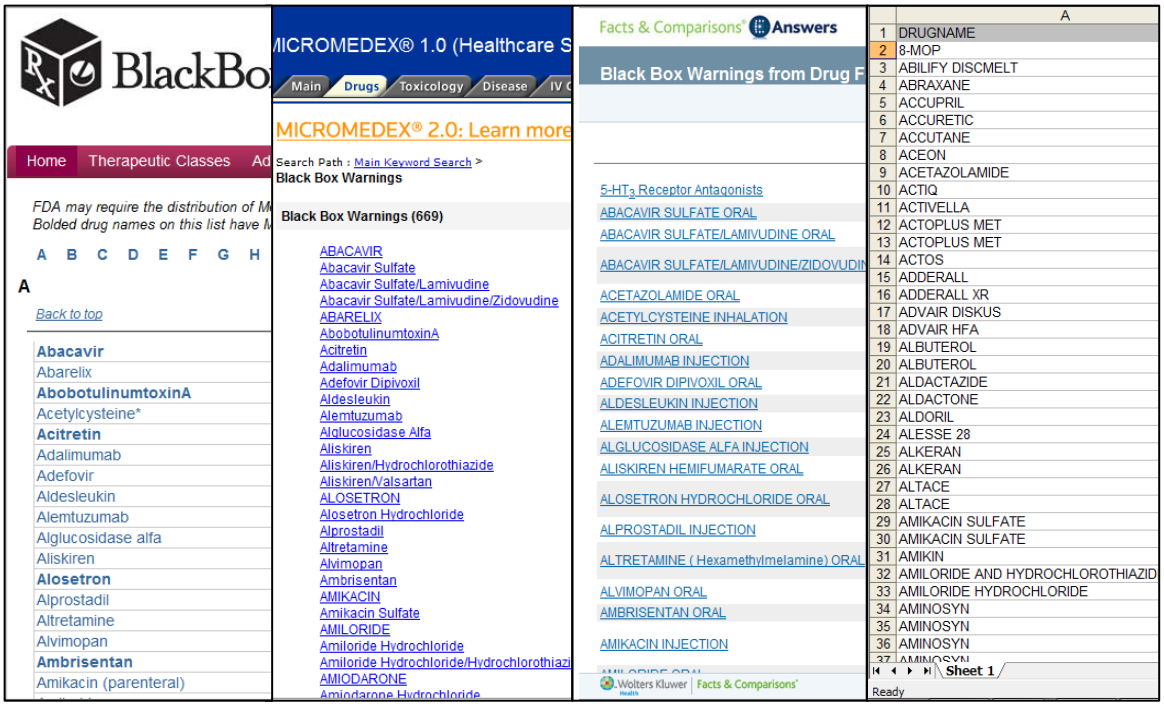


Figure 5: From left to right, screenshots of sections from the individual BBW lists for BlackBoxRx, Micromedex, Facts & Comparisons, and DailyMed.

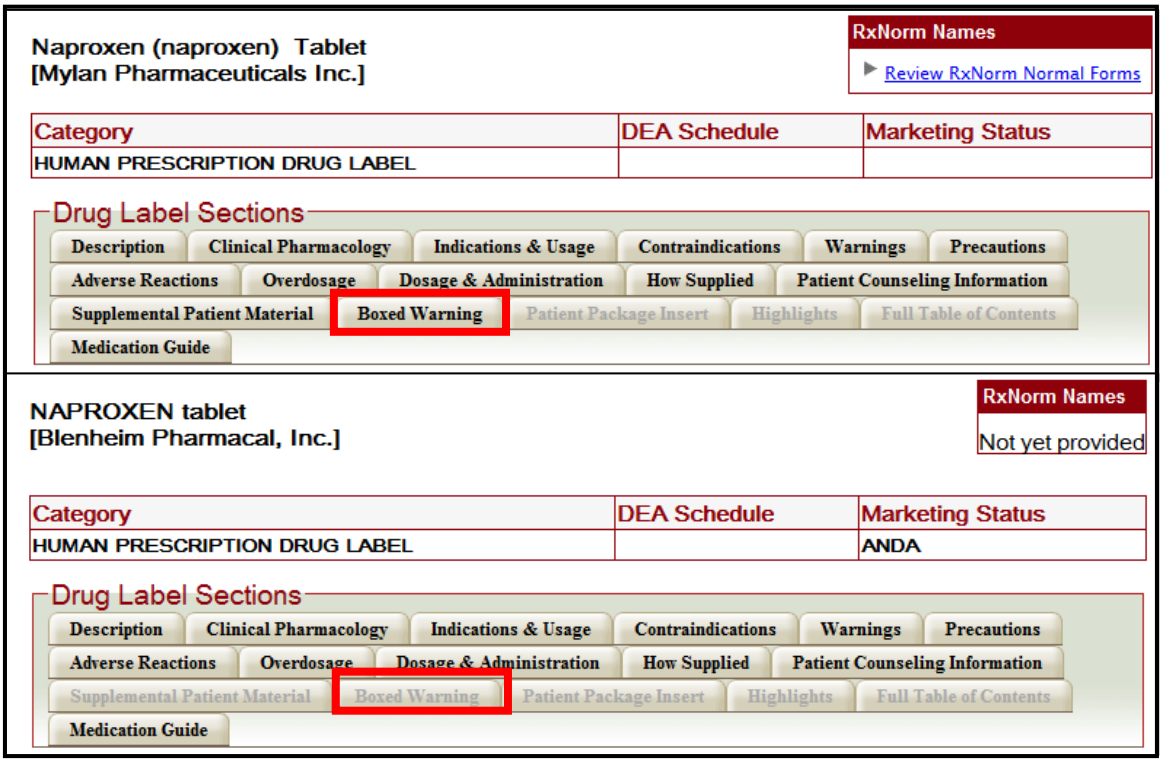
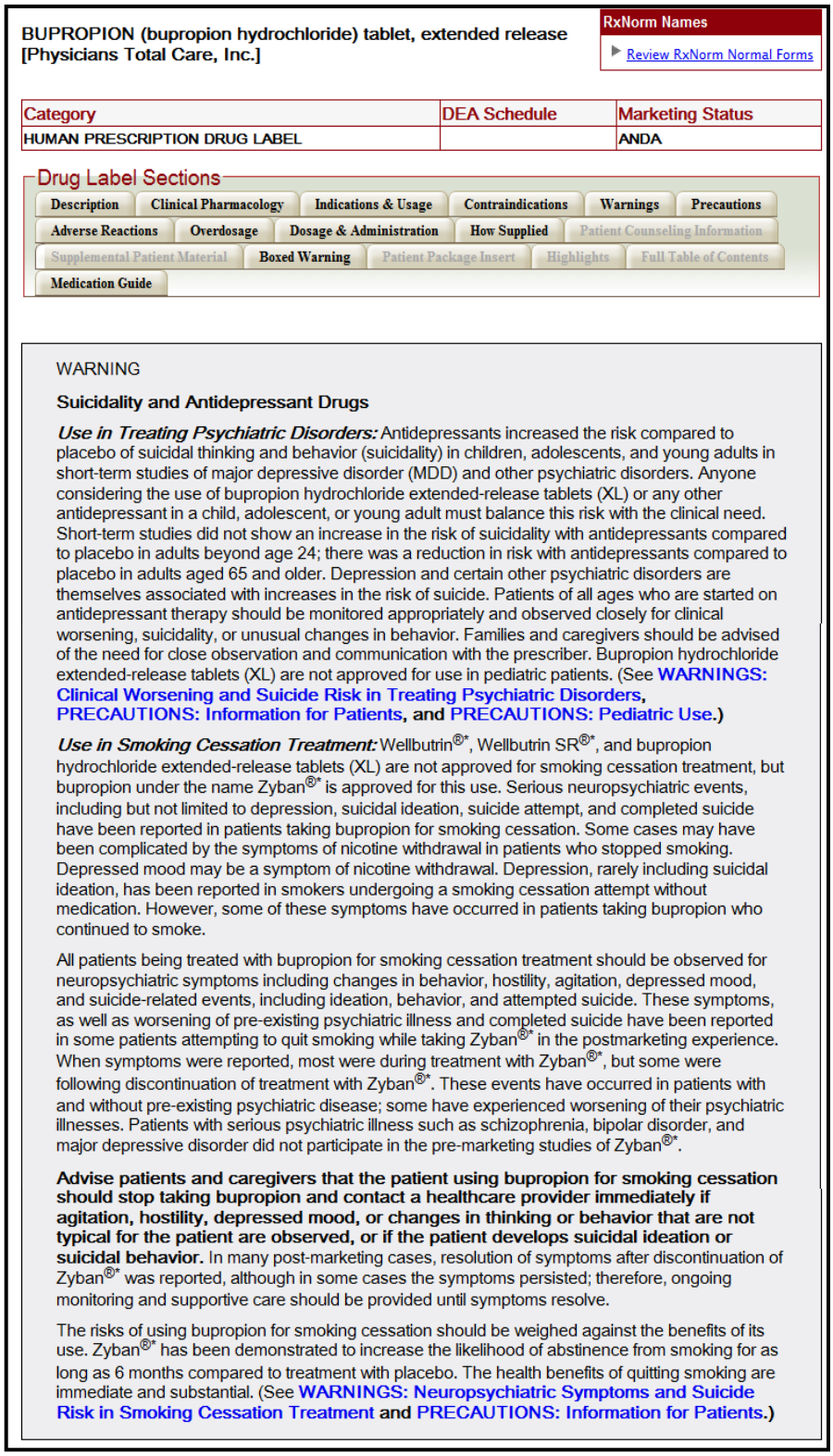


Figure 6: Screenshots of sections from two of the SPLs found in Daily Med for naproxen. The red boxes highlight the tab indicating the presence/absence of a BBW with each. Note that the SPL for naproxen above has a BBW while the one below does not.



BUPROPION (bupropion hydrochloride) tablet, extended release
[Physicians Total Care, Inc.]

RxNorm Names
Review RxNorm Normal Forms

Category	DEA Schedule	Marketing Status
HUMAN PRESCRIPTION DRUG LABEL		ANDA

Drug Label Sections

Description | Clinical Pharmacology | Indications & Usage | Contraindications | Warnings | Precautions
Adverse Reactions | Overdosage | Dosage & Administration | How Supplied | Patient Counseling Information
Supplemental Patient Material | Boxed Warning | Patient Package Insert | Highlights | Full Table of Contents
Medication Guide

WARNING

Suicidality and Antidepressant Drugs

Use in Treating Psychiatric Disorders: Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of bupropion hydrochloride extended-release tablets (XL) or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Bupropion hydrochloride extended-release tablets (XL) are not approved for use in pediatric patients. (See **WARNINGS: Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)**

Use in Smoking Cessation Treatment: Wellbutrin®*, Wellbutrin SR®*, and bupropion hydrochloride extended-release tablets (XL) are not approved for smoking cessation treatment, but bupropion under the name Zyban®* is approved for this use. Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking bupropion for smoking cessation. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking bupropion who continued to smoke.

All patients being treated with bupropion for smoking cessation treatment should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking Zyban®* in the postmarketing experience. When symptoms were reported, most were during treatment with Zyban®*, but some were following discontinuation of treatment with Zyban®*. These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of Zyban®*.

Advise patients and caregivers that the patient using bupropion for smoking cessation should stop taking bupropion and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of Zyban®* was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of using bupropion for smoking cessation should be weighed against the benefits of its use. Zyban®* has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (See **WARNINGS: Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment and PRECAUTIONS: Information for Patients.)**

Figure 7: Example of DailyMed as the source for BBW content. DailyMed BBW for a specific formulation of bupropion hydrochloride is shown. (Compare to Facts & Comparisons BBW for bupropion in Figure 8)

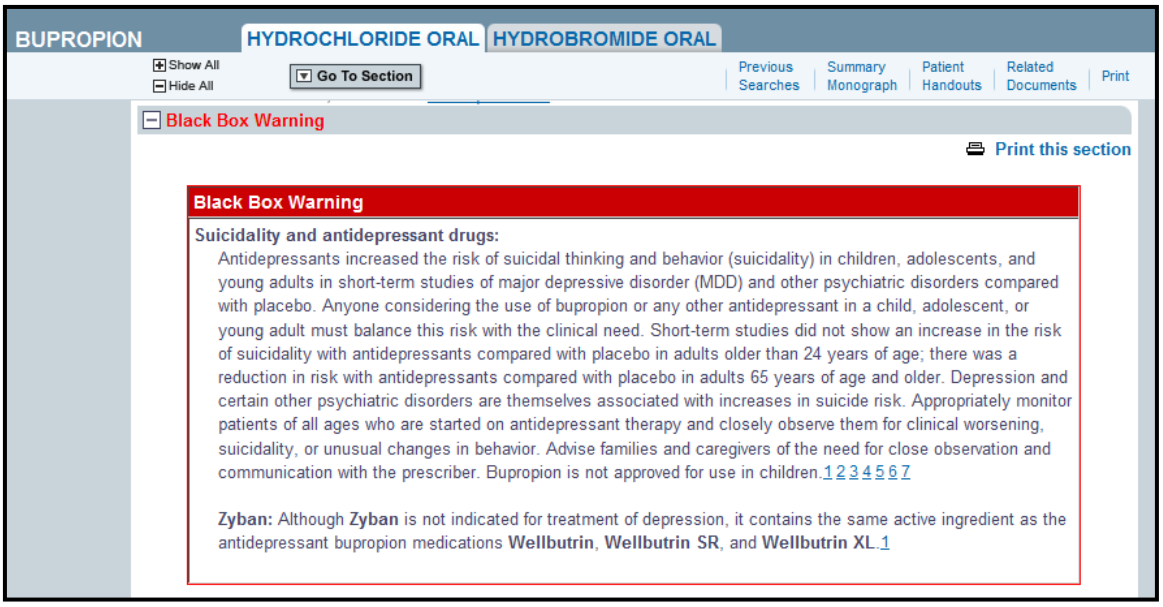


Figure 8: Facts & Comparisons black box warning for bupropion hydrochloride. Note that in this instance, when compared to the DailyMed BBW this warning provides less information.

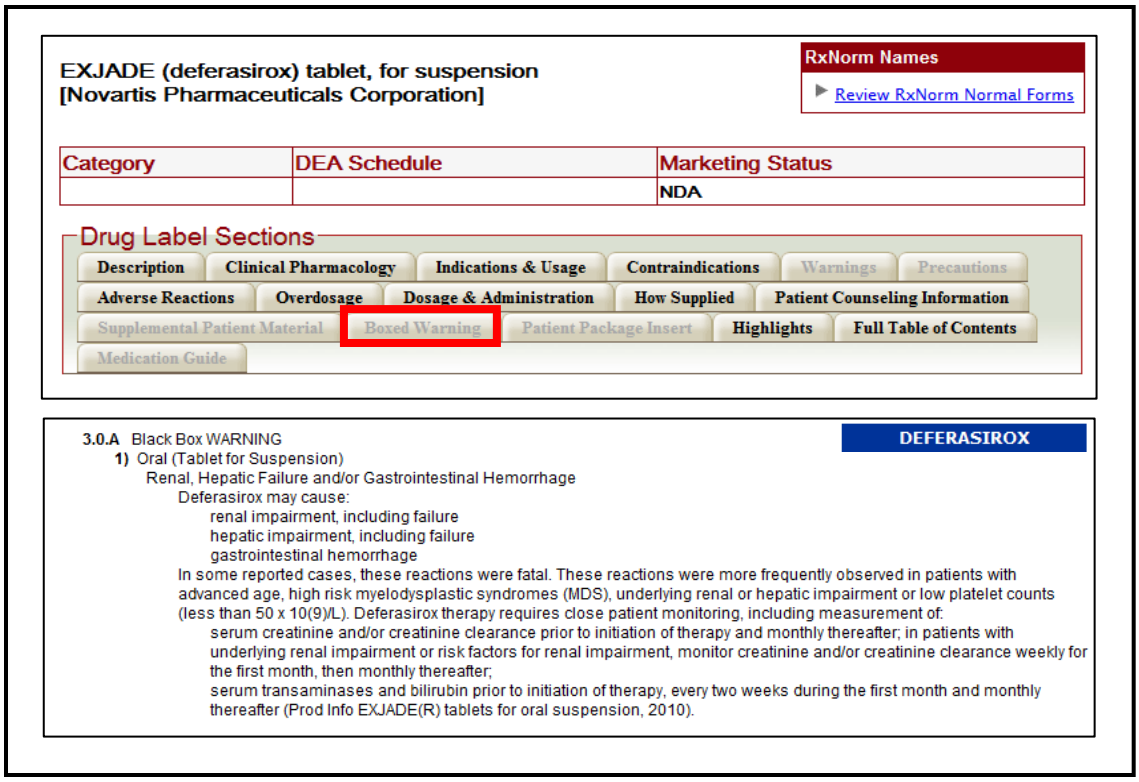


Figure 9: Example of Micromedex as the source for BBW content. Top: Screenshot of SPL excerpt for deferasirox showing no BBW (red box). Below: Micromedex BBW for deferasirox.

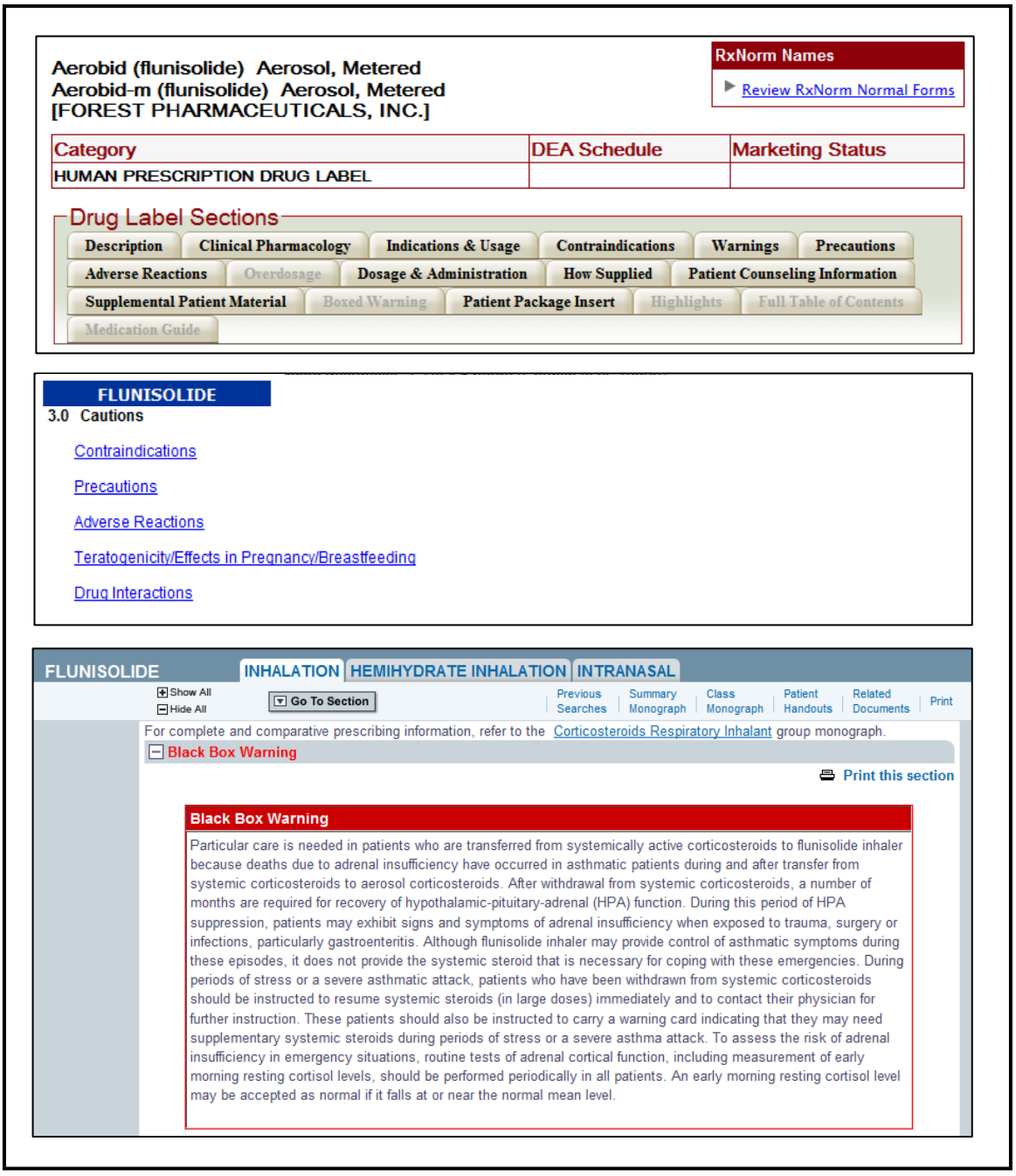


Figure 10: Example of Facts & Comparisons as source for BBW content. Top: DailyMed screenshot of SPL excerpt for Flunisolide showing no BBW. Middle: Micromedex screenshot also showing no BBW. Bottom: Facts & Comparisons BBW for Flunisolide.

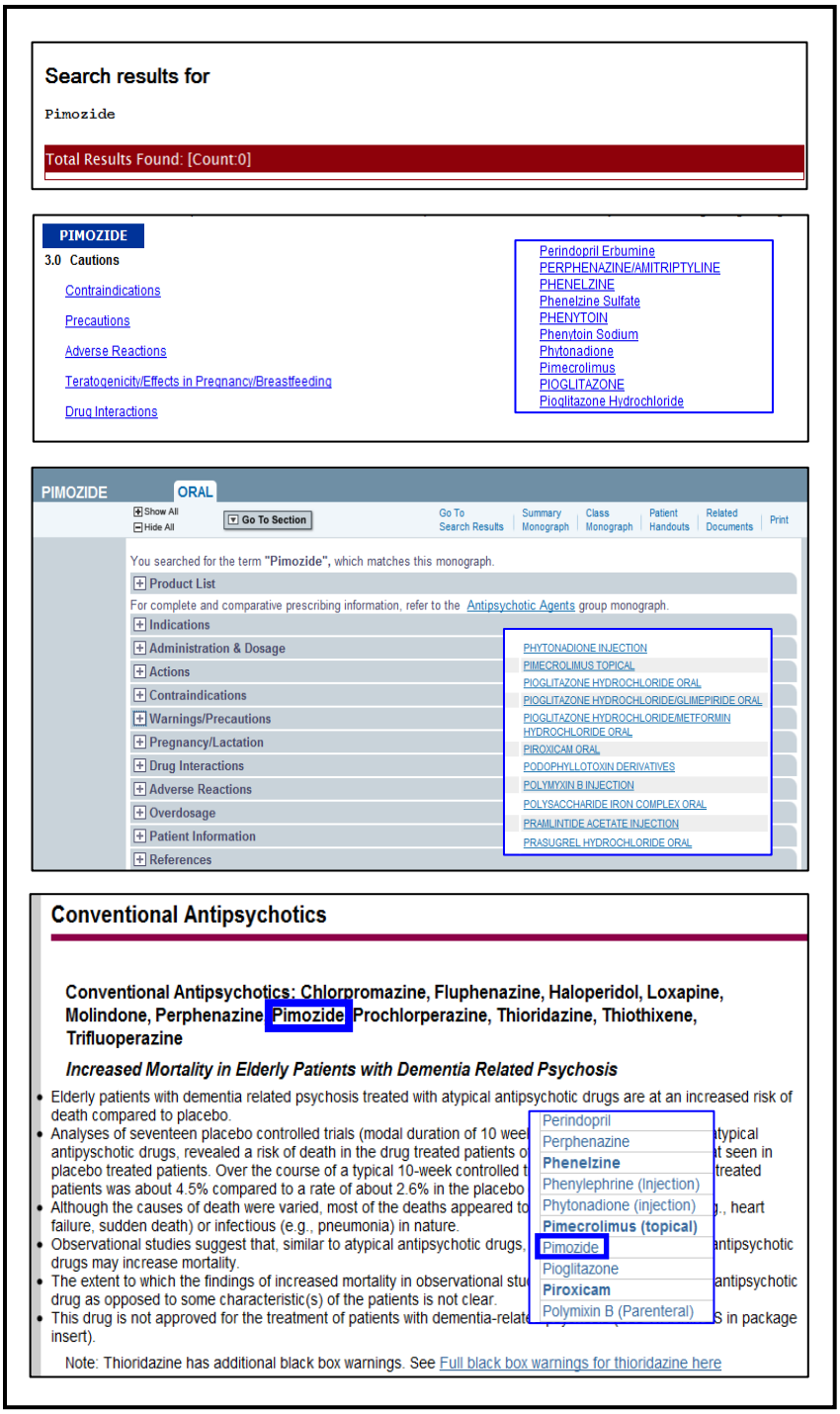


Figure 11: Example of BlackBoxRx as source for BBW content. Top: DailyMed screenshot of search for pimozide yielding no results. Second to top: Micromedex screenshot showing no BBW; smaller box with blue outline showing "pimozide" not on individual BBW list. Second to bottom: Facts & Comparisons showing no BBW; smaller box outlined in blue showing "pimozide" not on individual BBW list. Bottom: BlackBoxRx BBW for pimozide with smaller box outlined in blue showing "pimozide" on individual BBW list.

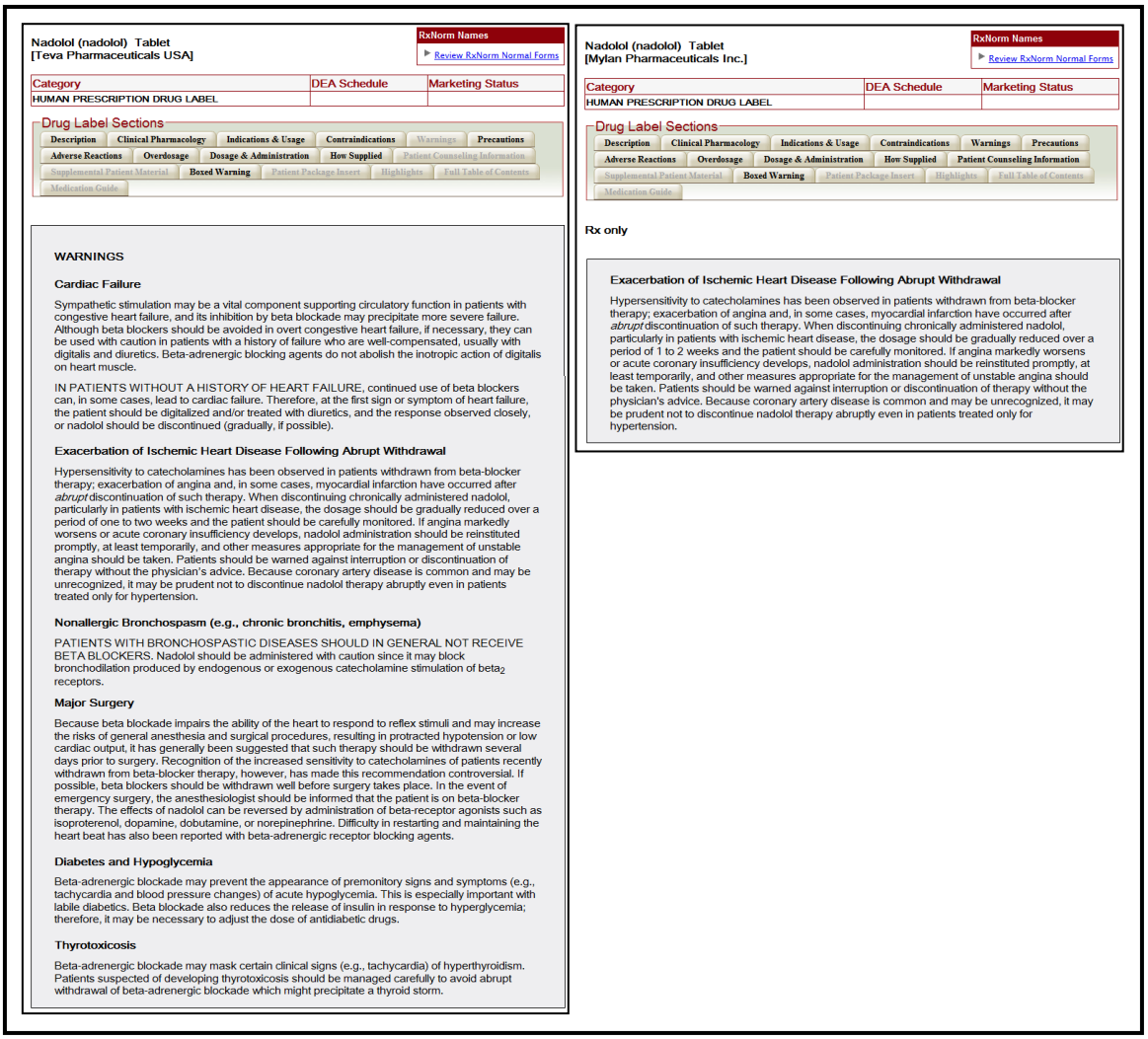


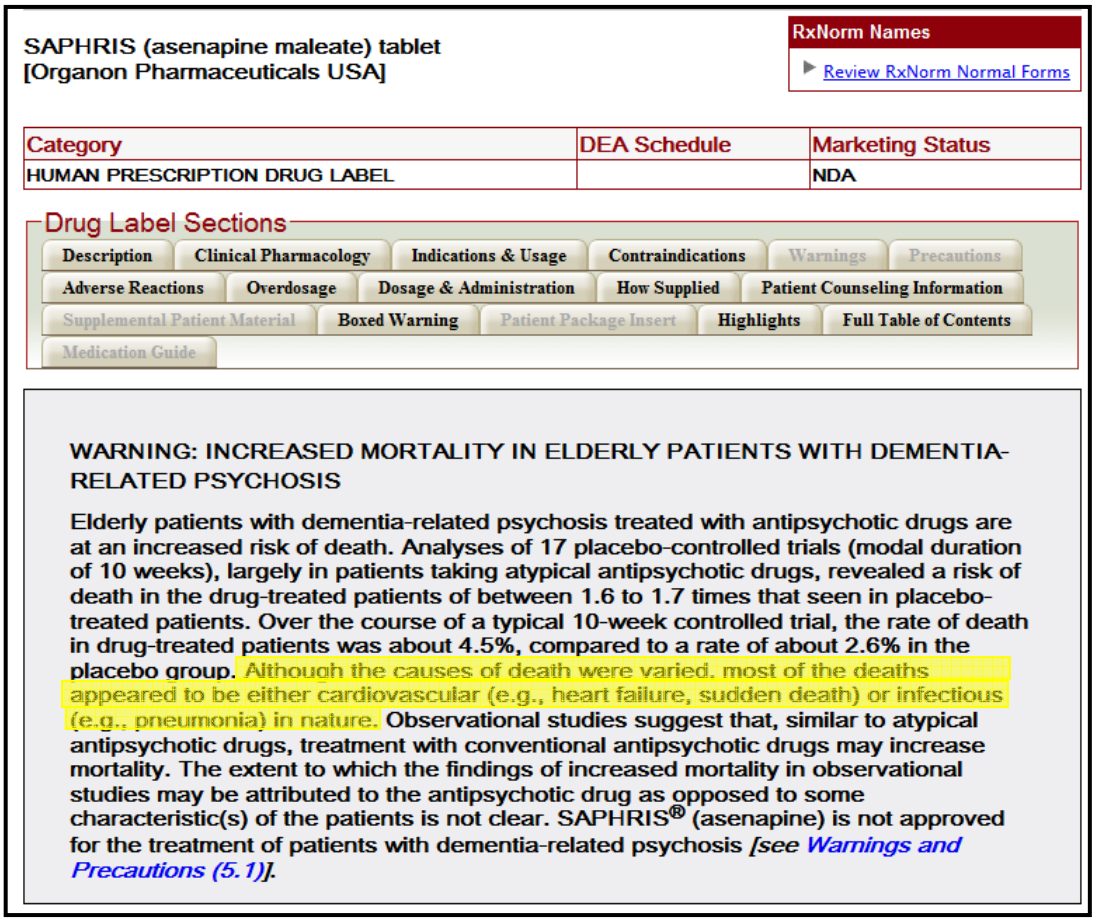
Figure 12: Nadolol as an example of BBW discrepancies within drug databases due to dosing, routes, and/or differing SPLs for different manufacturers. In DailyMed, above left shows BBW for nadolol USP which carries a more extensive BBW. Above right shows BBW for remaining four preparations of Nadolol listed on DailyMed.

Table 1: Warning Classification Examples

Effects on Organ Systems	Examples from Select Black Box Warnings
Cardiovascular	hypotension, syncope, arrhythmias, heart block, heart failure, sudden death, cardiovascular adverse events, cardiac arrest, cardiopulmonary arrest, exacerbation angina, myocardial infarction, hypertension, myocarditis,
Pulmonary	respiratory symptoms, dyspnea, pulmonary embolism, pulmonary toxicity, hypersensitivity pneumonitis, interstitial/alveolar pneumonitis, respiratory arrest, pneumonia, respiratory depression, hypoxia, resp paralysis
Hematologic/Bleeding	bone marrow suppression, leukopenia, anemia, thrombocytopenia, cytopenias, hemorrhagic diathesis, hemolytic/aplastic anemia, agranulocytosis, other blood dyscrasias, myelosuppression, DVT, lymphoma
Neurologic	dementia, headache, chemical arachnoiditis, seizures, stroke, CNS adverse events, confusion, neuropsychiatric events/disorders, ototoxicity, encephalitis, CNS-additive effects, neurotoxicity, quadraparesis,
Infectious Disease	hepatitis B exacerbation, increase susceptibility to infection, pneumonia, encephalitis, sepsis, disseminated infection, bacterial endocarditis, intra-abdominal abscess, progressive multifocal leukoencephalopathy
Teratogenicity/Fetal Harm	adversely affected fetal circulation, teratogenicity, birth defects, fetal death, major human fetal abnormalities, embryotoxic, injury and death to the developing fetus, neural tube defects, spina bifida,
Gastrointestinal	nausea, vomiting, diarrhea, abdominal pain, gastrointestinal bleeding/ulceration/perforation, peptic ulcers, dysphagia, pancreatitis, ischemic colitis, gastrointestinal adverse events, complications from constipation
Psychiatric	dementia, confusion, depression, neuropsychiatric events/disorders, suicidal thinking and behavior (suicidality), psychotic episodes, affect changes,
Oncologic	development of neoplasia, lymphoma, skin malignancies, breast cancer, mutagenic, tumorigenic, carcinogenic, thyroid C-cell tumor, endometrial cancer,
Hepatic	hepatomegaly with steatosis, liver injury, overt liver disease, hepatic/liver dysfunction/failure, hepatitis B exacerbation, hepatotoxicity, fulminant hepatic necrosis, elevation of liver aminotransferases, cirrhosis,
Hypersensitivity and Other Rxns	hypersensitivity reactions, systemic allergic reaction, anaphylaxis, bronchospasm, sensitization, infusion reactions, severe systemic reactions, hypersensitivity pneumonitis, severe idiosyncratic reaction,
Dermatologic/Soft Tissues	rash, skin malignancies, cutaneous/mucocutaneous reactions, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, severe tissue damage, oral ulceration, flushing, local tissue necrosis,
Renal	nephrotoxicity, renal insufficiency/impairment/injury, renal toxicity, nephropathy, acute renal failure, profound/osmotic diuresis,
Metabolic/Electrolyte Disturbance	lactic acidosis, electrolyte disturbances, hyperkalemia, metabolic acidosis/alkalosis, hypophospatemia, hypocalcemia, hyperosmolar non-ketotic states, dehydration, alterations in plasma minerals and electrolytes
Musculoskeletal	generalized muscle weakness, loss of bone mineral density, rhabdomyolysis, muscle rigidity, tendinitis, tendon rupture, contracture of arms, back pain, system fibrosis affecting muscle, skeletal muscle myopathy,
Genitourinary	urinary incontinence, testicular lesions, urinary tract obstruction, decreased fertility, hypospermia, endometrial cancer, uterine rupture, abnormal vaginal bleeding, aspermatogenesis, urotoxic side effects, hemorrhagic
Ophthalmic	diplopia, blurred vision, blindness, loss of visual accuity and color vision, lacrimation, occular damage, optic nerve dysfunction,
ENT (ears/nose/throat)	ototoxicity, deafness, hearing loss, cranial nerve VIII impairment, tinnitis, loss of high-frequency hearing, rhinitis, roaring in ears,
Endocrine	reduced the release of insulin, thyrotoxicosis, adrenal suppression, thyroid storm, thyroid C-cell tumor,
Autoimmune	autoimmune disorders, autoimmune idiopathic thrombocytopenia, autoimmune hemolytic anemia, lupus erythematosus-like syndrome,

Other Effects	Examples from Select Black Box Warnings
Caution Select Circumstances [A]	should not be used for/to treat [ ], Patients with [ ] advised against, caution used in patients having a history of [ ], not approved for the treatment of patients with [ ], increased risk of [ ] in [ ] patients, contraindicated in [ ]
Admin/Monitoring Instructions [B]	hospitalization required during administration, patient should be carefully observed, only physicians experienced in [ ] should prescribe, [drug A] and [drug B] are not bioequivalent, [labs] should be monitored, caution used
Concurrent Item Restriction [C]	avoid use of [ ] in combination with [ ], caution when [treatment] initiated in patients taking [ ], the concomitant use of [ ] with [ ] may result in [ ], not be used with [ ], risk increased in patients taking [ ], in state of EtOH
Reserve for Select Circumstances [D]	intended for/reserved for use only in patients with [disease/diagnosis], should be used primarily for treatment of patients with [ ], indicated for [ ], should be considered only for [ ], should restricted to patients with [ ]
Abuse Potential	high potential for abuse, abuse potential, do not prescribe for patients who are addiction-prone, known to cause dependence or abuse, psychological/drug dependence,
Overdose/Poisoning	exercise caution to prevent inadvertent overdose, overdose, resulting dose may be fatal,

[A] Caution or avoidance with select patient populations,indications, or clinical situations
[B] Administration or monitoring instructions
[C] Caution or avoidance of select concurrent medications, treatments, or substance use
[D] Use reserved for select patient populations, indications, or clinical situations
"[ ]" is intended to signify various mention comorbidities, risks, indications, and concurrent medications among the black box warnings.



SAPHRIS (asenapine maleate) tablet
[Organon Pharmaceuticals USA]

RxNorm Names

Review RxNorm Normal Forms

Category	DEA Schedule	Marketing Status
HUMAN PRESCRIPTION DRUG LABEL		NDA

Drug Label Sections

Description | Clinical Pharmacology | Indications & Usage | Contraindications | Warnings | Precautions
Adverse Reactions | Overdosage | Dosage & Administration | How Supplied | Patient Counseling Information
Supplemental Patient Material | Boxed Warning | Patient Package Insert | Highlights | Full Table of Contents
Medication Guide

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. SAPHRIS® (asenapine) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

Figure 13:Asenapine as an example of antipsychotics' BBW which cautions of "increased risk of death". In highlighted section, example causes of "heart failure", "sudden death", and "pneumonia" are given and as such are included on the BBW table.

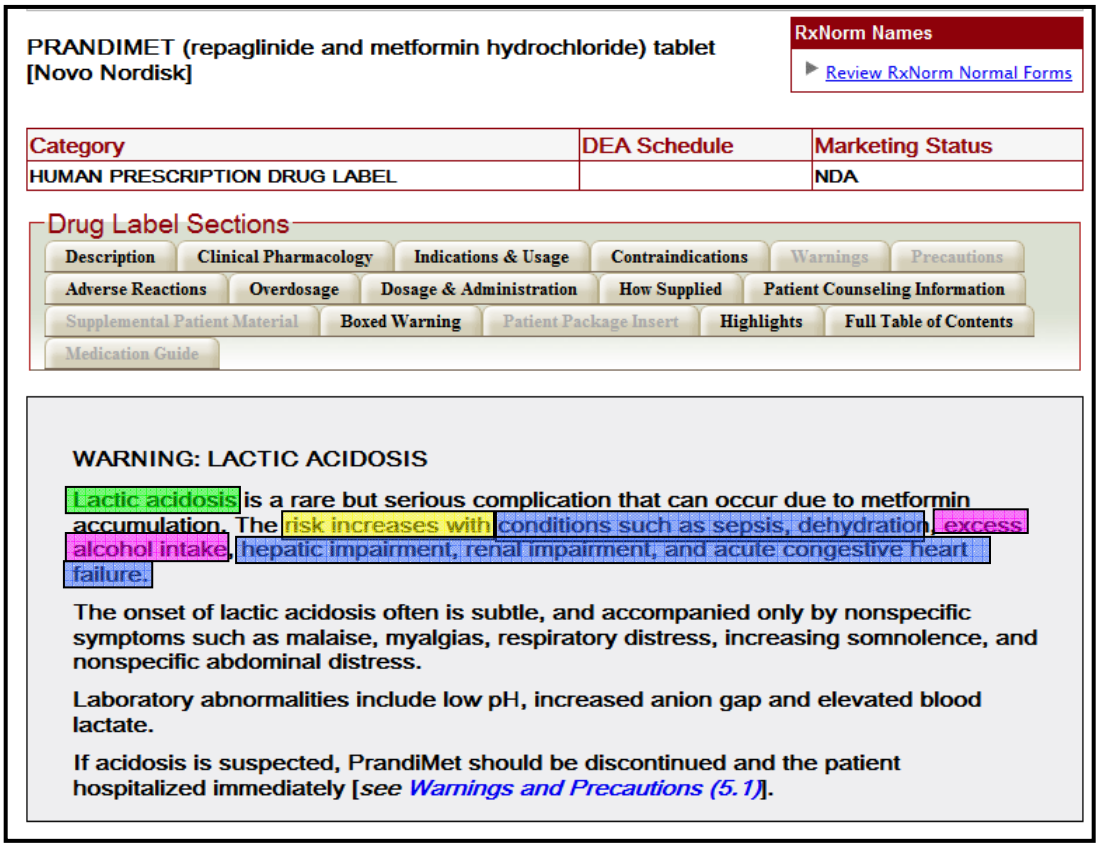


Figure 14: Metformin/Repaglinide BBW from DailMed. “Lactic acidosis” highlighted in green is classified on the BBW table under “Metabolic/Electrolyte Disturbance”. Blue highlight indicates comorbid conditions/illnesses that increase risk of lactic acidosis but are not themselves a result of metformin/repaglinide use. These are classified under “Caution Select Circumstances” Increased risk of lactic acidosis secondary to “excess alcohol intake” highlighted in pink is classified under “Concurrent Item Restriction”.

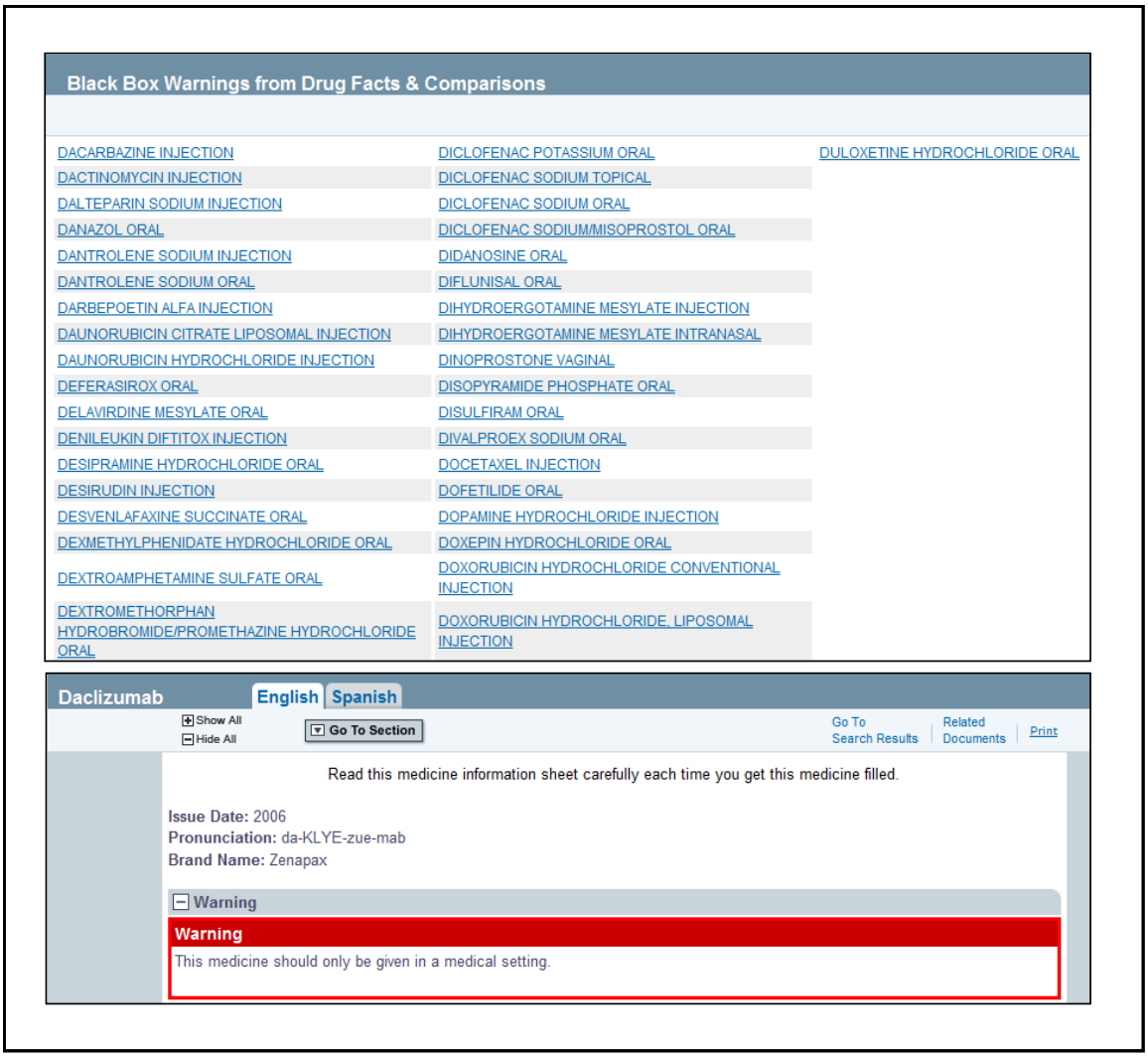


Figure 15: Daclizumab as an example of a drug not found on a database's individual BBW list, however, with further searching is discovered to have a BBW mentioned n that database. In this example, Facts & Comparisons does not list daclizumab on its individual BBW list (above); however, doing an individual search for daclizumab in Facts & Comparisons indeed shows that it does have a BBW in this database (below). Thus when calculating the relative comprehensiveness of the drug databases, this BBW was counted as present for Facts & Comparisons.

Table 2: Compiled Black Box Warning Table

Drugs (Generic Name):	Boxed Warnings:	Effects on Organ Systems																			Other Effects					
		Cardiovascular	Pulmonary	Hematologic/Bleeding	Neurologic	Infectious Disease	Teratogenicity/Fetal harm	Gastrointestinal	Psychiatric	Oncologic	Hepatic	Hypersensitivity & Other Reactions	Dermatologic/Soft Tissues	Renal	Metabolic/Electrolyte Disturabance	Musculoskeletal	Genitourinary	Ophthalmic	ENT (ears/nose/throat)	Endocrine	Autoimmune	Caution Select Circumstances [A]	Admin/Monitoring Instructions [B]	Concurrent Item Restriction [C]	Reserve for Select Circumstances [D]	Abuse Potential	Overdose/Poisoning
Abacavir Sulfate		•	•					•			•	•	•		•								•	•			
Abacavir Sulfate/Lamivudine		•	•			•		•			•	•	•		•							•	•	•			
Abacavir Sulfate/Lamivudine/Zidovudine		•	•	•		•		•			•	•	•		•							•	•	•			
Abarelix		•										•											•		•		
AbobotulinumtoxinA (botulinum toxin type a)			•		•			•								•	•	•				•					
Acetaminophen/Hydrocodone Bitartrate			•		•			•				•															
Acetaminophen/**Propoxyphene Hydrochloride**					•				•													•	•	•		•	•
Acetaminophen/**Propoxyphene Napsylate**					•				•													•	•	•		•	•
Acetazolamide			•	•							•	•	•											•			
Acetylcysteine Inhalant																							•				
Acitretin							•															•	•	•	•		
Adalimumab			•			•																	•				
Adefovir Dipivoxil						•					•			•	•								•				
Albuterol																							•	•			
Aldesleukin		•	•	•	•	•		•	•					•								•	•				
Alemtuzumab				•		•						•									•		•				
Alglucosidase Alfa		•	•									•										•	•				
Aliskiren							•															•					
Aliskiren/Hydrochlorothiazide							•															•					
Aliskiren/Valsartan							•															•					
Allergenic Extract (Box Elder Maple Pollen)												•											•				
Allergenic Extracts for Intradermal Testing												•											•	•			
Allergenic Extracts for Scratch, Prick, or Puncture Testing(pollens etc.)												•											•	•			
Alosetron Hydrochloride								•														•	•		•		
Alprostadil			•																			•	•				
Altretamine					•																		•				
Alvimopan																							•		•		
Ambrisentan							•	•			•											•	•	•			
Amikacin Sulfate			•		•									•					•			•	•	•			
Amiloride Hydrochloride															•							•	•				
Amiloride Hydrochloride/Hydrochlorothiazide															•							•	•				
Amino Acids (Novamine)																							•				
Aminosyn			•			•	•							•	•	•	•					•	•				
Amiodarone Hydrochloride		•	•								•	•										•	•	•	•		
Amitriptyline Hydrochloride									•													•	•				
Amitriptyline Hydrochloride/Chlordiazepoxide									•													•	•				
Amitriptyline/Perphenazine		•	•			•			•													•	•				
Amlodipine Besylate/**Olmesartan Medoxomil**							•															•					
Amlodipine Besylate/**Telmisartan**							•															•					
Amlodipine/**Benazepril**							•															•					
Amlodipine/Hydrochlorothiazide/**Valsartan**							•															•					
Amlodipine/**Valsartan**							•															•					
Amoxapine									•													•	•				
Amphetamine		•																					•			•	
Amphetamine/Dextroamphetamine		•																					•			•	
Amphotericin B		•	•																			•	•		•		•
Ampicillin/Sulbactam																							•				
Amprenavir																						•		•	•		
Antithymocyte Globulin Equine																							•				
Antithymocyte Globulin Rabbit (Thymoglobulin)																							•				
Antivenin (Crotalidae) Polyvalent (Equine Origin)													•										•				
Aprotinin												•										•	•		•		
Arformoterol Tartrate			•																								
Aripiprazole		•	•			•			•													•	•				
Armodafinil																										•	
Arsenic Trioxide		•	•	•																		•	•	•			
Asenapine		•	•			•																•					
Asparaginase												•											•				
Atenolol		•																				•	•				
Atomoxetine Hydrochloride									•													•	•		•		
Auranofin				•				•					•	•									•		•		
Azathioprine				•						•																	
Azathioprine Sodium				•						•																	
Bacillus of Calmette and Guerin (BCG) Vaccine, Live						•																	•				

Table 2: Compiled Black Box Warning Table (continued)

Drugs (Generic Name):	Boxed Warnings:	Effects on Organ Systems																			Other Effects					
		Cardiovascular	Pulmonary	Hematologic/Bleeding	Neurologic	Infectious Disease	Teratogenicity/Fetal harm	Gastrointestinal	Psychiatric	Oncologic	Hepatic	Hypersensitivity & Other Reactions	Dermatologic/Soft Tissues	Renal	Metabolic/Electrolyte Disturabance	Musculoskeletal	Genitourinary	Ophthalmic	ENT (ears/nose/throat)	Endocrine	Autoimmune	Caution Select Circumstances [A]	Admin/Monitoring Instructions [B]	Concurrent Item Restriction [C]	Reserve for Select Circumstances [D]	Abuse Potential	Overdose/Poisoning
Bacitracin														•									•	•	•		
Baclofen Intrathecal					•											•						•	•				
Bacteriostatic Water																						•					
Basiliximab																							•				
Becaplermin (Topical)										•												•			•		
Benazepril Hydrochloride							•															•					
Benazepril/Hydrochlorothiazide							•															•					
Bendroflumethiazide/**Nadolol**		•										•										•	•	•			
Bermuda Grass, Standardized		•	•									•										•	•	•			
Bevacizumab			•	•		•		•														•					
Bexarotene							•															•					
Bismuth Subcitrate Potassium/**Metronidazole**/Tetracycline										•																	
Bismuth Subsalicylate/**Metronidazole**/Tetracycline										•																	
Bleomycin Sulfate		•	•									•										•	•				
Bosentan							•	•			•											•	•	•			
Budesonide Inhalation																					•	•					
Budesonide/**Formoterol**			•																						•		
Bumetanide		•												•	•												
Bupivicaine (0.75% inj)		•			•																	•			•		
Bupropoin Hydrobromide									•													•	•				
Bupropion Hydrochloride				•					•													•	•				
Busulfan			•																				•				
Butorphanol Tartrate																							•	•		•	
Caffeine/**Ergotamine Tartrate**		•		•																				•			
Candesartan Cilexetil							•															•					
Candesartan Cilexetil/Hydrochlorothiazide							•															•					
Capecitabine				•																		•	•	•			
Capreomycin					•									•						•		•		•			
Captopril							•															•					
Captopril/Hydrochlorothiazide							•															•					
Carbamazepine				•									•									•	•				
Carbonyl Iron																						•					•
Carboplatin				•		•		•				•											•				
Carboprost																							•				
Carmustine Implant			•																			•					
Carmustine Injection			•	•		•																•	•				
Cat Hair												•											•				
Cat Hair, Standardized												•										•	•	•			
Cat Pelt, Standardized		•	•									•										•	•	•			
Cefaclor																									•		
Cefadroxil Monohydrate																									•		
Celecoxib		•		•	•			•														•					
Cephalexin																									•		
Certolizumab Pegol			•			•																	•	•			
Cetuximab		•	•									•										•	•	•			
Chenodiol								•			•											•	•		•		
Chlorambucil				•			•			•							•										
Chloramphenicol				•						•													•		•		
Chloroquine Phosphate																							•		•		
Chlorpromazine Hydrochloride		•	•			•																•					
Cidofovir				•			•			•				•			•						•	•	•		
Cilostazol																						•					
Ciprofloxacin																•						•		•			
Ciprofloxacin Hydrochloride																•						•		•			
Cisapride		•																				•	•	•			
Cisplatin		•	•	•	•			•				•		•						•			•				•
Citalopram Hydrobromide									•													•	•				
Cladribine				•	•									•									•	•			
Clarithromycin																							•				
Clindamycin Hydrochloride						•		•																	•		
Clindamycin Palmitate Hydrochloride						•		•																	•		
Clindamycin Phosphate						•		•																	•		
Clomipramine Hydrochloride									•													•	•				
Clonidine Hydrochloride Epidural		•																				•	•				
Clopidogrel Hydrogen Sulfate		•																				•	•				
Clozapine		•	•	•		•																•	•	•	•		
Coagulation Factor VIIa				•																			•				
Cocaine Hydrochloride																							•				
Codeine Phosphate/Phenylephrine Hydrochloride/**Promethazine Hydrochloride**			•																			•		•			

Table 2: Compiled Black Box Warning Table (continued)

Drugs (Generic Name):	Boxed Warnings:	Effects on Organ Systems																			Other Effects					
		Cardiovascular	Pulmonary	Hematologic/Bleeding	Neurologic	Infectious Disease	Teratogenicity/Fetal harm	Gastrointestinal	Psychiatric	Oncologic	Hepatic	Hypersensitivity & Other Reactions	Dermatologic/Soft Tissues	Renal	Metabolic/Electrolyte Disturabance	Musculoskeletal	Genitourinary	Ophthalmic	ENT (ears/nose/throat)	Endocrine	Autoimmune	Caution Select Circumstances [A]	Admin/Monitoring Instructions [B]	Concurrent Item Restriction [C]	Reserve for Select Circumstances [D]	Abuse Potential	Overdose/Poisoning
Codeine Phosphate/**Promethazine Hydrochloride**			•																			•		•			
Colistimethate Sodium																						•	•	•			
Conjugated Estrogens		•		•	•				•	•							•					•	•				
Conjugated Estrogens Synthetic A		•		•	•				•	•							•					•	•				
Conjugated Estrogens Synthetic B		•		•	•				•	•							•					•	•				
Conjugated Estrogens/Medroxyprogesterone Acetate		•	•	•	•				•	•												•					
Cyclosporine				•		•				•												•	•	•			
Cyclosporine, Modified		•		•		•				•			•	•								•	•				
Cysteine Hydrochloride																							•				
Cytarabine				•				•			•		•										•				
Cytarabine Liposome					•			•															•				
Dacarbazine				•			•			•	•												•				
Daclizumab																							•				
Dactinomycin							•			•			•			•						•	•				
Dalfopristin/Quinupristin																									•		
Dalteparin Sodium				•	•																		•	•			
Danazol		•		•	•		•	•			•							•				•	•				
Dantrolene Sodium											•											•	•	•			
Darbepoetin Alfa		•		•						•												•	•		•		
Daunorubicin Citrate Liposome		•		•									•			•						•	•				
Daunorubicin Hydrochloride		•		•		•							•									•	•				
Deferasirox				•				•			•			•								•	•				
Delavirdine																							•				
Denileukin Diftitox		•										•						•					•				
Deserpidine/Methylclothiazide																						•	•				
Desipramine Hydrochloride									•													•	•				
Desirudin				•	•																		•	•			
Desmopressin																						•					
Desogestrel/Ethinyl Estradiol		•																				•		•			
Desvenlafaxine Succinate									•													•	•				
Dexibuprofen		•		•	•			•														•					
Dexmethylphenidate Hydrochloride									•													•	•			•	
Dextroamphetamine Sulfate		•																								•	
Dextromethorphan Hydrobromide/**Promethazine Hydrochloride**			•																			•	•	•			
Dextrose Monohydrate																							•				
Diatrizoate Meglumine																							•				
Diatrizoate Sodium																							•				
Diatrizoate Meglumine/Diatrizoate Sodium																							•				
Diclofenac Epolamine		•		•	•			•														•					
Diclofenac Potassium		•		•	•			•														•					
Diclofenac Sodium		•		•	•			•														•					
Diclofenac Sodium/Misoprostol		•					•	•									•					•	•		•		
Didanosine								•			•				•							•		•			
Diflunisal		•		•	•			•														•					
Dihydroergotamine Mesylate		•			•																			•			
Dinoprostone																							•				
Disopyramide Phosphate		•																				•			•		
Disulfiram																								•			
Divalproex Sodium				•	•		•	•			•											•	•	•			
Docetaxel		•	•	•		•						•	•	•								•	•				
Dofetilide		•																					•				
Dopamine		•											•										•				
Doxepin Hydrochloride									•													•	•				
Doxorubicin Hydrochloride		•		•						•			•									•	•	•			
Doxorubicin Hydrochloride Liposome		•	•	•	•							•	•			•						•	•	•			
Dronedarone Hydrochloride																						•					
Droperidol		•																				•	•	•	•		
Drospirenone/Estradiol		•	•	•	•				•	•												•	•				
Drospirenone/Ethinyl Estradiol		•																				•		•			
Duloxetine Hydrochloride									•													•	•				
Ecallantide												•										•	•				
Echothiophate Iodide																							•				
Eculizumab						•																	•				
Edetate Calcium Disodium					•																	•	•				
Edetate Disodium																									•		
Efalizumab					•	•																	•				
Efavirenz/**Emtricitabine/Tenofovir**						•					•				•							•	•	•			
Eltrombopag Olamine											•												•				
Emtricitabine						•					•				•							•	•	•			

Table 2: Compiled Black Box Warning Table (continued)

Drugs (Generic Name): / Boxed Warnings:	Effects on Organ Systems																				Other Effects					
	Cardiovascular	Pulmonary	Hematologic/Bleeding	Neurologic	Infectious Disease	Teratogenicity/Fetal harm	Gastrointestinal	Psychiatric	Oncologic	Hepatic	Hypersensitivity & Other Reactions	Dermatologic/Soft Tissues	Renal	Metabolic/Electrolyte Disturabance	Musculoskeletal	Genitourinary	Ophthalmic	ENT (ears/nose/throat)	Endocrine	Autoimmune	Caution Select Circumstances [A]	Admin/Monitoring Instructions [B]	Concurrent Item Restriction [C]	Reserve for Select Circumstances [D]	Abuse Potential	Overdose/Poisoning
Emtricitabine/Tenofovir Disoproxil Fumarate					•					•				•							•	•	•			
Enalapril Maleate						•															•					
Enalapril Maleate/Felodipine						•															•					
Enalapril Maleate/Hydrochlorothiazide						•															•					
Enalaprilat						•															•					
Encainide Hydrochloride	•																				•			•		
Enoxaparin Sodium			•	•																		•	•			
Entecavir					•					•				•							•	•	•			
Epirubicin Hydrochloride	•		•						•			•									•	•	•			
Epoetin Alfa (Erythropoietin)	•		•						•												•	•		•		
Eprosartan Mesylate						•															•					
Eprosartan Mesylate/Hydrochlorothiazide						•															•					
Ergotamine Tartrate	•			•																			•			
Erlotinib Hydrochloride												BBW BOX IS EMPTY														
Erythromycin Estolate							•			•											•					
Escitalopram Oxalate								•													•	•				
Esterified Estrogens	•	•		•				•	•							•					•	•				
Esterified Estrogens/Methyltestosterone	•	•	•	•				•	•							•					•	•				
Estradiol	•	•	•	•				•	•							•					•	•				
Estradiol Acetate	•	•	•	•				•	•							•					•	•				
Estradiol Cypionate	•	•	•	•				•	•							•					•	•				
Estradiol Cypionate/Medroxyprogesterone Acetate	•	•	•	•				•	•							•					•	•				
Estradiol Valerate						•			•							•					•	•				
Estradiol/Levonorgestrel	•	•	•	•				•	•												•	•				
Estradiol/Norethindrone Acetate	•	•	•	•				•	•												•	•				
Estradiol/Norgestimate	•	•	•	•				•	•												•	•				
Estropipate						•			•							•					•	•				
Etanercept		•			•																	•				
Ethacrynate (Ethacrynic Acid)	•												•	•								•				
Ethinyl Estradiol/Ethynodiol Diacetate	•																				•		•			
Ethinyl Estradiol/Etonogestrel	•																				•		•			
Ethinyl Estradiol/Levonorgestrel	•																				•		•			
Ethinyl Estradiol/Norelgestromin	•																				•		•			
Ethinyl Estradiol/Norethindrone	•																				•		•			
Ethinyl Estradiol/Norethindrone Acetate (HRT)	•	•	•	•				•	•												•	•				
Ethinyl Estradiol/Norgestimate	•																				•		•			
Ethinyl Estradiol/Norgestrel	•																				•		•			
Etodolac	•						•														•					
Etoposide			•		•																	•				
Etoposide Phosphate			•		•																	•				
Fat Emulsion (Liposyn)		•																			•	•				
Felbamate			•		•		•			•											•	•	•	•		
Fenoprofen Calcium	•		•	•			•														•					
Fentanyl (transdermal)		•																			•	•	•	•	•	•
Fentanyl Citrate (buccal)		•																			•	•	•	•	•	•
Fentanyl Iontophoretic Transdermal System		•																				•		•	•	•
Ferrous Aspartate																					•					•
Ferrous Fumarate																					•					•
Flecainide Acetate	•																				•	•		•		
Floxuridine								•														•				
Flucytosine																					•	•				
Fludarabine Phosphate		•	•	•													•			•	•	•	•			
Flumazenil				•																	•	•	•			
Flunisolide																			•		•	•				
Fluorouracil																						•				
Fluoxetine Hydrochloride								•													•	•				
Fluoxetine Hydrochloride/Olanzapine	•	•			•			•													•	•				
Fluphenazine Decanoate	•	•			•																•					
Fluphenazine Hydrochloride	•	•			•																•					
Flurbiprofen	•		•	•			•														•					
Flutamide				•			•			•											•	•				
Fluticasone Propionate/**Salmeterol Xinafoate**		•																						•		
Fluvoxamine Maleate								•													•	•				
Fomepizole																						•				
Fondaparinux Sodium			•	•																		•	•			
Formoterol Fumarate		•																						•		
Foscarnet Sodium				•									•	•								•		•		
Fosinopril Sodium						•															•					

Table 2: Compiled Black Box Warning Table (continued)

Drugs (Generic Name):	Boxed Warnings:	Effects on Organ Systems																			Other Effects					
		Cardiovascular	Pulmonary	Hematologic/Bleeding	Neurologic	Infectious Disease	Teratogenicity/Fetal harm	Gastrointestinal	Psychiatric	Oncologic	Hepatic	Hypersensitivity & Other Reactions	Dermatologic/Soft Tissues	Renal	Metabolic/Electrolyte Disturabance	Musculoskeletal	Genitourinary	Ophthalmic	ENT (ears/nose/throat)	Endocrine	Autoimmune	Caution Select Circumstances [A]	Admin/Monitoring Instructions [B]	Concurrent Item Restriction [C]	Reserve for Select Circumstances [D]	Abuse Potential	Overdose/Poisoning
Fosinopril Sodium/Hydrochlorothiazide							•															•					
Furosemide		•												•	•								•				
Gadobenate Dimeglumine													•			•						•	•				
Gadodiamide													•			•						•	•				
Gadofosveset Trisodium													•			•						•	•				
Gadopentetate Dimeglumine													•			•						•	•				
Gadopentetic Acid													•			•						•	•				
Gadoteridol													•			•						•	•				
Gadoversetamide													•			•						•	•				
Gadoxetate Disodium													•			•						•	•				
Gallium Nitrate														•								•	•	•			
Gamma Hydroxybutyrate			•		•					•													•	•		•	
Ganciclovir (Oral)				•			•			•							•								•		
Ganciclovir Sodium (IV)				•			•			•							•								•		
Gemifloxacin Mesylate																•						•		•			
Gemtuzumab Ozogamicin			•	•				•			•	•			•							•	•	•			
Gentamicin Sulfate (Inj)					•		•							•						•		•	•	•			
Glimepiride/**Pioglitazone Hydrochloride**		•	•																			•	•				
Glimepiride/**Rosiglitazone Maleate**		•	•																			•	•				
Glipizide/**Metformin Hydrochloride**		•	•		•			•							•	•						•	•	•			
Glyburide/**Metformin Hydrochloride**		•	•		•			•							•	•						•	•	•			
Gold Sodium Thiomalate																							•				
Golimumab			•			•																	•	•			
Haloperidol		•	•			•																•					
Haloperidol Decanoate		•	•			•																•					
Haloperidol Lactate		•	•			•																•					
Hemin																							•				
Heparin																						•	•				
Histamine																							•				
Honey Bee Hymenoptera Venom Multidose												•										•	•	•			
House Dust Mite, Dermatophagoides Farinae												•											•	•			
Human Chorionic Gonadotropin																						•					
Human Immunoglobulin G														•								•	•	•			
Hyaluronate Sodium (Hyaluronic Acid)																							•				
Hydralazine Hydrochloride/Hydrochlorothiazide																						•	•				
Hydrochlorothiazide/**Irbesartan**							•															•					
Hydrochlorothiazide/**Lisinopril**							•															•					
Hydrochlorothiazide/**Losartan Potassium**							•															•					
Hydrochlorothiazide/Methyldopa																						•	•				
Hydrochlorothiazide/**Metoprolol Succinate**		•																				•	•				
Hydrochlorothiazide/**Metoprolol Tartrate**		•																					•				
Hydrochlorothiazide/**Moexipril**							•															•					
Hydrochlorothiazide/**Olmesartan Medoxomil**							•															•					
Hydrochlorothiazide/**Propranolol Hydrochloride**		•																				•	•				
Hydrochlorothiazide/**Quinapril**							•															•					
Hydrochlorothiazide/Spironolactone										•												•			•		
Hydrochlorothiazide/**Telmisartan**							•															•					
Hydrochlorothiazide/**Triamterene**															•							•	•				
Hydrochlorothiazide/**Valsartan**							•															•					
Hydrocodone Bitartrate/**Ibuprofen**		•		•	•			•														•					
Hydrocortisone Acetate/Pramoxine Hydrochloride																							•				
Hydromorphone Hydrochloride			•																			•	•	•	•	•	•
Hydroxychloroquine Sulfate																							•				
Hydroxyurea				•						•												•	•				
Ibritumomab Tiuxetan		•	•	•								•	•									•	•				
Ibuprofen		•		•	•			•														•					
Ibuprofen/Oxycodone		•		•	•			•														•					
Ibutilide Fumarate		•																					•		•		
Icodextrin					•										•								•				
Idarubicin Hydrochloride		•		•		•							•									•	•				
Idursulfase			•									•										•	•				
Ifosfamide				•	•												•						•				
Iloperidone		•	•			•																•					
Imipramine Hydrochloride									•													•	•				
Imipramine Pamoate									•													•	•				
Immune Globulin														•								•	•	•			
Indomethacin		•		•	•			•														•					
Infliximab			•	•		•				•												•	•	•			

Table 2: Compiled Black Box Warning Table (continued)

Drugs (Generic Name):	Boxed Warnings:	Effects on Organ Systems																			Other Effects					
		Cardiovascular	Pulmonary	Hematologic/Bleeding	Neurologic	Infectious Disease	Teratogenicity/Fetal harm	Gastrointestinal	Psychiatric	Oncologic	Hepatic	Hypersensitivity & Other Reactions	Dermatologic/Soft Tissues	Renal	Metabolic/Electrolyte Disturabance	Musculoskeletal	Genitourinary	Ophthalmic	ENT (ears/nose/throat)	Endocrine	Autoimmune	Caution Select Circumstances [A]	Admin/Monitoring Instructions [B]	Concurrent Item Restriction [C]	Reserve for Select Circumstances [D]	Abuse Potential	Overdose/Poisoning
Interferon Alfa-2a		•			•				•														•				
Interferon Alfa-2b		•			•				•												•		•				
Interferon Alfacon-1		•			•				•												•		•				
Interferon/Ribavirin							•															•					
Iodine (see Potassium Iodine)											•											•	•		•		
Iodipamide Meglumine																							•				
Iodixanol																							•				
Iopamidol																							•				
Ioversol		•		•	•							•		•		•					•		•	•			
Ioxaglate Meglumine/Ioxaglate Sodium		•		•	•							•		•		•					•		•	•			
Irbesartan							•															•						
Irinotecan Hydrochloride		•		•	•	•		•					•		•			•	•				•				
Iron Dextran												•											•		•		
Isocarboxazid									•													•	•				
Isoniazid					•			•			•		•									•	•	•			
Isoniazid/Pyrazinamide/Rifampin					•			•			•		•									•	•	•			
Isoniazid/Rifampin					•			•			•		•									•	•	•			
Isotretinoin							•															•	•				
Itraconazole		•																				•		•			
Ixabepilone				•																		•		•			
Kanamycin			•		•									•						•		•	•	•			
Ketoconazole		•									•												•	•			
Ketoprofen		•		•	•			•														•					
Ketorolac Tromethamine			•	•			•	•				•		•								•	•	•	•		
Lamivudine						•					•				•							•	•	•			
Lamivudine/Zidovudine				•		•					•				•	•						•	•	•			
Lamotrigine													•									•	•	•			
Lansoprazole/**Naproxen**		•		•	•			•														•					
Lapatinib Ditosylate											•																
Laronidase			•									•										•	•				
Leflunomide																						•					
Lenalidomide		•	•	•			•															•	•				
Levofloxacin																•						•		•			
Levomethadyl																							•	•	•		•
Levonorgestrel-Releasing Intrauterine System																						•					
Levothyroxine Sodium																						•		•			
Lincomycin Hydrochloride						•		•																	•		
Lindane					•																	•	•		•		
Liothyronine Sodium																						•		•			
Liotrix																						•		•			
Liraglutide																					•	•					
Lisdexamfetamine Dimesylate		•																								•	
Lisinopril							•															•					
Lithium Carbonate																							•				
Lithium Citrate																							•				
Lithium Hydroxide Monohydrate																							•				
Lomustine				•		•																	•				
Losartan Potassium							•															•					
Loxapine		•	•			•																•					
Lymphocyte Immune Globulin														•								•	•	•			
Maprotiline Hydrochloride									•													•	•				
Maraviroc				•						•	•	•															
Mechlorethamine Hydrochloride							•			•			•									•	•				
Medroxyprogesterone Acetate		•	•	•	•				•	•						•						•			•		
Mefenamic Acid		•		•	•			•														•					
Meloxicam		•		•	•			•														•					
Melphalan				•		•				•													•				
Melphalan Hydrochloride				•		•				•		•											•				
Mercaptopurine																							•		•		
Mesoridazine Besylate		•																							•		
Metformin Hydrochloride		•	•		•			•							•	•						•	•	•			
Metformin Hydrochloride/**Pioglitazone Hydrochloride**		•	•																			•	•				
Metformin Hydrochloride/Repaglinide			•		•			•							•	•						•		•			
Metformin Hydrochloride/Rosiglitazone Maleate		•	•		•			•							•	•						•	•				
Metformin Hydrochloride/Sitagliptin Phosphate			•		•			•							•	•						•		•			
Methacholine Chloride			•																			•	•		•		
Methadone Hydrochloride		•	•																				•		•		•
Methamphetamine Hydrochloride		•																				•			•		•

Table 2: Compiled Black Box Warning Table (continued)

Drugs (Generic Name):	Boxed Warnings:	Effects on Organ Systems																			Other Effects					
		Cardiovascular	Pulmonary	Hematologic/Bleeding	Neurologic	Infectious Disease	Teratogenicity/Fetal harm	Gastrointestinal	Psychiatric	Oncologic	Hepatic	Hypersensitivity & Other Reactions	Dermatologic/Soft Tissues	Renal	Metabolic/Electrolyte Disturabance	Musculoskeletal	Genitourinary	Ophthalmic	ENT (ears/nose/throat)	Endocrine	Autoimmune	Caution Select Circumstances [A]	Admin/Monitoring Instructions [B]	Concurrent Item Restriction [C]	Reserve for Select Circumstances [D]	Abuse Potential	Overdose/Poisoning
Methohexital Sodium		•	•																				•				
Methotrexate Sodium			•	•		•	•	•		•	•		•	•	•	•						•	•	•	•		
Methoxsalen										•			•					•					•		•		
Methoxy Polyethylene Glycol-Epoetin Beta		•		•						•												•	•				
Methylphenidate									•													•	•	•		•	
Methylphenidate Hydrochloride									•													•	•	•		•	
Methysergide Maleate		•	•																						•		
Metoclopramide Hydrochloride					•																	•					
Metolazone																							•				
Metoprolol Succinate		•																				•	•				
Metoprolol Tartrate		•																			•	•	•				
Metronidazole										•															•		
Mexiletine Hydrochloride		•									•											•			•		
Midazolam Hydrochloride		•	•		•																	•	•	•			
Midodrine Hydrochloride		•																							•		
Mifepristone		•		•		•		•								•											
Milnacipran Hydrochloride									•													•	•				
Minoxidil		•																				•	•	•	•		
Mirtazapine									•													•	•				
Misoprostol							•										•					•	•		•		
Mitomycin				•		•								•									•	•			
Mitotane																				•			•				
Mitoxantrone Hydrochloride		•		•		•				•			•									•	•	•			
Modafinil																										•	
Moexipril Hydrochloride							•															•					
Molindone Hydrochloride		•	•			•																•					
Moricizine Hydrochloride		•																				•			•		
Morphine Sulfate			•																				•		•	•	
Morphine Sulfate/Naltrexone Hydrochloride																						•	•	•	•		•
Moxifloxacin Hydrochloride																•						•		•			
Muromonab-CD3		•	•		•							•						•					•				
Mycophenolate Mofetil				•		•	•			•												•	•				
Mycophenolate Sodium				•		•	•			•												•	•				
Nabumetone		•		•	•			•														•					
Nadolol		•	•									•									•	•	•				
Naloxone Hydrochloride/Pentazocine Hydrochloride												•											•	•			
Naltrexone Hydrochloride											•											•	•				
Nandrolone Decanoate		•		•						•	•																
Naproxen		•		•	•			•														•					
Naproxen Sodium/Sumatriptan Succinate		•		•	•			•														•					
Natalizumab					•	•																	•	•	•		
Nefazodone Hydrochloride								•	•		•											•	•				
Nelarabine					•																		•				
Neomycin			•		•									•					•			•	•	•			
Nevirapine											•	•	•									•	•	•			
Nilotinib Hydrochloride		•																				•	•	•			
Nilutamide		•	•																				•				
Nimodipine																							•				
Nitroprusside Sodium		•																					•				•
Norepinephrine Bitartrate													•														
Norfloxacin																•						•		•			
Nortriptyline Hydrochloride									•													•	•				
Ofloxacin																•						•		•			
Olanzapine		•	•			•																•					
Olanzapine Pamoate (inj)		•	•			•			•													•	•				•
Olmesartan Medoxomil							•															•					
Omalizumab		•	•									•	•										•				
OnabotulinumtoxinA			•		•			•								•	•	•				•					
Ondansetron Hydrochloride																						•	•				
Oprelvekin												•															
Oxaliplatin												•															
Oxandrolone		•		•						•	•																
Oxaprozin		•		•	•			•														•					
Oxycodone Hydrochloride			•																				•		•	•	•
Oxymetholone		•		•						•	•																
Oxymorphone Hydrochloride																							•	•	•	•	•
Oxytocin																						•					
Paclitaxel		•	•	•		•						•	•									•	•				
Paclitaxel Protein-Bound				•		•																•	•				
Paliperidone		•	•			•																•					
Pancuronium Bromide																							•				

Table 2: Compiled Black Box Warning Table (continued)

Drugs (Generic Name):	Boxed Warnings:	Effects on Organ Systems																			Other Effects					
		Cardiovascular	Pulmonary	Hematologic/Bleeding	Neurologic	Infectious Disease	Teratogenicity/Fetal harm	Gastrointestinal	Psychiatric	Oncologic	Hepatic	Hypersensitivity & Other Reactions	Dermatologic/Soft Tissues	Renal	Metabolic/Electrolyte Disturabance	Musculoskeletal	Genitourinary	Ophthalmic	ENT (ears/nose/throat)	Endocrine	Autoimmune	Caution Select Circumstances [A]	Admin/Monitoring Instructions [B]	Concurrent Item Restriction [C]	Reserve for Select Circumstances [D]	Abuse Potential	Overdose/Poisoning
Panitumumab												•	•														
Paroxetine Hydrochloride									•													•	•				
Paroxetine Mesylate									•													•	•				
Pazopanib Hydrochloride											•												•				
Peginterferon Alfa-2a		•			•	•			•												•		•	•			
Peginterferon Alfa-2b		•			•	•			•												•		•	•			
Pemoline								•			•												•		•		
Penicillamine																							•				
Penicillin G Benzathine		•	•																				•				
Penicillin G Benzathine/Penicillin G Procaine																							•				
Pentostatin			•		•						•			•								•	•	•			
Peramivir																						•	•		•		
Perflutren Lipid Microsphere		•	•																			•	•				
Perflutren Protein Type A Microsphere		•	•																			•	•				
Pergolide Mesylate		•	•														•					•	•				
Perindopril Erbumine							•															•					
Perphenazine		•	•			•																•					
Phenelzine Sulfate									•													•	•				
Phenylephrine Hydrochloride																							•				
Phenylephrine Hydrochloride/**Promethazine Hydrochloride**			•																			•	•	•			
Phenytoin Sodium																							•				
Phytonadione		•	•									•													•		
Pimecrolimus				•						•			•									•					
Pimozide		•	•			•																•					
Pioglitazone Hydrochloride		•	•																			•	•				
Piroxicam		•		•	•			•														•					
Polymixin B Sulfate			•		•									•				•				•		•	•		
Polysaccharide Iron Complex																						•	•				•
Polythiazide/Prazosin Hydrochloride																						•	•				
Polythiazide/Reserpine																						•	•				
Pooled Plasma (human) SD Treated				•							•											•					
Potassium Chloride																							•				
Potassium Iodide (see Iodine)												•										•	•		•		
Pramlintide Acetate															•								•	•			
Prasugrel Hydrochloride		•		•	•																	•		•			
Primaquine Phosphate																							•				
Procainamide Hydrochloride				•																	•		•		•		
Procarbazine Hydrochloride																							•				
Prochlorperazine		•	•			•																•					
Progesterone		•	•	•	•				•	•												•	•				
Promethazine Hydrochloride			•																			•	•	•			
Propafenone Hydrochloride		•																				•					
Propoxyphene Hydrochloride					•				•													•	•	•		•	•
Propoxyphene Napsylate					•				•													•	•	•		•	•
Propranolol Hydrochloride		•																				•	•				
Protamine Sulfate		•	•									•										•	•	•			•
Protriptyline Hydrochloride									•													•	•				
Pyridostigmine Bromide																						•	•		•		
Pyrimethamine/Sulfadoxine				•		•							•														
Quetiapine Fumarate		•	•			•			•													•	•				
Quinapril Hydrochloride							•															•					
Quinidine Gluconate																						•					
Quinidine Polygalacturonate																						•					
Quinidine Sulfate																						•					
Ractopamine Hydrochloride																						•	•				
Raloxifene Hydrochloride		•	•	•	•																	•					
Ramipril							•															•					
Ranitidine																							•				
Rasburicase				•								•			•							•	•				
Rho(D) Immune Globulin			•	•										•								•	•				
Ribavirin		•	•	•			•			•							•					•	•				
RimabotulinumtoxinB			•		•			•														•					
Risperidone		•	•			•																•					
Ritonavir											•													•			
Rituximab		•	•		•	•						•	•	•	•												
Rosiglitazone Maleate		•	•																			•	•				
Salmeterol Xinafoate			•																						•		
Salsalate		•		•	•			•														•					
Saquinavir																							•				
Selegiline									•													•	•				

Table 2: Compiled Black Box Warning Table (continued)

Drugs (Generic Name):	Boxed Warnings:	Effects on Organ Systems																			Other Effects					
		Cardiovascular	Pulmonary	Hematologic/Bleeding	Neurologic	Infectious Disease	Teratogenicity/Fetal harm	Gastrointestinal	Psychiatric	Oncologic	Hepatic	Hypersensitivity & Other Reactions	Dermatologic/Soft Tissues	Renal	Metabolic/Electrolyte Disturabance	Musculoskeletal	Genitourinary	Ophthalmic	ENT (ears/nose/throat)	Endocrine	Autoimmune	Caution Select Circumstances [A]	Admin/Monitoring Instructions [B]	Concurrent Item Restriction [C]	Reserve for Select Circumstances [D]	Abuse Potential	Overdose/Poisoning
Sertraline Hydrochloride									•													•	•				
Sirolimus			•	•		•				•	•											•	•	•			
Smallpox Vaccine		•			•	•	•						•					•				•		•			
Sodium Chloride																							•				
Sodium Nitroprusside (see Nitroprusside Sodium)		•																					•				•
Sodium Oxybate			•		•					•													•			•	
Sodium Phosphate Dibasic/Sodium Phosphate Monobasic														•								•	•	•			
Sodium Polystyrene Sulfonate											CATION-EXCHANGE RESIN																
Soft (Hydrogel) Contact Lens Products																							•				
Sotalol Hydrochloride		•																				•	•				
Soybean Oil (See Fat Emulsion)			•																			•	•				
Soybean Oil, Egg Yolk Phospholipids and Glycerin			•																			•	•				
Spironolactone										•															•		
Stanozolol		•		•						•	•																
Stavudine								•			•				•							•		•			
Streptomycin			•		•									•				•	•			•	•	•	•		
Streptozocin				•				•		•	•			•									•				
Succinylcholine Chloride		•													•	•						•			•		
Sulindac		•		•	•			•														•					
Tacrolimus				•		•				•			•									•	•		•		
Tamoxifen Citrate		•	•		•					•							•								•		
Telavancin Hydrochloride							•															•	•				
Telbivudine						•					•				•								•	•			
Telithromycin			•																			•					
Telmisartan							•															•					
Temozolomide																							•				
Teniposide				•		•						•											•				
Tenofovir Disoproxil Fumarate						•					•				•							•		•			
Teriparatide										•						•						•			•		
Testosterone (gel)																	•					•					
Tetanus Toxoid																							•				
Tetrabenazine									•													•	•				
Thalidomide		•	•	•			•															•	•	•			
Thioridazine Hydrochloride		•																							•		
Thiothixene		•	•			•																•					
Thrombin, Bovine				•																		•					
Thyroid																						•		•			
Ticlopidine Hydrochloride				•																		•	•				
Timolol Maleate		•																					•	•			
Tinidazole										•															•		
Tinzaparin Sodium				•	•																		•	•			
Tipranavir				•	•						•											•					
Tobramycin					•		•							•					•			•	•	•			
Tocainide Hydrochloride		•	•	•		•																•	•		•		
Tocilizumab			•			•																•	•	•			
Tolcapone								•			•		•									•	•		•		
Tolmetin Sodium		•		•	•			•														•					
Tolvaptan					•				•													•	•	•			
Topotecan Hydrochloride				•		•																	•		•		
Tositumomab				•			•					•										•	•				
Trandolapril							•															•					
Trandolapril/Verapamil Hydrochloride							•															•					
Tranylcypromine Sulfate									•													•	•				
Trastuzumab		•	•									•										•		•			
Trazodone Hydrochloride									•													•	•				
Tretinoin		•	•	•			•				•			•								•	•		•		
Triamterene															•							•	•				
Triazolam																										•	
Trichophyton mentagrophytes/Trichophyton rubrum												•											•				
Trifluoperazine		•	•			•																•					
Trimetrexate Glucuronate																							•				
Trimipramine Maleate									•													•	•				
Trovafloxacin Mesylate											•														•		
Urokinase				•																			•				
Vaccinia Immune Globulin, Human														•								•	•	•			
Valdecoxib												•	•														
Valganciclovir Hydrochloride				•						•							•										
Valproate Sodium							•	•			•											•	•	•			

Table 2: Compiled Black Box Warning Table (continued)

Drugs (Generic Name):	Boxed Warnings:	Effects on Organ Systems																			Other Effects					
		Cardiovascular	Pulmonary	Hematologic/Bleeding	Neurologic	Infectious Disease	Teratogenicity/Fetal harm	Gastrointestinal	Psychiatric	Oncologic	Hepatic	Hypersensitivity & Other Reactions	Dermatologic/Soft Tissues	Renal	Metabolic/Electrolyte Disturabance	Musculoskeletal	Genitourinary	Ophthalmic	ENT (ears/nose/throat)	Endocrine	Autoimmune	Caution Select Circumstances [A]	Admin/Monitoring Instructions [B]	Concurrent Item Restriction [C]	Reserve for Select Circumstances [D]	Abuse Potential	Overdose/Poisoning
Valproic Acid							●	●			●											●	●	●			
Valsartan							●															●					
Varenicline					●				●													●	●				
Varicella-Zoster Immune Globulin						●					●	●															
Vecuronium Bromide																							●				
Venlafaxine Hydrochloride									●													●	●				
Vigabatrin																			●			●	●	●			
Vinblastine Sulfate													●										●				
Vincristine Sulfate													●										●				
Vinorelbine Tartrate				●		●							●										●				
Warfarin Sodium				●																		●	●				
Water (Sterile Water)																							●				
Zalcitabine					●			●			●				●							●		●			
Zaleplon																										●	
Zanamivir																							●				
Ziconotide					●				●													●	●				
Zidovudine				●							●				●	●						●		●			
Ziprasidone Hydrochloride		●	●			●																●					
Ziprasidone Mesylate		●	●			●																●					
Zolpidem tartrate																										●	
Total number of BBWs pertaining to each classification:		200	144	143	120	89	78	77	74	64	61	60	52	39	39	37	26	12	9	8	8	416	402	156	93	26	24

[A] Caution or avoidance with select patient populations,indications, or clinical situations

[B] Administration or monitoring instructions

[C] Caution or avoidance of select concurrent medications, treatments, or substance use

[D] Use reserved for select patient populations, indications, or clinical situations

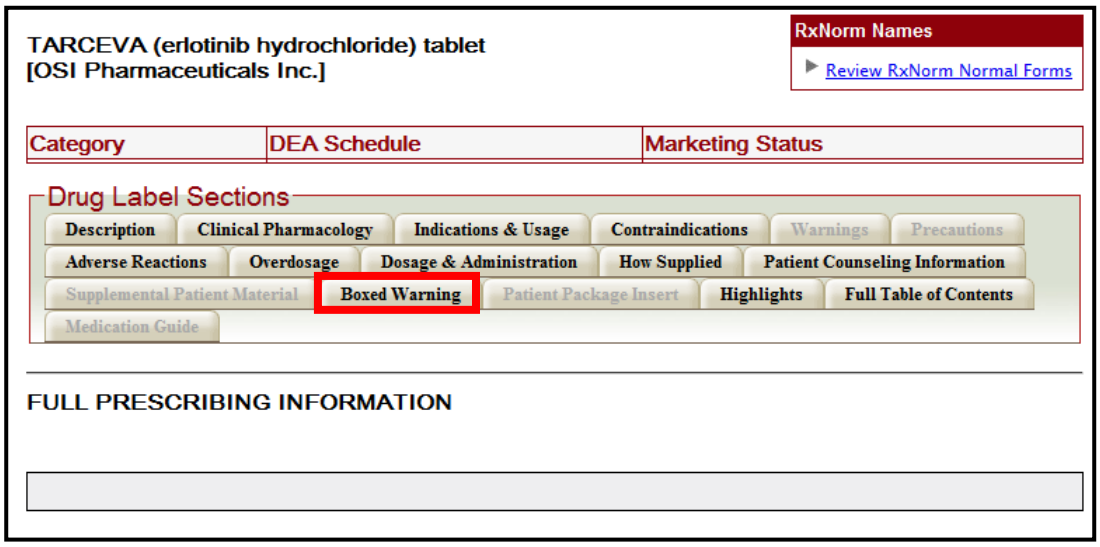


Figure 16: Section of SPL for erlotinib hydrochloride in DailyMed. DailyMed lists erlotinib as having a black box warning (red box), however, the black box warning is empty.

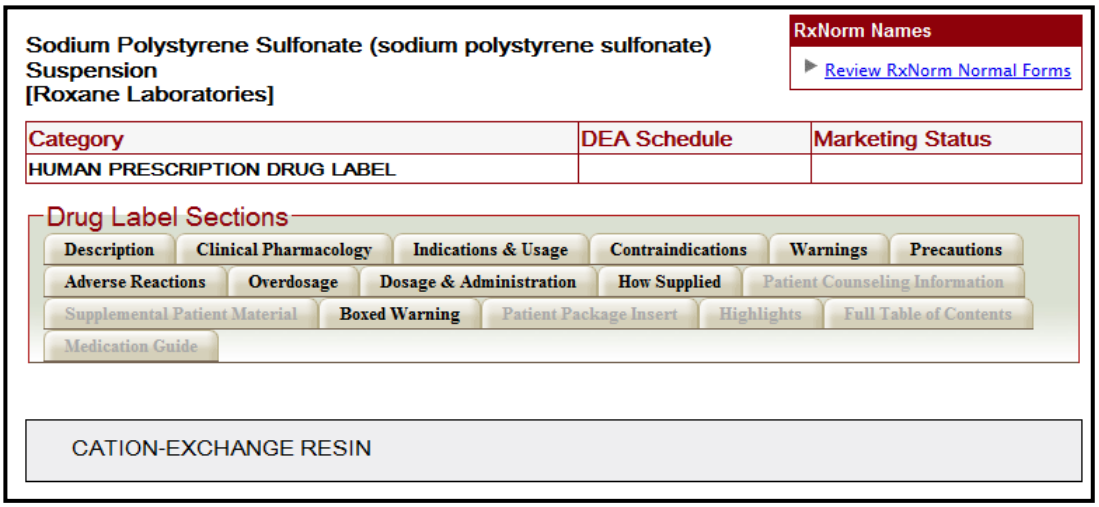


Figure 17: BBW for sodium polystyrene sulfonate in DailyMed.

Table 3: Frequency of black box warning classifications

Effects on Organ Systems	Frequency of BBWs
Total numer of drug BBWs	**635**
Cardiovascular	200
Pulmonary	144
Hematologic/Bleeding	143
Neurologic	120
Infectious Disease	89
Teratogenicity/Fetal harm	78
Gastrointestinal	77
Psychiatric	74
Oncologic	64
Hepatic	61
Hypersensitivity & Other Reactions	60
Dermatologic/Soft Tissues	52
Renal	39
Metabolic/Electrolyte Disturabance	39
Musculoskeletal	37
Genitourinary	26
Ophthalmic	12
ENT (ears/nose/throat)	9
Endocrine	8
Autoimmune	8

Other Effects	Frequency of BBWs
Total numer of drug BBWs	**635**
Caution Select Circumstances [A]	416
Admin/Monitoring Instructions [B]	402
Concurrent Item Restriction [C]	156
Reserve for Select Circumstances [D]	93
Abuse Potential	26
Overdose/Poisoning	24

[A] Caution or avoidance with select patient populations,indications, or clinical situations

[B] Administration or monitoring instructions

[C] Caution or avoidance of select concurrent medications, treatments, or substance use

[D] Use reserved for select patient populations, indications, or clinical situations

Table 4: Relative comprehensiveness of drug databases reflected by total BBW drugs present/absent

	Individual BBW Lists				Collective BBW List
	DailyMed	Micromedex	Facts & Comparisons	BlackBoxRx	
Total number of drugs with a BBW present in each database	**551**	**514**	**500**	**536**	**635**
Combination drugs with a BBW	95	79	71	28	101
Other combination drugs with a BBW considered present in BlackBoxRx [A]	N/A	N/A	N/A	63	N/A
Total number of drugs with a BBW present on the collective BBW list but *absent* from each respective database	**84**	**121**	**135**	**99**	**0**
BBW drugs *absent* from database due to listing as *bolded warning only* [B]	7	N/A	N/A	7	N/A
BBW drugs absent from database due to listing *without a BBW* even though drug present in database	23	83	94	2	N/A
BBW drugs absent from database due to *complete absence of drug* from database	54	38	41	90	N/A

[A] See methods section

[B] See introduction section

Table 5: Relative consisency of drug databases in listing drugs with BBWs

	DailyMed	Micromedex	Facts & Comparisons	BlackBoxRx[A]
Total number of BBW drugs present in each database:	**551**	**514**	**500**	**536**
BBW drugs present in database as well as all 3 other databases	416	416	416	416
BBW drugs present in database as well as 2 of the other databases	54	69	58	80
BBW drugs present in database as well as 1 of the other databases	26	18	9	35
BBW drugs with one database as only source where listed with BBW	55	11	17	5
Total number of BBW drugs present on collective BBW list but absent from each database:	**84**	**121**	**135**	**99**
BBW drugs absent from database as well as 2 of the other databases	33	77	71	83
BBW drugs absent from database as well as 1 of the other databases	18	26	35	9
BBW drugs absent from only from this database	33	18	29	7

[A] Figures for BlackBoxRx include combination drugs not listed as described in methods section

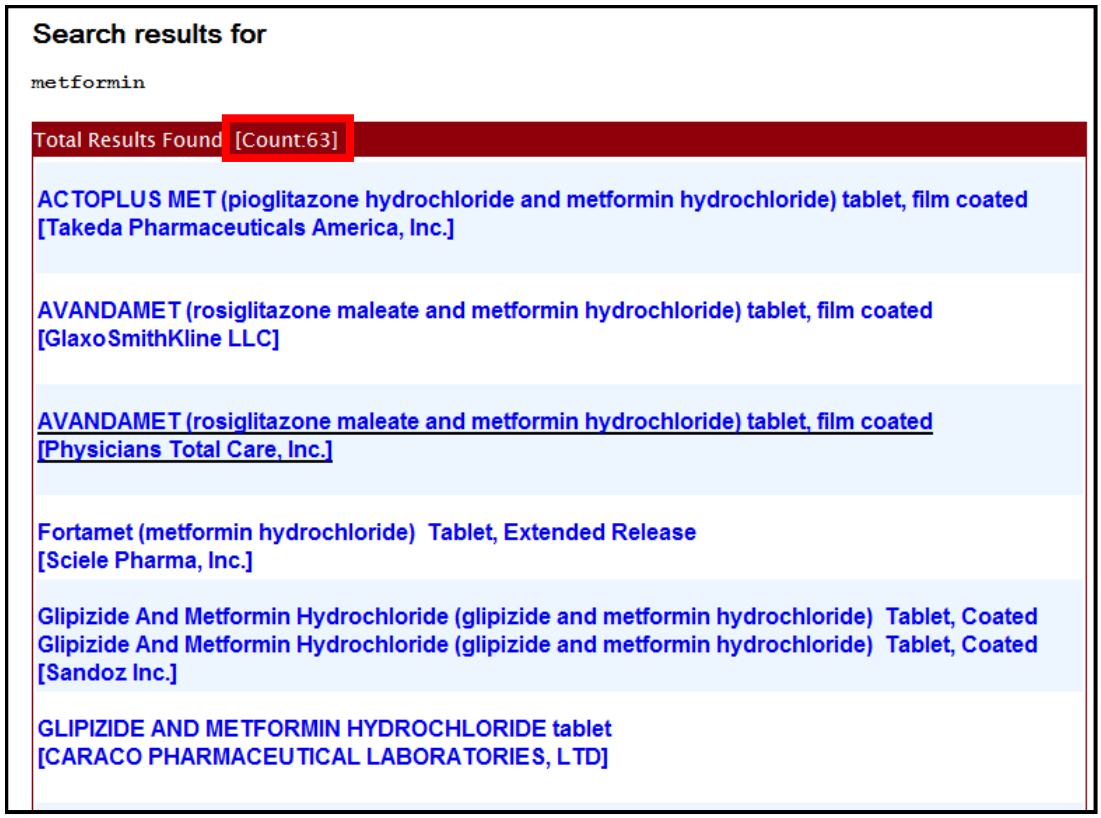


Figure 18: DailyMed search results for "metformin". Red box highlights number of results from search.

WARNINGS

Lactic Acidosis:

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride tablets, USP is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin hydrochloride tablets, USP treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin hydrochloride tablets, USP since alcohol potentiates the effects of metformin hydrochloride tablets, USP on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS). The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). Metformin hydrochloride tablets, USP should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms, could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride tablets, USP are dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS AND PRECAUTIONS).

Figure 19: DailyMed accompanying black box warning for majority of metformin and metformin containing combination drugs.

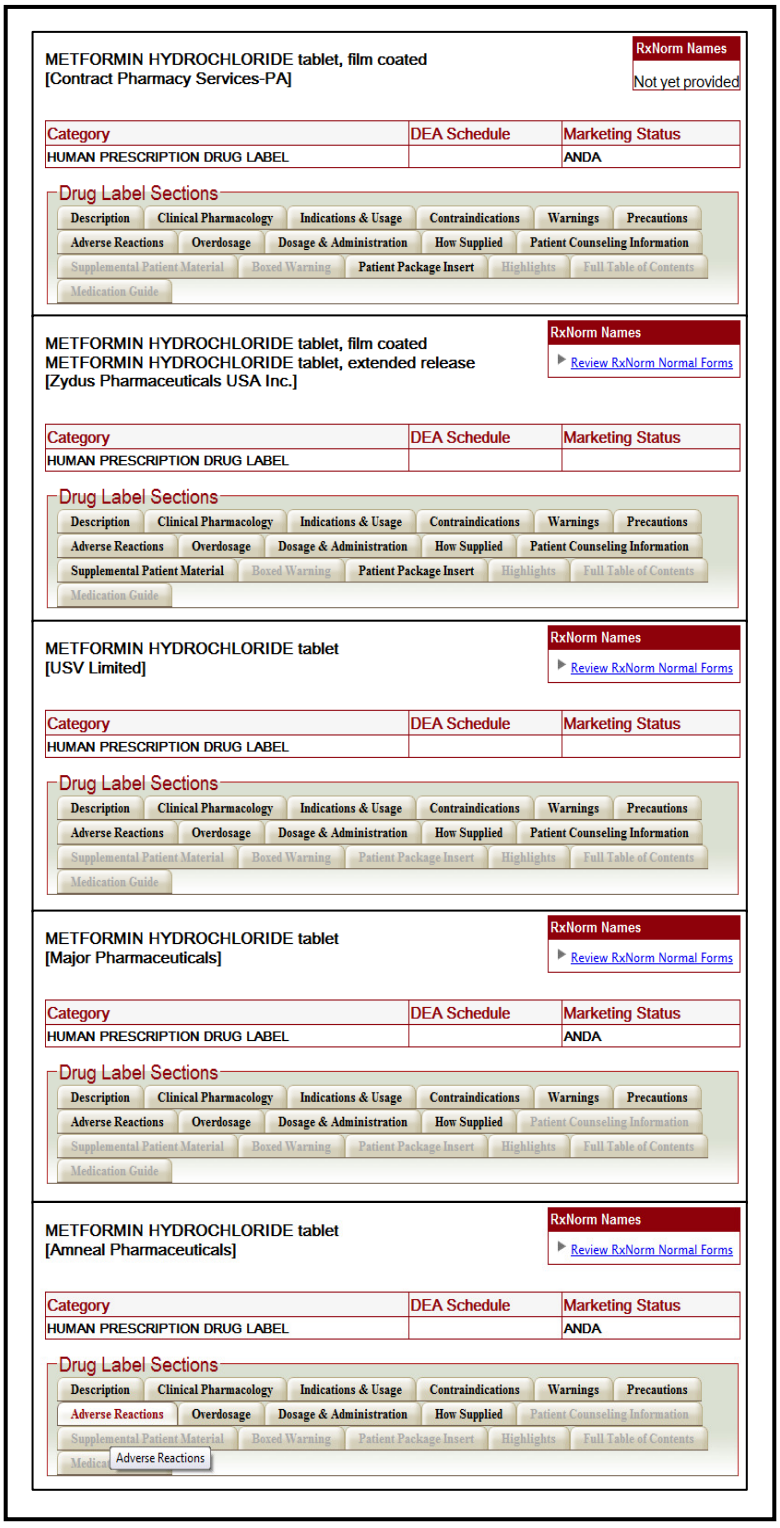


Figure 20: In DailyMed, sections of SPLs for five different formulations of metformin hydrochloride demonstrating that these do not carry a black box warning.

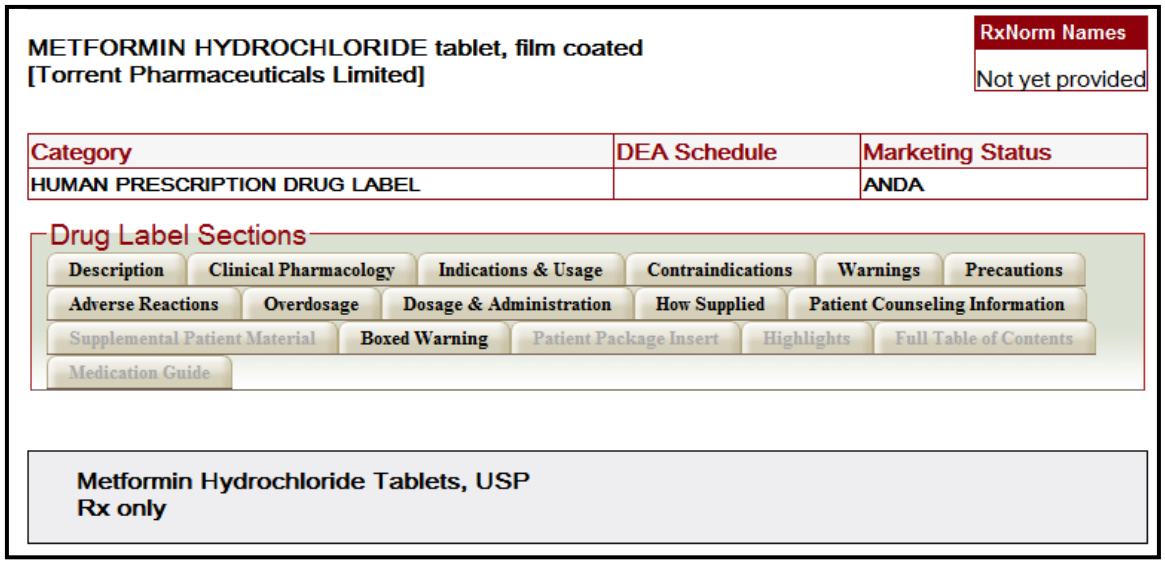


Figure 21: In DailyMed, portion of SPL for one formulation of metformin hydrochloride and its BBW (compare to Figure 19).

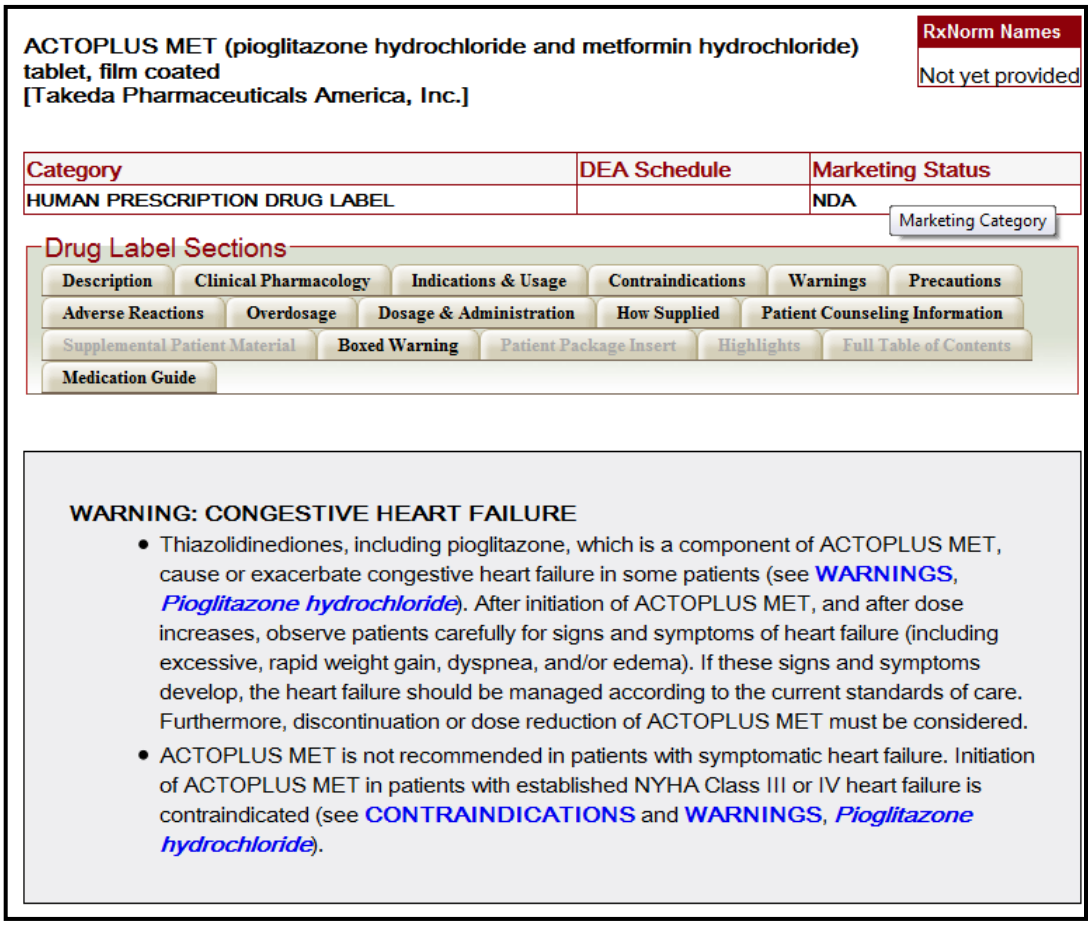


Figure 22: In DailyMed, black box warning for metformin hydrochloride/pioglitazone hydrochloride. No mention of risks of lactic acidosis etc. pertaining to metformin is made in BBW.

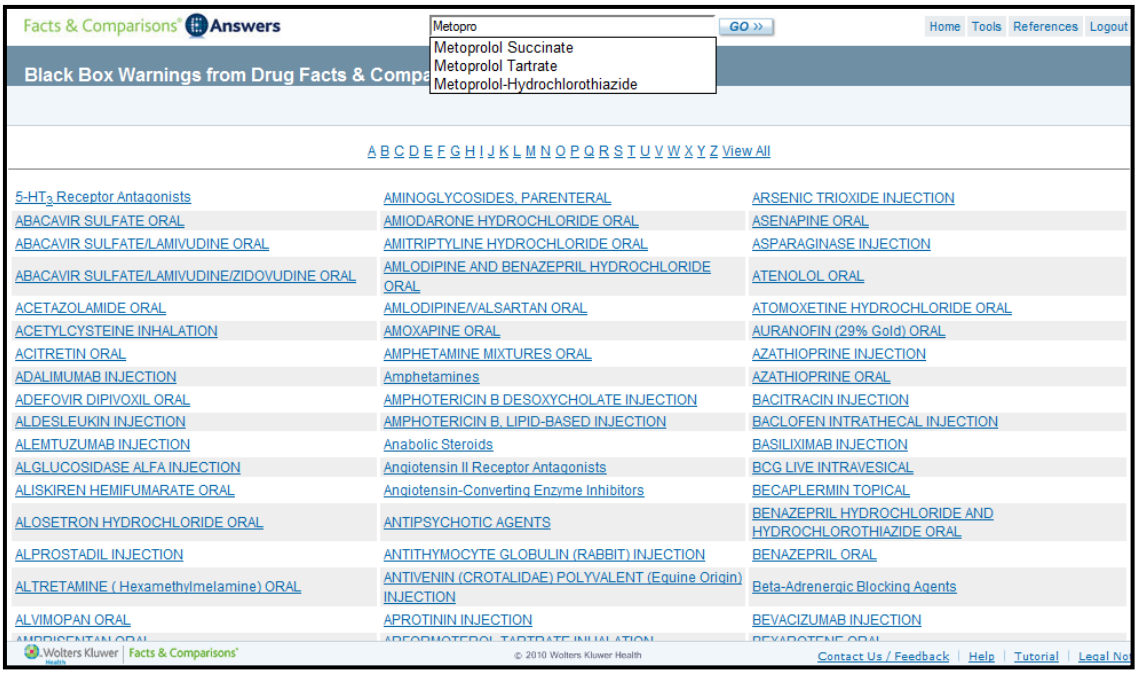


Figure 23: Facts & Comparisons BBW list with auto fill feature noted at top. As an example, typing “metopro” yields a dropdown selection of three potential drug/drug combos.

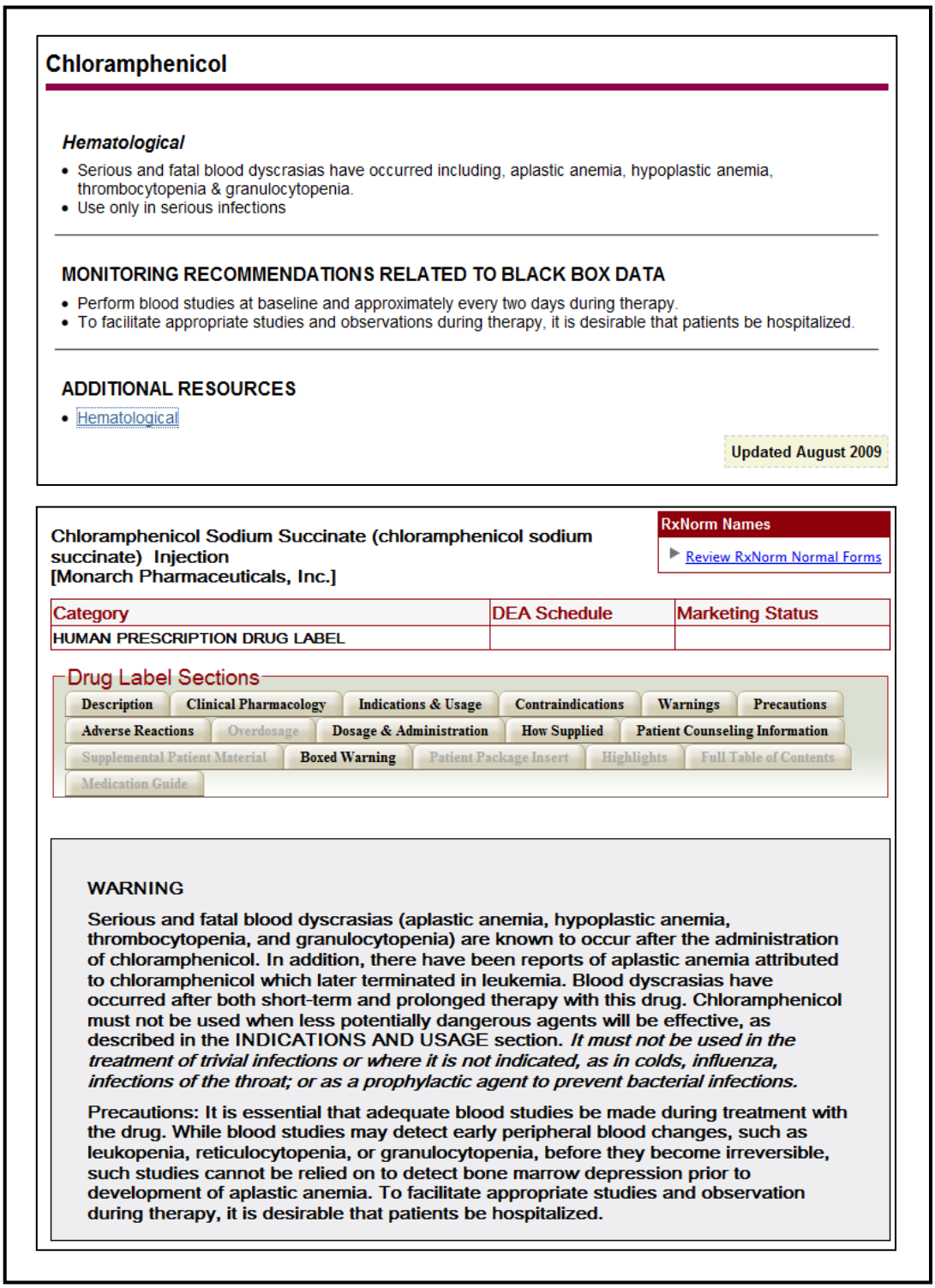


Figure 24: BBW for chloramphenicol as presented in BlackBoxRx (above) and DailyMed (below) as an example of how BlackBoxRx truncates BBW information in bullet point format.

References:

1. Halloran K, Barash PG. Inside the Black Box: Current Policies and Concerns With the United States Food and Drug Administration's Highest Drug Safety Warning System. Curr Opin Anaesthesiol 2010; Publication pending.

2. Legislation. fda.gov. [last viewed 4/1/10] Available from: http://www.fda.gov/regulatoryinformation/legislation/default.htm.

3. Watson KT, Barash PG. The new Food and Drug Administration drug package insert: Implications for patient safety and clinical care. Anes Analg 2009;108:211-18.

4. Murphy S, Roberts R. "Black box" 101: how the Food and Drug Administration evaluates, communicates, and manages drug benefit/risk. J Allergy Clin Immunol 2006;117:34-9.

5. Guidance for industry: Providing regulatory submissions in electronic format - drug establishment registration and drug listing. fda.gov. 5/2009 [last viewed 4/1/10]. Available from: http://www.fda.gov/downloads/ForIndustry/DataStandards/StructuredProductLabeling/UCM164053.pdf.

6. Beach JE, Faich GA, Bormel FG, Sasinowski FJ. Black box warnings in prescription drug labeling: results of a survey of 206 drugs. Food Drug Law J 1998;53:403-11.

7. Liang BA. FDA use of the black box warning: Time for reevaluation as a safety tool. (Editorial) J Clin Anesth 2002;14:561-63.

8. Szefler SJ, Whelan GJ, Leung DY. "Black box" warning: wake-up call or overreaction? J Allergy Clin Immunol 2006;117:26-9.

9. Halloran K. Inside The Black Box: Current Policies and Problems With the FDA's Highest Drug Safety Warning. Yale School of Medicine thesis submission 2009.

10. Wagner AK, Chan KA, Dashevsky I, Raebel MA, Andrade SE, Lafata JE, Davis RL, Gurwitz JH, Soumerai SB, Platt R. FDA drug prescribing warnings: is the black box half empty or half full? Pharmacoepidemiol Drug Saf 2006;15:369-86.

11. Fonacier L, Spergel J, Charlesworth EN, Weldon D, Beltrani V, Bernhisel-Broadbent J, et al. Report of the Topical Calcineurin Inhibitor task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2005;115:1249-53.

12. Micromedex® 1.0 (Healthcare Series). [last viewed 03/29/10]. Available from: http://www.thomsonhc.com (subscription required).

13. Facts & Comparisons®. [last viewed 03/29/10]. Available from: http://www.factsandcomparisons.com (subscription required).

14. DailyMed. [last viewed 03/31/10]. Available from: http://dailymed.nlm.nih.gov.

15. About Daily Med. dailymed.hlm.nih.gov. [last viewed 3/31/10] Available from: http://dailymed.nlm.nih.gov/dailymed/about.cfm.

16. BlackBoxRx.com. [last viewed 03/29/10]. Available from: http://blackboxrx.com

17. Capecitabine structured product labeling black box warning. dailymed.hlm.nih.gov [last viewed 3/31/10]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=17339.

18. Capecitabine black box warning. thomsonhc.com [last viewed 3/31/10]. Available from: http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_CPR/BlackBoxWarnings/ND_PR/Drugs/CS/962B4C/DUPLICATIONSHIELDSYNC/5FF330/ND_PG/PRIH/ND_B/HCS/SBK/1/ND_P/Drugs/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/924719/ContentSetId/100/SearchTerm/Capecitabine/SearchOption/BeginWith#blackBoxWarningSection (subscription required).

19. Capecitabine black box warning. factsandcomparisons.com [last viewed 3/31/10]. Available from: http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp12231&book=DFC&#warnbox (subscription required).

20. Capecitabine black box warning. blackboxrx.com [last viewed 3/31/10]. Available from: http://blackboxrx.com/app/display.php?id=36.

21. Micromedex black box warnings [last viewed 3/29/10]. Available from: http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/521EC0/DUPLICATIONSHIELDSYNC/7D78A3/ND_PG/PRIH/ND_B/HCS/ND_P/Main/PFActionId/hcs.drugs.BlackBoxWarnings#. (subscription required)

22. Black box warnings from Facts & Comparisons. [last viewed 3/29/10]. Available from: http://online.factsandcomparisons.com/ListViewer.aspx?section=warning&start=0. (subscription required)

23. DailyMed BBW list file all_blk_box_20090701.xls provided by Dr. Stuart Nelson on 7/1/09.

24. Muromonab-CD3 structured product labeling black box warning. dailymed.hlm.nih.gov [last viewed 3/31/10]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=16414.

25. Methoxsalen structured product labeling black box warning. dailymed.hlm.nih.gov [last viewed 3/31/10]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=9158.

26. Erlotinib hydrochloride structured product labeling black box warning. dailymed.hlm.nih.gov [last viewed 3/31/10] Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=8467#nlm34066-1.

27. Sodium polystyrene sulfonate structured product labeling black box warning. dailymed.hlm.nih.gov [last viewed 3/31/10] Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=3990#nlm34066-1.

28. Metoprolol tartrate structured product labeling black box warning. dailymed.hlm.nih.gov [last viewed 3/31/10] Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=15604.

29. White PF. Droperidol: A cost-effective antiemetic for over thirty years. Anes Analg 2002;95:789-90.

30. Gan TJ, Meyer T, Apfel CC, et al. Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg 2003;97:62-71.

31. Fortney JT, Gan TJ, Graczyk S, et al. A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. S3A-409 and S3A-410 Study Groups. Anesth Analg 1998;86:731-8.

32. White PF, Watcha MF. Postoperative nausea and vomiting: prophylaxis versus treatment (editorial). Anesth Analg 1999;89:1337-9.

33. Watcha MF. The cost-effective management of postoperative nausea and vomiting. Anesthesiology 2000;92:931-3.

34. Tramer MR, Reynolds DJM, Goodman NW. Whose drug is it anyway? Lancet 2001;258:1275.

35. Reilly JG, Ayes SA, Ferrier IN, et al. QTc interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000;335:1048-52.

36. Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. Drugs 2002;62(11):1649-71.

37. Bailey P, Norton R, Karan S. The FDA droperidol warning: is it justified? Anesthesiology 2002;97:288–9.

38. Habib AS, Gan TJ. The use of droperidol before and after the Food and Drug Administration black box warning: a survey of the members of the Society of Ambulatory Anesthesiology. J Clin Anesth 2008;20(1):35-9.

39. Droperidol structured product labeling black box warning. dailymed.hlm.nih.gov [last viewed 3/31/10] Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2750.

40. Habib AS, Gan TJ (#3). Food and Drug Administration black box warning on the perioperative use of droperidol: A review of cases. Anesth Analg 2003;96:1377-9.

41. Habib AS, Gan TJ (#2). Pro: The Food and Drug Administration Black box warning on droperidol is not justified. Anesth Analg 2008;106(5):1414-7.

42. Sheth HS, Verrico MM, Skledar SJ, Towers AL. Promethazine adverse events after implementation of a medication shortage interchange. Ann Pharmacother 2005;39:255–61.

43. Ludwin DB, Shafer, SL. Con: The black box warning on droperidol should not be removed (but should be clarified!). Anesth Analg 2008;106(5):1418-20.

44. Henzi I, Sonderegger J, Tramer MR. Efficacy, dose-response, and adverse effects of droperidol for prevention of postoperative nausea and vomiting. Can J Anaesth 2000;47:537–51.

45. Nuttall GA, Eckerman KM, Jacob KA, Pawlaski EM, Wigersma SK, Marienau ME, Oliver WC, Narr BJ, Ackerman MJ. Does low-dose droperidol administration increase the risk of drug-induced QT prolongation and torsade de pointes in the general surgical population? Anesthesiology 2007;107:531-6.

46. IOM Recommendations: FDA Actions Update. fda.gov. [last viewed 3/29/10] Available from: http://www.fda.gov/Safety/SafetyofSpecificProducts/ucm184598.htm.