

FDA drug prescribing warnings: is the black box half empty or half full?[†]

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SUMMARY

Purpose Black box warnings (BBWs) are the Food and Drug Administration's (FDA) strongest labeling requirements for high-risk medicines. It is unknown how frequently physicians prescribe BBW drugs and whether they do so in compliance with the warnings. The purpose of the present study was to assess the frequency of use of BBW medications in ambulatory care and prescribing compliance with BBW recommendations.

Methods This retrospective study used automated claims data of 929 958 enrollees in 10 geographically diverse health plans in the United States to estimate frequency of use in ambulatory care of 216 BBW drugs/drug groups between 1/1/99 and 31/6/01. We assessed dispensing compliance with the BBW requirements for selected drugs.

Results During a 30-month period, more than 40% of enrollees received at least one medication that carried a BBW that could potentially apply to them. We found few instances of prescribing during pregnancy of BBW drugs absolutely contra-indicated in pregnancy. There was almost no co-prescribing of contra-indicated drugs with the two QT-interval-prolonging BBW drugs evaluated. Most non-compliance occurred with recommendations for baseline laboratory monitoring (49.6% of all therapy initiations that should have been accompanied by baseline laboratory monitoring were not).

Conclusions Many individuals receive drugs considered to carry the potential for serious risk. For some of these drugs, use is largely consistent with their BBW, while for others it is not. Since it will not be possible to avoid certain drug-associated risks, it will be important to develop effective methods to use BBWs and other methods to minimize risks. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — black box warnings; drug labeling; Food and Drug Administration; prescribing safety; regulatory actions; risk communication

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BACKGROUND

'Black box warnings' (BBWs) are the strongest warning that the Food and Drug Administration (FDA) imposes on medicines that carry the risk of '[s]pecial problems, particularly those that may lead to death or serious injury.'¹ BBWs can only be issued following an FDA mandate and are intended to alert prescribers to the high risks associated with a drug.² BBWs describe the risks and may list specific precautions for the drug's use. BBWs must appear on all promotional materials. Although BBWs have significant implications for manufacturers; their effectiveness as a risk communication tool is debatable.³⁻⁷ In ambulatory care where approximately 1.4 billion prescriptions are written per year,^{8,9} there is no information about how frequently physicians prescribe BBW drugs for patients to whom the warnings apply, nor whether prescribing is consistent with the stipulations of the BBW.

We therefore determined the frequency of use of BBW medications in ambulatory care in 10 U.S. health plans. For selected BBW medications, we assessed frequency of prescribing in compliance with specific warning requirements.

METHODS

Study population and data sources

This retrospective study used automated membership, demographic, utilization, and drug dispensing claims data from 1 January 1999 to 30 June 2001 for a representative 2 000 000 member sample created for the Prescribing Safety Study, conducted in the 10 geographically diverse health plans that form the HMO Research Network's Center for Education and Research on Therapeutics (CERTs; <http://www.certs.hhs.gov/>; accessed 17 October 2003).¹⁰ To assess *prevalence of dispensing of BBW medications*, we restricted the sample to 929 958 health plan members who were continuously enrolled and who had ongoing drug benefits (and therefore could have medication claims). To assess *prescribing compliance with the BBW*, we restricted the sample to enrollees ($n = 216\,694$) who received 1 of 19 selected BBW medications or groups of medications. Additional criteria including those for selecting a BBW drug or drug group for the compliance assessment are described below. We required health plan enrollment with drug benefit throughout the period when prescribing was evaluated (see below). The Institutional Review Boards of each participating organization approved the study.

Drugs with BBW

We searched the Physicians' Desk Reference for 1999-2001,¹¹⁻¹³ the FDA website,¹⁴ and a recently published list of BBW drugs¹⁵⁻¹⁸ to identify BBW medications. We combined dosages, salts, and combinations containing a drug if they carried the same BBW. We grouped drugs by pharmacologic class if class members had the same BBW. We excluded drugs for which the BBW was introduced after the end of the study period and those with a BBW that only mentioned storage, handling, distribution conditions, compounding directions, or administration or dosing guidelines. We only evaluated prescribing compliance with BBW in existence during the study period. We classified BBWs as applying to (1) all patients; (2) children (0-14 years old) only; (3) women only; and (4) women of childbearing age (15-44 years old). We considered BBWs that required laboratory monitoring, those that listed contra-indicated co-medications, and those that identified pregnancy as a contraindication feasible for study with claims data. For the compliance analysis, we selected the 19 drugs or drug groups with BBW feasible for assessment with claims data, sufficient use in the study population, and on the U.S. market in December 2004.

Data analysis

Frequency of BBW medication use. For each BBW medication/group, we identified individuals who had received the BBW medication and to whom the content of the BBW could apply. For example, we considered only women of childbearing age to assess compliance with a BBW requirement for pregnancy testing before start of therapy.

Prescribing potentially non-compliant with the BBW. We defined potentially non-compliant prescribing with four types of BBWs: BBWs requiring laboratory monitoring before therapy initiation or during continued therapy, BBWs listing contra-indicated co-medications, and BBWs mentioning contra-indicated prescribing during pregnancy. Compliance with recommended laboratory monitoring and use in pregnancy in this population was also subject of analyses by Raebel *et al.*¹⁹ and Andrade *et al.*,²⁰ respectively. However, these authors did not distinguish between compliance with BBW and other types of recommendations.

Laboratory monitoring before therapy initiation. Study drugs for baseline laboratory monitoring (and

laboratory tests assessed) were valproic acid (aspartate aminotransferase, AST, or alanine aminotransferase, ALT), carbamazepine (complete blood count with platelets), isoniazid (AST or ALT in patients >35 years old), triamterene and combinations (serum potassium, K⁺), amiloride and combinations (K⁺), isotretinoin (pregnancy test), acitretin (pregnancy test), and misoprostol and combinations (pregnancy test). We identified new dispensings of these drugs as those without dispensing during the preceding 180 days for patients with continuous enrollment during the 180 days before and 14 days after the first dispensing date. For drugs requiring pregnancy tests before the start of therapy, we defined potentially non-compliant prescribing as the absence of a claim for a pregnancy test in the 60 days before and 14 days after the first dispensing date (to not misclassify as potential non-compliant prescribing instances where a prescriber may have ordered a laboratory test and prescribed a medication during the office visit, and instructed the patient to delay starting the medication until laboratory results were available). Otherwise, non-compliant prescribing was defined as the absence of recommended baseline laboratory monitoring during the 180 days before or 14 days after the first dispensing date. Raebel *et al.* have previously validated claims-based laboratory test identification against laboratory test reports in medical records.¹⁹

Laboratory monitoring during continued therapy. We defined episodes of continued drug therapy as consecutive dispensings of a BBW drug with gaps less than the sum of the number of days supplied plus 1.5 times the number of days supplied, beginning with the second dispensing. When the BBW did not recommend a specific monitoring frequency, we used published guidelines, guidelines from participating health plans, and recommendations of members of the National CERTs Steering Committee. Eligible episodes needed to be long enough to allow for the required laboratory monitoring (e.g., for valproic acid, the continued drug therapy was at least 2 months to allow monitoring for ALT/AST every 2 months for the first 6 months of therapy). Potentially non-compliant prescribing was conservatively defined as an eligible episode without any claims for the recommended laboratory tests, and stratified by duration of episode to account for different frequencies of monitoring requirements. Study drugs included valproic acid (AST or ALT every 2 months for the first 6 months, then yearly), isoniazid (AST or ALT every 2 months in patients >35 years old), triamterene and combinations (K⁺ yearly), amiloride and combinations (K⁺

yearly), ticlopidine (CBC every 2 weeks for 3 months), cyclosporine (cyclosporine levels and serum creatinine, Scr yearly), and metformin and combinations (Scr yearly).

Contra-indicated co-medications. We assessed ketorolac, methotrexate, itraconazole, and ritonavir and their co-prescribing with 35 contra-indicated medications. We conservatively defined potentially non-compliant prescribing as a dispensing of a BBW medication that occurred on the same day as the dispensing of a contra-indicated medication. For example, dispensing of itraconazole and pimozide on the same day constituted prescribing contrary to the BBW. For co-prescribing of QT-interval-prolonging BBW medications (itraconazole, ritonavir), we also assessed co-prescribing of a contra-indicated medication during the 14 days before and after prescribing of the BBW medication.

Contra-indicated prescribing during pregnancy. Study drugs contra-indicated in pregnancy were ribavirin/interferon, methotrexate, ACE inhibitors, isotretinoin, acitretin, misoprostol and combinations, megestrol, and leflunomide. We defined delivery dates and types (normal and pre-mature) using a method similar to that described by Andrade *et al.*²⁰ Delivery dates were dates on which a delivery procedure was conducted. For enrollees with pregnancy diagnosis claims without delivery procedure claims, we used the most recent inpatient pregnancy diagnosis date as the delivery date ($n = 127$ [12%] enrollees). Deliveries were classified as normal or pre-mature using pregnancy diagnosis codes. An expert clinician panel had previously identified delivery procedure codes and pregnancy diagnosis codes likely associated with pre-mature delivery (such as multiple pregnancy).¹⁹ We defined potentially non-compliant prescribing as a dispensing of a BBW drug contra-indicated in pregnancy during an assumed gestational period of 270 days before a delivery date, and classified each dispensing during the 270 days by delivery type and trimester. Eligible patients were women aged 15–44 years who were continuously enrolled with continuous drug coverage for at least 270 days during the study period.

RESULTS

We identified 216 BBW medications/groups of which 96 were dispensed to more than 100 individuals (Appendix) during the 30-month study period. For

Table 1. Number of enrollees receiving at least one medication with a potentially relevant BBW, by age and gender

Group	Number of HMO enrollees	Number receiving at least one BBW medication, <i>n</i> (%)	Range across HMOs of % enrollees receiving at least one BBW medication
Total	929 958	387 576 (41.7)	34.5–46.5
Children, 0–14 years	181 763	21 906 (12.1)	8.9–16.0
Women, age group (years)			
15–44	184 237	102 599 (55.7)	45.5–62.3
45–64	139 446	97 736 (70.1)	60.8–77.4
65–74	42 101	31 591 (75.0)	63.9–83.2
75–84	27 374	20 734 (76.7)	63.9–83.8
85+	7031	5058 (71.9)	59.3–85.3
Male, age group (years)			
15–44	161 906	29 238 (18.1)	13.3–23.1
45–64	127 599	45 996 (36.1)	29.3–43.5
65–74	35 828	19 235 (53.7)	38.5–60.9
75–84	19 242	11 443 (59.5)	43.8–68.2
85+	3431	2040 (59.5)	51.9–70.9

BBW, black box warning; HMO, Health Maintenance Organization.

20 (20.8%) of 96 BBW medications/groups, the BBW recommends laboratory monitoring, for 6 (6.3%) it lists contra-indicated co-medications, for 8 (8.3%) contra-indicated illnesses, and 8 (8.3%) are contra-indicated in pregnancy.

Forty-three per cent of the study population was female. Most (65.9%) were between 15 and 64 years old (Table 1). During the 30-month study period, 387 576 (41.7%) of health plan members received at least one dispensing of a medication with a BBW that could apply to them (Table 1). Adult enrollees received BBW medications more frequently than children. Women received BBW medications more frequently than men, reflecting the fact that oral contraceptives and estrogens for hormone replacement therapy carry BBWs, and a number of drugs carry BBWs contra-indicating use in pregnancy.

Among the 10 most frequently dispensed BBW-containing medications were drugs with recommendations against rapid discontinuation (atenolol and metoprolol), drugs with alerts for specific indications in which the drugs should only be used (clindamycin, levothyroxine, metronidazole) or not used (propoxyphene, medroxyprogesterone), and drugs with warnings about adverse effects that require monitoring (triamterene, triamcinolone, fluticasone, metformin).

Overall, almost half of the 74 666 new dispensings of BBW medications with baseline monitoring recommendations did not have a claim for the test (Table 2). Frequencies of potentially inconsistent prescribing varied by drug and ranged from 25.0%

for isoniazid and isotretinoin to 66.4% for misoprostol and combinations.

There were no claims for a recommended laboratory test for 6605 (12.8%) of the 51 560 episodes of continued use of BBW medications that should be accompanied by routine monitoring (Table 2). Liver enzyme tests for valproic acid (29.5% of episodes) and isoniazid (25.2% of episodes) were missing most frequently. Most (1152/1912 = 60.3%) valproic acid episodes without liver function monitoring had a duration of 2–6 months, but 30.9% were between 6 and 18 months, and 8.9% between 18 and 30 months. Similarly, most (46/71 = 64.8%) isoniazid episodes without liver function monitoring lasted 2–6 months. Most frequently, the duration of diuretic use without potassium monitoring was between 12 and 24 months (65.1% triamterene and 54.6% amiloride), but episodes without any monitoring also lasted between 24 and 30 months (34.9% triamterene and 45.5% amiloride). Almost all cyclosporine episodes were accompanied by renal function and cyclosporine level monitoring.

Of 55 971 dispensings of the 4 drugs with warnings about co-medications which we evaluated, 5199 (9.3%) were prescribed on the same day as a contra-indicated drug; all involved dispensings of methotrexate with non-steroidal anti-inflammatory drugs (NSAIDs) or ketorolac with other NSAIDs (11.0% and 7.6%, respectively). There were no dispensings on the same day of itraconazole or ritonavir and contra-indicated medications. When the co-prescribing interval was widened to 14 days, there remained no

Table 2. Prevalence of prescribing non-compliant with BBW recommendations

BBW medication	Baseline laboratory monitoring		
	Baseline laboratory test	Eligible dispensings, <i>n</i>	Eligible dispensings without baseline laboratory test, <i>n</i> (%)
Misoprostol with or without diclofenac	Pregnancy test	417	277 (66.4)
Acitretin	Pregnancy test	35	22 (62.9)
Triamterene with or without HCTZ	Serum potassium	56 182	28 762 (51.2)
Valproic acid products	ALT or AST	8514	4138 (48.6)
Amiloride with or without HCTZ	Serum potassium	967	462 (47.8)
Carbamazepine	CBC with platelets	6695	2896 (43.3)
Isoniazid	ALT or AST in patients >35 years	517	129 (25.0)
Isotretinoin	Pregnancy test	1339	334 (24.9)
Total baseline laboratory monitoring		74 666	37 020 (49.6)
BBW medication	Ongoing laboratory monitoring		
	Laboratory test and assessment frequency	Eligible episodes, <i>n</i>	Eligible episodes without any requested laboratory test, <i>n</i> (%)
Valproic acid products	ALT or AST every 2 months for first 6 months, then yearly	6485	1912 (29.5)
Isoniazid	ALT and AST in patients >35 years every 2 months	282	71 (25.2)
Ticlopidine	CBC every 2 weeks for 3 months	1152	204 (17.7)
Triamterene and combinations	Serum potassium every year	27 527	3340 (12.1)
Amiloride and combinations	Serum potassium every year	599	66 (11.0)
Metformin and combinations	SCr yearly	13 994	968 (6.9)
Cyclosporine	Levels yearly	657 [#]	36 (5.5)
	SCr yearly	864 [#]	8 (0.9)
Total ongoing laboratory monitoring:		51 560	6605 (12.8)
BBW medication	Contra-indicated with/warning about use of co-medication(s)		
	Contra-indicated medications	Eligible dispensings, <i>n</i>	Eligible dispensings with same-day contra-indicated co-dispensing, <i>n</i> (%)
Methotrexate	NSAIDS*	44 320	4875 (11.0)
Ketorolac	NSAIDS*	4262	324 (7.6)
Itraconazole	Pimozide, quinidine	3733	0 (0.0)
Ritonavir	Amiodarone, bepridil, flecainide, propafenone, quinidine, dilydroergotamine, ergotamine, midazolam, triazolam, pimoziide	3656	0 (0.0)
Total contra-indicated co-medications		55 971	5199 (9.3)

Continues

Table 2. Continued

BBW medication	Contra-indicated in/warning about concomitant pregnancy	
	BBW	Eligible dispensings among women age 15–44, <i>n</i>
ACE inhibitors		
Isotretinoin	Discontinue immediately in pregnancy	58 788
Methotrexate	Contra-indicated in pregnancy	83 377
	Should not use in pregnant patients with rheumatoid arthritis or psoriasis	64 449
Megestrol acetate	Contra-indicated in pregnancy	1830
Misoprostol and combinations	Contra-indicated in pregnancy	1055
Ribavirin/interferon	Contra-indicated in pregnancy	1273
Acitretin	Contra-indicated in pregnancy	242
Leflunomide	Contra-indicated in pregnancy	866
Total contra-indicated in pregnancy		78 840

Eligible dispensings during pregnancy, *n* (%)Eligible dispensings among women age 15–44, *n*

BBW

Contra-indicated in/warning about concomitant pregnancy

ACE, angiotensin converting enzyme; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BBW, black box warning; CBC, complete blood count; NSAIDS, non-steroidal anti-inflammatory drugs; SCr, serum creatinine.

*NSAIDS: bromfenac, celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketotifen, meclizolamine, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, oxyphenbutazone, phenylbutazone, raloxifene, rofecoxib, sulfindac, tolmetin, toremifene, valdecoxib.

#Cyclosporine episode numbers differ for cyclosporine levels and serum creatinine tests because claims data of one HMO lacked all cyclosporine levels noted in medical records. We excluded cyclosporine episodes at this HMO from the calculation of cyclosporine level monitoring frequency.

co-dispensings of itraconazole and only three dispensings of ritonavir with a contra-indicated medication.

Women of childbearing age received 78 840 dispensings of BBW medications that should be avoided during pregnancy; 95 (0.3%) of these dispensings may have occurred during pregnancy. For three (ribavirin/interferon, acitretin, leflunomide) of six medicines absolutely contra-indicated in pregnancy, we found no dispensings during pregnancy. We found six dispensings of isotretinoin and one each of misoprostol and megestrol. Of 58 788 dispensings of an ACE inhibitor to women of childbearing age, 81 (0.1%) may have occurred during pregnancy, with 11 during the assumed second and third trimester of normal pregnancy, and 23 during the assumed second and third trimester of a pregnancy with pre-term delivery. Six (0.1%) of 6449 methotrexate dispensings may have occurred during normal pregnancies, although we do not know whether women were treated for rheumatoid arthritis or psoriasis, the only conditions in which the BBW recommends against methotrexate use during pregnancy.

DISCUSSION

The finding that more than 40% of ambulatory care patients received at least one potentially relevant BBW medication during a 30-month study period, and that compliance with BBWs was highly variable, indicates the need for better methods of ensuring the safe use of medications that are considered to carry serious risks. BBWs are the FDA's primary^{21,22} instrument to protect the public from potentially dangerous effects of medicines. No comprehensive official list of BBW medications or clear guidelines as to which events prompt a BBW exist,²³ and whether they are an effective safety tool remains controversial.^{2,24}

Because our data stem from a heterogeneous sample of ambulatory care patients in health plans across the U.S., we believe that the results are likely to be representative of other ambulatory care settings in U.S.

Our study cannot answer the question 'How effective are BBWs in protecting the public's health?' Nevertheless, we believe our data shed light on adherence to BBW recommendations and provide a preliminary basis for recommendations to improve communication about the risks of medicines. The BBW drugs for which we found excellent compliance with the warning explicitly state the contraindications (pregnancy) or name the contra-indicated drugs (for QT-interval-

prolonging drugs). For example, the BBW for itraconazole begins with 'co-administration of astemizole, cisapride, pimozone, or quinidine with SPORANOX[®] (itraconazole) capsules, injection, or oral solution is contra-indicated.'¹³ In contrast, the last sentence in a lengthy paragraph on hepatotoxicity of the BBW for valproic acid says 'liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months.'¹³ It is possible that concise and focused wording of a BBW is more effective than less direct wording.⁵ Alternatively, means of risk communication other than BBWs may have successfully conveyed the risk of these drugs to prescribers: a separate FDA risk classification system of and textbooks on medication use in pregnancy²⁵ exist, as well as FDA-mandated consent forms for some of the BBW medications absolutely contra-indicated in pregnancy (isotretinoin, acitretin).

For other BBW recommendations, non-compliance was high. These include recommendations for baseline laboratory monitoring, despite a wide time window allowed for in our analyses. Non-compliance with potassium level and liver enzyme monitoring was particularly high. Since it is unclear whether liver function monitoring prevents liver toxicity,²⁶⁻²⁸ BBW non-compliance may reflect this consideration on the part of the prescriber.

Our study has the limitations of a claims-based study. Medicines and procedures not paid for by the health plan (e.g., over-the-counter NSAIDs) or not billed for separately (e.g., occurring during a hospitalization) are not part of claims data. However, such undercounting would have led us to underestimate the prevalence of use of BBW medications. This may be particularly true for Medicare+Choice members who face restricted annual medicines benefit amounts. If patients paid out-of-pocket for pregnancy tests, we would have overestimated non-compliance with baseline pregnancy test requirements. If drugs were initiated in hospitals (with recommended baseline laboratory monitoring), we would have overestimated non-compliance with baseline laboratory monitoring requirements; however, hospitalization was not sufficiently common in this population to meaningfully affect the overall rates of non-compliance. The assumed gestational period of 270 days before a delivery procedure or diagnosis claim may not correctly estimate pregnancy duration and over- or underestimated the amount of medication use during pregnancy. However, effects of this misclassification would likely be small,²⁹ particularly in the estimated second and third trimester. Lastly, we do not know the reasons for prescribers' or

patients' decisions to not follow a particular BBW recommendation.

Prescribers face the challenge of keeping track of many different BBWs. Studies of risk communication efforts for cisapride and troglitazone showed that labeling changes, including BBWs, and mailings to prescribers, failed to change prescribing behavior,^{6,7,30,31} and ultimately the drugs were withdrawn from the market. Patient-specific automated alerts to BBW drugs/recommendations at the points of prescribing and dispensing may be more effective.³² Designing effective decision support for such a system requires, at a minimum, complete, consistent,³³ and current lists of BBW medicines and clinical circumstances associated with risk of morbidity and mortality. We recommend that the FDA establish and maintain such a list. Although computerized order-entry may help close the gap between recommendations and performance, it will be essential to test this possibility. Recognizing that BBWs may be insufficient in some circumstances, FDA has used more stringent measures for some drugs. Examples include the restricted distribution system for clozapine,¹³ a drug that requires hematologic monitoring, and the recently announced enhanced risk management program for isotretinoin requiring patient, provider, and pharmacy registry and proof of a negative pregnancy test.³⁴

Since it will not be possible to avoid certain drug-associated risks, it will be important to develop effective methods to minimize them. Our findings indicate that BBWs are currently not reliably able to accomplish this goal. We need several things: to be clear about the magnitude of risk that justifies a BBW and the evidence that underlies a BBW monitoring recommendation, to communicate BBW content clearly to both clinicians and patients, and to create systems that promote adherence to recommended practice. Achieving these goals will require new information about risks, about the way drugs are used in everyday practice, about effective methods of influencing clinicians' prescribing, and about ensuring that patients understand how to use their drugs as safely as possible.

DATA ACCESS AND RESPONSIBILITY

Authors had access to study data, take responsibility for the integrity of the data and the accuracy of the data analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication.

KEY POINTS

- More than 40% of ambulatory care patients in 10 United States Health Maintenance Organizations received at least one drug of interest, that is, a drug considered to carry the potential for serious risks (and labeled with a so-called 'Black-Box Warning [BBW]') during a 30-month study period.
- Compliance with the BBW was highly variable: for some drugs, use was largely consistent with BBW recommendations, for others it was not.
- It is necessary to develop effective methods of ensuring the safe use of drugs that are considered to carry serious risks.

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Appendix

Appendix. Number (percent) of health plan members with dispensing of BBW medications in ambulatory care ($n = 929\,958$, unless otherwise indicated*)

Generic name (route if not oral only)	Relevant users* <i>n</i> (%)	Abbreviated BBW content
Analgesics		
Fentanyl patch (transdermal)	1427 (0.15)	<ul style="list-style-type: none"> • Hypoventilation—contra-indicated in acute or post-operative pain, including outpatient surgery, mild or intermittent pain responsive to as needed or non-opioid treatment, in doses >25 mcg/hour at initiation of opioid treatment • Should not administer in children < 12 years old or patients < 18 years and weighing < 50 kg, except in authorized research • Indicated for chronic pain unresponsive to acetaminophen-opioid, NSAIDs or as needed opioids, requiring continuous opioids • 50+ mcg doses should only be used for patients already on and tolerant to opioid treatment
Ketorolac tromethamine (oral and parenteral)	2030 (0.22)	<ul style="list-style-type: none"> • Indicated for severe pain up to 5 days of therapy • Gastrointestinal (GI), renal, bleeding, hypersensitivity effects • Contra-indicated: in patients with active peptic ulcer disease, recent GI bleeding or perforation, history of peptic ulcer disease or GI bleeding; advanced renal impairment; at risk for renal failure due to volume depletion; suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis; at high-risk of bleeding; as prophylactic analgesic before major surgery; intraoperatively when hemostasis is critical; intrathecal and epidural administration; in labor and delivery; in nursing mothers; concomitantly with NSAIDs • Adjust dose for age >65 or weight <50 kg to max 60 mg/day • Tablets only as continuation of injection, combined duration is not to exceed 5 days
Morphine (sustained release)	2018 (0.22)	<ul style="list-style-type: none"> • Daily dose of tablets lower than injection • Should not break, chew, or crush • Consider sustained-release formulation in event of adverse reaction or overdose • Caution with antagonist administration in physically dependent who overdosed: withdrawal
Morphine sulfate (parenteral)	340 (0.04)	<ul style="list-style-type: none"> • When epidural or intrathecal administration, patients must be observed in specialized setting for at least 24 hour after initial dose • Naloxone and resuscitative equipment must be available in case of life threatening side effects and when treatment is initiated • Intrathecal dose = 1/10th of epidural • Safety and handling instructions
Pentazocine/naloxone hydrochloride	257 (0.03)	<ul style="list-style-type: none"> • Intended for oral use only—severe reactions from injection misuse
Propoxyphene containing products	48 103 (5.17)	<ul style="list-style-type: none"> • Do not prescribe in suicidal and addiction-prone patients • Prescribe with caution in patients on tranquilizers, anti-depressants, alcohol • Tell patient to not exceed dose and limit
Anti-convulsants		
Carbamazepine	4747 (0.51)	<ul style="list-style-type: none"> • Aplastic anemia, agranulocytosis, leucopenia • Complete pre-treatment hematological testing should be obtained as baseline • Monitor patient closely if white blood cell count decreases • Consider discontinuation if evidence of significant bone marrow depression

Continues

FDA DRUG PRESCRIBING WARNINGS

Appendix. Continued

Generic name (route if not oral only)	Relevant users* <i>n</i> (%)	Abbreviated BBW content
Divalproex sodium, valproic acid, valproate sodium (oral and parenteral)	5518 (0.59)	<ul style="list-style-type: none"> ● Fatal hepatotoxicity (especially in < 2 year olds) ● Should monitor LFTs at baseline and frequent intervals, especially during first 6 months ● Teratogenicity-evaluate benefits-risk ● Pancreatitis-monitor symptoms
Lamotrigine	799 (0.09)	<ul style="list-style-type: none"> ● Serious rashes, more frequently in children: indication in children only for Lennox–Gastaut Syndrome ● Possibly increased frequency with valproic acid co-administration, and higher than recommended initial dose or dose escalation
Anti-infectives—aminoglycosides Gentamicin sulfate (parenteral)	249 (0.03)	<ul style="list-style-type: none"> ● Patients should be under close clinical observation ● Nephrotoxicity, ototoxicity: should closely monitor renal and 8th nerve function, urine specific gravity, protein, cells; should periodically determine serum creatinine, BUN, creatinine clearance when feasible; recommended to obtain audiograms ● Evidence of ototoxicity or nephrotoxicity require dosage adjustments or discontinuation should monitor aminoglycoside serum concentrations when feasible ● Should avoid concurrent and/or sequential systemic or topical use of cisplatin, cephaloridine, amikacin, streptomycin, viomycin, polymyxin A, B, E, paromomycin, tobramycin, vancomycin, kanamycin, and neomycin, ethacrynic acid, furosemide
Tobramycin (injection)	106 (0.01)	<ul style="list-style-type: none"> ● Ototoxicity; nephrotoxicity; neurotoxicity; ● Should monitor renal (urinalysis, BUN, creatinine) and 8th nerve function ● Should monitor peak and trough levels periodically ● When feasible, serial audiograms ● Should avoid concurrent or sequential use of neurotoxic, ototoxic drugs (amikacin, streptomycin, neomycin, kanamycin, gentamicin, paromomycin, cephaloridine, viomycin, polymyxin B, colistin, cisplatin, vancomycin) ● Risk increased with advanced age and dehydration ● Should not give with potent diuretics (ethacrynic acid, furosemide) ● Can cause fetal harm when administered to pregnant women
Anti-infectives—anti-fungals Itraconazole (oral and parenteral)	900 (0.10)	<ul style="list-style-type: none"> ● CYP3A4 inhibitor-increases levels of drugs metabolized by CYP3A4 ● QT interval prolongation: co-administration of astemizole, cisapride, pimozide, quinidine, dofetilide contra-indicated ● Should not use in patients with (history of) ventricular dysfunction (CHF)
Ketoconazole	2216 (0.24)	<ul style="list-style-type: none"> ● Hepatic toxicity ● Terfenadine, astemizole, cisapride coadministration contra-indicated
Anti-infectives—anti-tuberculins Isoniazid and combinations	995 (0.11)	<ul style="list-style-type: none"> ● Hepatitis, risk is age-related, increased with alcohol use and other factors ● Should monitor carefully and interview patients monthly for symptoms ● Patients >35 years: LFTs (AST and ALT) prior to treatment and periodically throughout; possibly more frequent monitoring in risk groups ● Strongly consider discontinuation if LFTs >5 times normal ● Instruct patients to report symptoms promptly ● Discontinue drug promptly if symptoms; reinstitute only slowly ● Defer preventive therapy in patients with acute hepatic disease
Anti-infectives—anti-virals Amprenavir	105 (0.01)	<ul style="list-style-type: none"> ● No data on long-term suppression of HIV RNA or disease progression; ● Oral solution: toxicity from propylene glycol-contra-indicated in age <4; pregnant women; patients with hepatic or renal failure; patients on disulfiram or metronidazole; use oral solution only when capsules or other protease inhibitor not an option

Continues

Appendix. Continued

Generic name (route if not oral only)	Relevant users* <i>n</i> (%)	Abbreviated BBW content
Lamivudine and combinations	999 (0.11)	<ul style="list-style-type: none"> ● Lactic acidosis, hepatomegaly ● Lamivudine contains higher dose than lamivudine-HBV: HIV + patients should receive only dosing form appropriate for HIV
Stavudine	565 (0.06)	<ul style="list-style-type: none"> ● Lactic acidosis, severe hepatomegaly with steatosis with anti-retroviral nucleosides, pancreatitis with didanosine
Abacavir sulfate	282 (0.03)	<ul style="list-style-type: none"> ● Hypersensitivity: should not restart after symptoms ● Lactic acidosis and hepatomegaly ● Indicated in combination therapy for HIV-1 ● No information on long-term suppression of HIV RNA or disease progression
Didanosine	265 (0.03)	<ul style="list-style-type: none"> ● Pancreatitis—should discontinue in patients with confirmed pancreatitis ● Lactic acidosis and hepatomegaly ● Didanosine and stavudine in pregnancy led to lactic acidosis and hepatomegaly: only use if benefits outweigh risks
Efavirenz	384 (0.41)	<ul style="list-style-type: none"> ● Indicated for HIV infection based on surrogate markers: no data on effect on long-term HIV RNA suppression ● Do not use in monotherapy or add as one sole agent to failing regimen, always use in combination with one other new anti-retroviral drug
Ganciclovir/ganciclovir sodium (oral and parenteral)	139 (0.01)	<ul style="list-style-type: none"> ● Granulocytopenia, anemia, thrombocytopenia; carcinogenic; teratogenic; aspermatogenesis; ● iv: only for CMV retinitis treatment in immunocompromised patients and prevention in transplant patients ● Oral: only for CMV retinitis prevention in advanced HIV, treatment in immunocompromised, and prevention of CMV in solid organ transplant patients ● Capsules associated with more rapid rate of CMV retinitis progression: evaluate risk-benefit of oral-iv
Nelfinavir mesylate	356 (0.04)	<ul style="list-style-type: none"> ● Indicated for HIV infection based on surrogate markers: no data on effect on survival or opportunistic infections
Nevirapine	265 (0.03)	<ul style="list-style-type: none"> ● Skin reactions: must discontinue immediately ● Hepatotoxicity ● Should always administer in combination, not in monotherapy
Ribavirin (oral) /interferon alpha 2b (parenteral)	665 (0.07)	<ul style="list-style-type: none"> ● Contra-indicated in pregnant women and male partners of pregnant women
	94 (0.05)**	<ul style="list-style-type: none"> ● Must use two reliable forms of contraception ● Ribavirin monotherapy should not be used for treatment of chronic hepatitis C ● Neuropsychiatric, autoimmune, ischemic, infectious disorders: monitor clinically and with laboratory tests
Ritonavir	249 (0.03)	<ul style="list-style-type: none"> ● Coadministration with certain non-sedating anti-histamines, sedative hypnotics, anti-arrhythmics, or ergot alkaloids may result in potentially serious and/or life threatening events—see Contraindications and Precautions ● CYP3A inhibition: amiodarone, bepridil, flecainide, propafenone, quinidine, astemizole, terfenadine; dihydroergotamine, ergotamine, midazolam, triazolam; cisapride, pimozone are contra-indicated; others to be used with caution
Zidovudine (oral and parenteral)	194 (0.02)	<ul style="list-style-type: none"> ● Hematologic toxicity and myopathy of zidovudine ● Lactic acidosis, hepatomegaly
Anti-infectives—miscellaneous Clindamycin hydrochloride and phosphate (oral and parenteral)	22 832 (2.46)	<ul style="list-style-type: none"> ● Pseudomembraneous colitis ● Reserve for serious infections—do not use in non-bacterial (most upper respiratory tract) infections
Chloroquine and combinations; hydroxychloroquine sulfate	5530 (0.59)	<ul style="list-style-type: none"> ● For malaria and extra-intestinal amebiasis; physician should familiarize him/herself with complete contents of leaflet

Continues

FDA DRUG PRESCRIBING WARNINGS

Appendix. Continued

Generic name (route if not oral only)	Relevant users* <i>n</i> (%)	Abbreviated BBW content
Erythromycin estolate	713 (0.08)	<ul style="list-style-type: none"> ● Hepatic dysfunction ● Severe abdominal pain simulating abdominal surgical emergency ● Contra-indicated in patients with hypersensitivity and pre-existing liver disease
Metronidazole (oral and parenteral)	36 550 (3.93)	<ul style="list-style-type: none"> ● Carcinogenic: reserve use for conditions described in Indications and Usage
Trovaflaxacin (oral and parenteral)	277 (0.03)	<ul style="list-style-type: none"> ● Serious liver injury, particularly if given >2 weeks ● Should be reserved for patients with serious limb or life-threatening infections who receive initial therapy in an inpatient setting ● Should not use when safer anti-microbial alternative available
Anti-neoplastics		
Carboplatin (parenteral)	177 (0.02)	<ul style="list-style-type: none"> ● Specialist prescriber recommendation ● Myelosuppression, vomiting, anaphylaxis: epinephrine, steroids, anti-histamines have been employed to alleviate symptoms
Chlorambucil	176 (0.02)	<ul style="list-style-type: none"> ● Bone marrow suppression, carcinogenic, mutagenic, teratogenic, produces infertility
Etoposide	128 (0.01)	<ul style="list-style-type: none"> ● Specialist prescriber recommendation ● Myelosuppression
Doxorubicin hydrochloride (parenteral)	337 (0.04)	<ul style="list-style-type: none"> ● Tissue necrosis with extravasation: must not give im or sc ● Myocardial toxicity: pediatric patients at increased risk for delayed cardiotoxicity ● Should reduce dose with impaired hepatic function ● Myelosuppression
Fluorouracil (parenteral)	326 (0.04)	<ul style="list-style-type: none"> ● Specialist prescriber recommendation ● Specialist prescriber recommendation ● Recommended that patients be hospitalized at least during initial course
Flutamide	215 (0.02)	<ul style="list-style-type: none"> ● Liver failure: should measure serum transaminases prior to starting therapy ● Not recommended in patients with ALT twice upper limit of normal ● Should measure serum transaminases monthly for the first four months and periodically thereafter ● Should get LFTs at first signs and symptoms suggestive of liver dysfunction ● If patient has jaundice or if ALT above 2 times upper limit of normal, should discontinue immediately and closely follow LFTs until resolution
Melphalan (oral and parenteral)	103 (0.01)	<ul style="list-style-type: none"> ● Specialist prescriber recommendation ● Bone marrow suppression—more with iv formulation ● Hypersensitivity reactions with iv ● Leukemogenic; mutagenic
Methotrexate (oral and parenteral)	3194 (0.34)	<ul style="list-style-type: none"> ● Specialist prescriber recommendation ● Use only in severe disease ● Caution with high dose therapy ● Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate ● Reduced dose in certain conditions ● Fatal bone marrow suppression and GI toxicity when coadministration with NSAIDs ● Periodic liver biopsies for psoriasis patients on long-term therapy are usually recommended ● Lung disease, GI disease, lymphoma, tumor lysis syndrome, skin reactions, opportunistic infections, necrosis with radiotherapy
Paclitaxel (parenteral)	255 (0.03)	<ul style="list-style-type: none"> ● Specialist prescriber recommendation ● Anaphylaxis: should pre-treat all patients ● Frequent peripheral blood cell counts recommended ● Should not give in solid tumors and Kaposi's when neutrophil count low
Vincristine sulfate (parenteral)	138 (0.01)	<ul style="list-style-type: none"> ● Specialist prescriber recommendation ● Extravasation: treat with hyaluronidase and heat ● For iv use only-fatal if given intrathecally

Continues

Appendix. Continued

Generic name (route if not oral only)	Relevant users* <i>n</i> (%)	Abbreviated BBW content
Cardiovascular agents—anti-arrhythmics		
Amiodarone hydrochloride	1884 (0.20)	<ul style="list-style-type: none"> Intended for use only in patients with the indicated life-threatening arrhythmias, alternative agents first Pulmonary, liver toxicity Proarrhythmic: hospitalize patients for therapy initiation and possibly dosage adjustments
Disopyramide phosphate	233 (0.03)	<ul style="list-style-type: none"> Proarrhythmic: should reserve for life-threatening ventricular arrhythmias
Flecainide acetate	446 (0.05)	<ul style="list-style-type: none"> Increased mortality over placebo, especially in non-life threatening arrhythmias: avoid in non-life-threatening ventricular arrhythmias Ventricular proarrhythmic effect in atrial fibrillation/flutter: not recommended for chronic atrial fibrillation Concomitant digoxin or betablockers may decrease risk of increased ventricular rate
Mexiletine hydrochloride	100 (0.01)	<ul style="list-style-type: none"> Proarrhythmic-increased mortality when recent MI—should reserve for patients with life-threatening arrhythmia
Quinidine gluconate, polygalacturonate, sulfate	302 (0.03)	<ul style="list-style-type: none"> Increased mortality over placebo and other anti-arrhythmics in non-life threatening arrhythmias
Procainamide hydrochloride	270 (0.03)	<ul style="list-style-type: none"> Positive ANA titer with prolonged administration: assess benefit-risk equation with positive ANA titer Increased mortality when used after recent MI: use only in life-threatening arrhythmias Blood dyscrasias: should perform weekly CBC with WBC and differential and platelet monitoring during first 3 months and periodically thereafter and promptly when signs of infection Discontinue in hematologic condition Caution when pre-existing marrow failure
Propafenone hydrochloride	522 (0.06)	<ul style="list-style-type: none"> Increased mortality over placebo, especially in non-life threatening arrhythmias: avoid in non-life-threatening ventricular arrhythmias
Sotalol hydrochloride	798 (0.09)	<ul style="list-style-type: none"> Proarrhythmic: initial treatment in facility that can provide CPR, ECG, creatinine clearance Do not exchange Betapace and Betapace AF
Cardiovascular agents—other		
Amiloride hydrochloride with or without hydrochlorothiazide	713 (0.08)	<ul style="list-style-type: none"> Hyperkalemia: essential to monitor serum K⁺ levels carefully, particularly when first introduced, at time of dose adjustments, during illness affecting renal function Greater incidence of hyperkalemia in renal impairment, diabetes mellitus, old age, severe illness Amiloride only: concomitant thiazide use reduces risk Teratogenicity in 2nd and 3rd trimester: should immediately discontinue in pregnancy
Angiotensin converting enzyme inhibitors (oral and parenteral)	3777 (2.05)**	<ul style="list-style-type: none"> Do not discontinue abruptly, taper
Beta blockers (oral and parenteral)	90 666 (7.75)	<ul style="list-style-type: none"> Spiroonolactone tumorigenic: use only in conditions listed under Indications and Usage
Spiroonolactone	5310 (0.57)	<ul style="list-style-type: none"> Spiroonolactone tumorigenic: use only in conditions listed under Indications and Usage Fixed dose combinations not indicated for initial therapy of edema and hypertension
Spiroonolactone/ hydrochlorothiazide	1101 (0.12)	<ul style="list-style-type: none"> Hyperkalemia: must frequently monitor serum potassium, especially when start, change dose, with illnesses affecting renal function
Triamterene with or without hydrochlorothiazide	39 691 (4.27)	
Central nervous system agents—neuroleptics		
Clozapine	110 (0.01)	<ul style="list-style-type: none"> Agranulocytosis: must have WBC before therapy and weekly during first 6 months and for 4 weeks if discontinued Specific monitoring requirements depending on results and duration of therapy

Continues

FDA DRUG PRESCRIBING WARNINGS

Appendix. Continued

Generic name (route if not oral only)	Relevant users* <i>n</i> (%)	Abbreviated BBW content
		<ul style="list-style-type: none"> ● Should not initiate treatment if WBC <3500/mm³, or history of myeloproliferative disorder, or clozapine-induced agranulocytosis ● Available through specialized distribution system only ● Seizures: caution in patients with predisposing factors; advise patients not to engage in risky behavior ● Orthostatic hypotension: caution when use with benzodiazepines or other psychotropic drugs
Haloperidol (oral and parenteral)	1279 (0.14)	<ul style="list-style-type: none"> ● Dosing guidelines for adults and children ● Safety of prolonged use of 100 mg/d in adults not demonstrated ● Little evidence for behavior improvement with >6 mg/d in children
Lithium carbonate or citrate	2757 (0.30)	<ul style="list-style-type: none"> ● Lithium toxicity: facilities for prompt and accurate level determination should be available before therapy initiation
Central nervous system agents—stimulants		
Dextroamphetamine sulfate or other salts and amphetamine salts	6244 (0.67)	<ul style="list-style-type: none"> ● High potential for abuse: must avoid administration for prolonged periods; should be prescribed or dispensed sparingly
Methylphenidate hydrochloride	10 087 (1.08)	<ul style="list-style-type: none"> ● Drug dependence: give with caution to patients with history of drug dependence or alcoholism; supervise withdrawal
Pemoline	267 (0.03)	<ul style="list-style-type: none"> ● Discontinue in patients without clinical benefit after 3 weeks ● Monitoring requirement ● Should only start in patients without liver disease and with normal baseline LFTs ● Hepatic failure: should monitor LFTs (ALT) at baseline and every 2 weeks ● Discontinue if ALT ≥ 2 times normal or if symptoms ● Written consent prior to therapy
Dermatologic agents		
Acitretin	279 (0.03)	<ul style="list-style-type: none"> ● Contra-indicated in pregnancy and women of childbearing potential unless seven conditions met
	25 (0.01)**	<ul style="list-style-type: none"> ● Negative pregnancy test before start and regular pregnancy testing should happen ● Contraception with two methods, unless abstinence or hysterectomy, for at least 3 years following discontinuation of therapy ● Use of alcohol contra-indicated concurrently and 2 months after discontinuation ● Special competence prescriber recommendation ● Hepatotoxicity, pancreatitis, pseudotumor cerebri (some with isotretinoin and tetracyclines)
Isotretinoin	1069 (0.58)**	<ul style="list-style-type: none"> ● Contra-indicated in women of childbearing potential unless eight conditions met ● Negative pregnancy test before start of therapy and repeated pregnancy testing recommended ● Effective contraception with two methods unless abstinence or hysterectomy ● Specialist prescriber education ● Specialized prescriber recommendation and constant supervision of therapy by MD ● Restricted to severe psoriasis, not responsive to other treatments, and diagnosis supported by biopsy ● Ocular damage, skin aging, skin cancer ● For photopheresis, see special information do not interchange 8-MOP (hard gelatin capsules) with Oxisoralen Ultra (soft gelatin capsules) without retitration
Methoxsalen	161 (0.02)	<ul style="list-style-type: none"> ● Restricted to severe psoriasis, not responsive to other treatments, and diagnosis supported by biopsy ● Ocular damage, skin aging, skin cancer ● For photopheresis, see special information do not interchange 8-MOP (hard gelatin capsules) with Oxisoralen Ultra (soft gelatin capsules) without retitration
Gastrointestinal agents		
Cisapride	2760 (0.30)	<ul style="list-style-type: none"> ● Arrhythmias: contra-indicated in patients on clarithromycin, erythromycin, troleandomycin, nefazodone, fluconazole, itraconazole, ketoconazole, indinavir, ritonavir, and many others

Continues

Appendix. Continued

Generic name (route if not oral only)	Relevant users* <i>n</i> (%)	Abbreviated BBW content
Misoprostol with or without diclofenac	283 (0.15)**	<ul style="list-style-type: none"> ● Contra-indicated in patients with conditions with prolonged QT interval (listed in BBW) ● Should not exceed recommended doses ● Contra-indicated in pregnancy
Trimethobenzamide hydrochloride (oral, parenteral, per rectum)	340 (0.19)^	<ul style="list-style-type: none"> ● Use in women of childbearing potential if four conditions met, including ● Negative serum pregnancy test within 2 weeks prior to beginning treatment ● Uterine rupture when administered vaginally and perforation with vaginal/oral administration ● Caution when administering to children: not recommended to treat uncomplicated vomiting in children due to possible contribution to Reye's Syndrome in viral illness ● Extrapramidal symptoms to be confused with CNS disorder ● Hepatotoxic drugs may alter course of Reye's Syndrome
Hematological agents		
Cilostazol	184 (0.02)	<ul style="list-style-type: none"> ● Phosphodiesterase III inhibitor: decreased survival in pts with CHF, contra-indicated in patients with CHF of any severity
Dalteparin sodium (parenteral)	127 (0.01)	<ul style="list-style-type: none"> ● Spinal/epidural hematomas in patients anti-coagulated with low molecular weight heparin and heparinoids who receive epidural/spinal anesthesia; risk increased with indwelling catheters or concomitant use of NSAIDs, platelet inhibitors, other anti-coagulants: monitor neurologic status ● Consider benefit-risk before neuraxial intervention in anti-coagulated patients
Enoxaparin sodium (parenteral)	2969 (0.32)	<ul style="list-style-type: none"> ● Spinal/epidural hematomas in patients anti-coagulated with low molecular weight heparin and heparinoids who receive epidural/spinal anesthesia; risk increased with indwelling catheters or concomitant use of NSAIDs, platelet inhibitors, other anti-coagulants: should monitor pts frequently for neurologic impairment ● Consider risk-benefit before neuraxial intervention in anti-coagulated patients
Ticlopidine hydrochloride	849 (0.09)	<ul style="list-style-type: none"> ● Hematologic toxicity: monitor evidence for thrombotic thrombocytopenic purpura and neutropenia hematologically and clinically for first 3 months ● Aplastic anemia
Hormones—inhaled corticosteroids		
Triamcinolone acetonide (oral inhalation)	26 894 (2.89)	<ul style="list-style-type: none"> ● Potential adrenal insufficiency when transfer patients from systemic steroid, especially during stress: supplement with oral steroid
Beclomethasone dipropionate (oral inhalation)	10 235 (1.10)	<ul style="list-style-type: none"> ● Potential adrenal insufficiency when transfer patients from systemic steroid, especially during stress: supplement with oral steroid ● To assess risk, should routinely test adrenal corticol function, including early morning resting cortisol, periodically; may accept as normal an early morning cortisol level only if it falls at or near normal mean level
Budesonide (oral Inhalation)	3612 (0.39)	<ul style="list-style-type: none"> ● Potential adrenal insufficiency when transfer patients from systemic steroid, especially during stress: instruct patirnts to resume oral steroids (in large doses) immediately during stress (trauma, surgery, infection, severe asthma attack)
Flunisolide (oral Inhalation)	2469 (0.27)	<ul style="list-style-type: none"> ● Potential adrenal insufficiency when transfer patients from systemic steroid, especially during stress: supplement with oral steroid ● To assess risk, should test adrenal corticol function, including resting early morning cortisol, periodically
Fluticasone propionate (oral inhalation)	18 662 (2.00)	<ul style="list-style-type: none"> ● Potential adrenal insufficiency when transfer patients from systemic steroid, especially susceptible are patients previously maintained on 20 mg or more per day of prednisone; especially during stress: supplement with oral steroid
Hormones—sex hormones		
Danazol	133 (0.01)	<ul style="list-style-type: none"> ● Contra-indicated in pregnancy
	61 (0.03)**	<ul style="list-style-type: none"> ● Sensitive pregnancy test (beta subunit test, if available) immediately before treatment is recommended

Continues

FDA DRUG PRESCRIBING WARNINGS

Appendix. Continued

Generic name (route if not oral only)	Relevant users* <i>n</i> (%)	Abbreviated BBW content
Estrogen containing products	95 776 (0.24)*** 6296 (3.41)**	<ul style="list-style-type: none"> • Should use non-hormonal contraception • Discontinue if patient becomes pregnant and apprise of risks • Thromboembolism, peliosis hepatitis, hepatic adenoma, intracranial hypertension • Endometrial cancer: "adequate diagnostic measures including endometrial sampling when indicated" in case of bleeding • Teratogenicity: estrogens should not be used during pregnancy • Ineffective to prevent abortion and not indicated to prevent breast engorgement post-partum: do not use during pregnancy
Medroxyprogesterone acetate	7146 (3.88)**	<ul style="list-style-type: none"> • Teratogenicity: not recommended during first 4 months of pregnancy, prudent to avoid, apprise patient of risk
Norethindrone acetate	6258 (3.40)**	<ul style="list-style-type: none"> • Teratogenicity: not recommended in first 4 months of pregnancy due to lack of effect on prevention of abortion, apprise pt of risks if pregnant
Oral contraceptives	64 231 (16.05)***	<ul style="list-style-type: none"> • Cigarette smoking increases cardiovascular disease risk-do not smoke
Thyroid hormones		
Levothyroxine sodium (oral and parenteral)	49 055 (5.27)	<ul style="list-style-type: none"> • Replacement doses ineffective for weight reduction in euthyroid patients • Larger doses toxic especially with sympathomimetic amines
Immunosuppressants		<ul style="list-style-type: none"> • Synthroid: thyroid hormones should not be used for treatment of obesity
Azathioprine (oral and parenteral)	1239 (0.14)	<ul style="list-style-type: none"> • Physicians should be familiar with risks of neoplasia, mutagenicity, hematologic toxicity
Cyclosporine (oral and parenteral)	704 (0.08)	<ul style="list-style-type: none"> • Specialist prescriber recommendation • Infection, neoplasm • Should administer with adrenal corticosteroids (but not with other immunosuppressants) • Non-bioequivalence of Sandimmune and Neoral • Should monitor levels • Skin cancer in patients with psoriasis, hypertension • Nephrotoxicity: must monitor renal function during therapy
Mycophenolate mofetil	369 (0.04)	<ul style="list-style-type: none"> • Immunosuppression
Tacrolimus	256 (0.03)	<ul style="list-style-type: none"> • Specialist prescriber and facility recommendation • Specialist prescriber and facility recommendation immunosuppression: infection and neoplasm
Miscellaneous agents		
Astemizole	181 (0.02)	<ul style="list-style-type: none"> • QT prolongation/arrhythmias mostly at higher than recommended doses; emphasize adherence to recommended dose of 10 mg/d; advise patients not to use prn; concomitant use of ketoconazole, itraconazole, erythromycin, clarithromycin, troleandomycin, mifebradil, or quinine contra-indicated • Use in patients with hepatic dysfunction contra-indicated
Disulfiram	752 (0.08)	<ul style="list-style-type: none"> • Discontinue immediately in case of syncope and evaluate patient • Never admit to intoxicated patient or without patient's full knowledge • Physician to instruct relatives
Isometheptene/ dichloralphenazone/ acetaminophen	11 110 (1.19)	<ul style="list-style-type: none"> • Classified as "possibly effective" in treatment of migraine headaches
Leflunomide	78 (0.04)**	<ul style="list-style-type: none"> • Pregnancy must be excluded before start of treatment • Contra-indicated in pregnancy and women of childbearing potential without reliable contraception
Meclizine hydrochloride	14 436 (1.55)	<ul style="list-style-type: none"> • Indications classified as 'effective': nausea, vomiting, dizziness of motion sickness; 'possibly effective': vertigo associate with vestibular system diseases; 'less than effective': further investigation needed
Megestrol acetate	394 (0.21)**	<ul style="list-style-type: none"> • Contra-indicated in pregnancy: teratogenicity and not effective to prevent abortion

Continues

Appendix. Continued

Generic name (route if not oral only)	Relevant users* <i>n</i> (%)	Abbreviated BBW content
Metformin hydrochloride with or without glyburide	18 066 (1.94)	<ul style="list-style-type: none"> ● Lactic acidosis: monitor renal function, symptoms, other labs if symptoms ● Use lowest dose, especially among elderly ● Should not initiate among those >80 years unless demonstrated adequate renal function ● Discontinue promptly in any condition associated with hypoxemia, sepsis, dehydration, radiopaque study, surgery ● Should avoid when clinical or laboratory evidence of hepatic disease ● Do not use with alcohol ● Hemodialysis in case of lactic acidosis
Naltrexone hydrochloride	319 (0.03)	<ul style="list-style-type: none"> ● Hepatocellular injury in high doses (≤ 5 times recommended) ● Contra-indicated in acute hepatitis or liver failure ● Carefully consider use in patients with active liver disease ● Discontinue when symptoms of acute hepatitis
Phenobarbital/hyoscyamine/ atropine/scopolamine	4272 (0.46)	<ul style="list-style-type: none"> ● Classified as 'possibly effective' in irritable bowel syndrome
Troglitazone	909 (0.10)	<ul style="list-style-type: none"> ● Not shown whether anti-cholinergic/anti-spasmodic drugs aid in healing of duodenal ulcer ● Hepatotoxicity: should check serum alanine transferase at start and monthly for first year; quarterly afterwards ● Should not start therapy if history of liver disease, clinical evidence of active liver disease, alcohol use, ALT > 1.5 times upper limit ● LFTs when symptomatic ● If ALT > 1.5-2 times upper limit of normal, should repeat LFTs immediately and then weekly until return to normal ● Discontinue if LFTs > 3 times upper limit

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CBC, complete blood count; CHF, congestive heart failure; CPR, cardio-pulmonary resuscitation; CYP, cytochrome-P; ECG, electrocardiogram; HIV, human immunodeficiency virus; im, intramuscular; iv, intravenous; LFTs, liver enzyme tests; NSAIDs, non-steroidal anti-inflammatory drugs; RNA, ribonucleic acid; sc, subcutaneous; SCr, serum creatinine.

*Note: **, among women age 15–44 ($n = 184\,237$); ***, among all women age 15–85+ ($n = 400\,189$); ^, among children age 0–14 years ($n = 181\,763$); BBW medications dispensed to fewer than 100 enrollees during the 30-month study period are not listed.