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Thru:	Dr. Mark Avigan, Director, Division of Drug Risk Evaluation (DDRE)
From:	Jenna Lyndly, R.N., Safety Evaluator Division of Drug Risk Evaluation (DDRE)
Subject:	Bleeding; NME Review Follow-up
Drug Name(s):	Duloxetine (Cymbalta)
Application Type/Number:	21-427, 21-733
Applicant/sponsor:	Lilly
OSE RCM #:	2007-1096

CONTENTS

EXECUTIVE SUMMARY

The objective of this review is to analyze post-marketing data concerning duloxetine and bleeding events, and is being performed as follow-up suggested by the Duloxetine NME Review team that met on March 13, 2007[1].

Duloxetine is a serotonin-norepinephrine reuptake inhibitor approved to treat major depressive disorders, diabetic peripheral neuropathic pain and generalized anxiety disorders. OSE retrieved and analyzed 170 unique post-marketing cases with reports of bleeding during duloxetine therapy. While the GI system bleeding was the most frequently reported location of bleeding, bleeding was also reported in locations throughout the body and ranged in severity from bruising to a fatal GI hemorrhage. Six reports of death were included in the case series. Four[2] of the deaths were unrelated to duloxetine; however, a role for duloxetine cannot be excluded in two of the deaths.[3] In addition, 33 of 51 hospitalizations were reportedly due to the bleeding event, with one death and 12 hospitalizations concomitantly using anti-coagulants, ASA and/or NSAIDS. The case series included reports of platelet dysfunction, thrombocytopenia, and increased PT/INR results associated with duloxetine therapy. Sixty positive dechallenges were described, but most compelling were the four positive rechallenges.

The duloxetine case series and the current literature are supportive of an increased risk of bleeding with drugs that inhibit serotonin, particularly in those patients using ASA, anticoagulants and/or NSAIDs. The literature has urged health care providers to use caution when prescribing a drug that inhibits serotonin to patients of advanced age, patients with a medical condition that might affect hemostasis, and patients concomitantly using drugs that affect hemostasis. An increased risk may also be present for patients with an underlying hemostatic defect, either a coagulation defect or a platelet dysfunction. As of December 2006, over 3 million patients were prescribed duloxetine. Adding language similar to the SSRIs (see 1.3 Product Labeling) to the Precautions, Drug Interactions and Patient Information sections in both SNRI labels, duloxetine and venlafaxine, will alert the practicing community and patients to potential bleeding complications with SNRI therapy.

Therefore, OSE recommends:

1 Add the precaution for "abnormal bleeding" found in the SSRI labels to the SNRI (duloxetine and venlafaxine) labels. Also, add language describing duloxetine associated thrombocytopenia or platelet dysfunction.

2 Add the drug interaction language for warfarin and drugs that interfere with hemostasis (ASA, NSAIDS and anticoagulants) found in the SSRI labels to the SNRI labels.

3 Add patient information language regarding concomitant use of ASA, NSAIDs or anticoagulants found in the SSRI labels to the SNRI labels.

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[1] New Molecular Entity (NME) Postmarketing Evaluation, NDA 21-427, March 13, 2007

[2] ISR # 4540780 – decompensated heart insufficiency with lung edema, ISR # 5260807 – central pontine myelinosis due to rapid sodium level correction, ISR # 5159352 – accidental death due to multiple drug intoxication, ISR # 4860668 – congestive heart failure

[3] ISR #4674574 – cerebral hemorrhage, ISR # 4800401 – cardiac arrest secondary to hypovolemic shock secondary to GI hemorrhage

BACKGROUND

1.1 INTRODUCTION

The FDA is piloting a regularly intervaled review process for drugs classified as new molecular entities[4] (NME). Duloxetine was selected as the first drug product to undergo the NME review process. On March 13, 2007, OND and OSE brought together a multidisciplinary team to review the safety profile of duloxetine since its approval in August of 2004. The review process identified potential bleeding disorders as a DPP concern and also a topic of ongoing surveillance by the sponsor.

DDRE reviewed SSRI[5] post-marketing adverse event reports for bleeding in 2000 concluding SSRI use "may contribute to an increased risk of bleeding in various body systems" and "may be associated with serious outcomes including death or disability."[6] The review recommended that all SSRIs have labeling regarding a potential risk for increased bleeding. In 2003, OND determined there was sufficient evidence of increased bleeding risk associated with use of SSRIs and requested class labeling.[7]

Duloxetine is an inhibitor of serotonin reuptake, providing biological plausibility for a concern of potential increased bleeding risk with use of duloxetine. As a result of this concern, the multidisciplinary review team recommended an analysis of duloxetine post-marketing reports of bleeding, which this analysis provides.

1.2 REGULATORY HISTORY

Duloxetine is classified as a serotonin-norepinephrine reuptake inhibitor (SNRI), and was originally approved in the US on August 3, 2004 as Cymbalta™ to treat major depressive disorders. Cymbalta™ was approved to treat diabetic peripheral neuropathic pain on September 3, 2004 and generalized anxiety disorder on February 23, 2007. Duloxetine is available in 20mg, 30mg and 60mg doses

1.3 PRODUCT LABELING[8]

The current duloxetine labeling addresses some specific events related to bleeding in the Adverse Reactions section.

> In the "Other Adverse Events Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine" section:
>
> Gastrointestinal Disorders – Rare: hematochezia, melena.

[4] A new molecular entity (NME) means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.
[5] SSRI – selective serotonin reuptake inhibitor
[6] Phelan, Kathleen. OPDRA Postmarketing Safety Review, Hemorrhages with Serious Outcomes, May 8, 2000
[7] Hughes, Alice and Judith Racoosin, Review and Evaluation of Clinical Data, November 19, 2003
[8] Drugs@FDA, Cymbalta, NDA 021427, label approved on 02/23/2007

Skin and Subcutaneous Tissue Disorders – Infrequent: increased tendency to bruise; Rare: ecchymosis.
Blood and Lymphatic System Disorders — Infrequent: anemia; Rare*:* leukopenia and thrombocytopenia.

In the "Drug-Drug Interactions" section:

Drugs Highly Bound to Plasma Protein — Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events.

The SSRIs include class labeling in the Precautions section addressing the potential for increased bleeding. (See below):

General[9]

Abnormal Bleeding — Published case reports have documented the occurrence of bleeding Episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (*see* DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Prozac with NSAIDs, aspirin, or other drugs that affect coagulation.

In addition, the SSRI labels include similar to the Prozac[10] labeling shown below:

In the Information for Patients section:

Patients should be cautioned about the concomitant use of fluoxetine and NSAIDs, aspirin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents have been associated with an increased risk of bleeding.

In the Drug Interactions section:

Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.) — Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin

[9] NDA 18936, Prozac label approved 08/02/07, Drugs@FDA
[10] NDA 18936, Prozac label approved 08/02/07, Drugs@FDA

potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with fluoxetine.

Warfarin — Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

OSE utilized adverse event reports retrieved from the AERS database, drug use information from Verispan[11] and an analysis of the AERS database by WebVDME[12] (data mining) as data sources for this review.

2.2 DATA MINING

OSE utilized data mining, which scores drug-event combinations based on disproportional analysis comparing a drug-event against the AERS database. Because AERS is a spontaneous adverse events reporting system and confounding is not evaluated prior to inclusion in the database, the actual risk for a drug-event cannot be determined from data mining. Data mining provides a signal that must be further investigated. The absence of an elevated EB05 score for a drug-event cannot be interpreted as a definite lack of toxicity for that drug-event or the absence of a signal. Eli Lilly, the sponsor of duloxetine, was granted a waiver for non-serious labeled adverse events on February 7, 2005[13]; therefore, non-serious, labeled adverse events may be under-represented in the data mining analysis. Additional information concerning data mining as a surveillance tool is included in Appendix 1.

OSE queried WebVDME on January 3, 2007 for duloxetine and adverse events with an EB05 score > 2.0. [14]

2.3 LITERATURE SEARCH

On July 9, 2007, OSE queried PubMed Central with the terms “duloxetine and bleeding”, “duloxetine and hemorrhage”, “duloxetine and coagulation”, “duloxetine and purpura”, duloxetine and thrombocytopenia”, “SNRI and bleeding”, “serotonin and norepinephrine reuptake inhibitor and bleeding”, “serotonin and bleeding”, “venlafaxine and bleeding” and “serotonin and coagulation”. Titles and selected abstracts were reviewed in all search results to identify relevant case reports of bleeding disorders associated with duloxetine and/or SNRIs.

[11] Verispan, LLC: Total Patient Tracker, Aug04-Dec06, Extracted Feb07. Files: TPT Cymbalta AUG04-DEC06 Aggregate Product Brand Report.xls, TPT Cymbalta aug04-dec06 Aggregate Gender Report.xls
[12] Developed by Lincoln Technologies, Inc. in cooperation with the FDA
[13] The non-serious labeled reports of bleeding are most likely under-represented in the AERS database, and consequently under-represented in WebVDME.
[14] OSE Post-Marketing Data Mining Analysis, February 20, 2007, Marilyn Pitts

2.4 AERS SELECTION OF CASES

OSE queried the AERS database as follows:

Table 1: AERS Search Strategy

Date of Search:	April 26, 2007
Drug Name Search Terms:	Duloxetine active ingredient and related verbatim terms
MedDRA Adverse Event Search Terms:	Standardized MedDRA Query (SMQ) "Haemorrhage terms (excl laboratory terms)
Search Level:	Preferred Terms (PT)

A description of the AERS database and a listing of the preferred terms included in the Haemorrhage SMQ are provided in Appendix 2.

2.5 DRUG USE DATA

We utilized drug use data obtained by the Division of Surveillance, Research and Communication Support (DSRCS) provided during the March 13, 2007 NME review for duloxetine. DSRCS obtained prescription volume data and patient gender data from Verispan, LLC. A description of the Verispan database is provided in Appendix 3.

3 RESULTS

3.1 DATA MINING

The January 3, 2007 query did not identify any preferred terms related to bleeding with an EB05 score greater than 2.0.

3.2 LITERATURE SEARCH

The literature includes a large number of articles related to bleeding and SSRIs and/or serotonin. To provide an overview, four recent reviews were identified with the search terms "serotonin and bleeding." One relevant article from each of the search terms "duloxetine and coagulation" and "duloxetine and bleeding" was identified. An abstract from an article not available in English and two articles were located with the search terms "venlafaxine and bleeding."

Serotonin Inhibition and Bleeding

Four current reviews, two published in 2007, and two in 2006 were identified to provide an overview of the current knowledge of serotonin inhibition and bleeding. Turner et al. (2007) reviewed literature from 1966 to May 2006, including case reports and nine observational studies. They noted that multiple theories have been proposed for the potential mechanism of action for increased bleeding with SSRI use including blockade of calcium mobilization,

inhibition of nitric oxide "synthase", decreased platelet secretion in response to collagen, decreased platelet binding affinity and decreased serotonin in platelets.[15] Six of the nine studies reviewed showed an increased risk of bleeding with SSRI use. In addition, Turner et al. identified an increased risk of bleeding with SSRIs and ASA/or NSAIDS that exceeded the additive effect of the medications.

Halperin and Reber (2007) reviewed published case studies, epidemiological studies, and prospective studies with a focus on studies with hemostasis laboratory values for patients taking anti-depressants. Retrospective studies reviewed by Halperin and Reber supported a causal association between abnormal bleeding and antidepressants, especially the SSRIs. While the prospective studies they reviewed had conflicting results, they concluded the studies "clearly indicate that anti-depressants modify primary hemostasis."[16] Decreased platelet aggregability and activity, and prolonged bleeding time were the two most frequently altered primary hemostasis laboratory values in the data reviewed. However, about 50% of the case reports reviewed by Halperin and Reber had normal hemostasis markers, which they indicated was an expected result, as the majority of hemostasis laboratory values have a low sensitivity. They noted that platelet aggregation tests show the highest sensitivity but are not routinely performed.[17]

SSRI and upper gastrointestinal (UGI) bleeding were the topics of a search from 1980 to May of 2005 used by Yuan et al. (2006) to identify observational and interventional studies for their review. They noted that multiple mechanisms of actions have been proposed, but one mechanism has not been clearly identified. The currently purported mechanism was described as a "decrease in platelet serotonin leading to a defect in platelet aggregation, resulting in an impairment of hemostatic function leading to a prolonged bleeding time and abnormal platelet count."[18] While Yuan et al. noted that the evidence provides "weak support" for an increased risk of UGI bleeding with SSRI use in most patients, the literature does support an increased risk of UGI bleeding in patients using NSAIDS, ASA and/or anticoagulants, patients with a history of GI bleeding or elderly patients. They advised caution when using SSRIs in patients concomitantly using NSAIDs/aspirin who have a risk of increased bleeding as the literature includes a case of a fatal GI bleed in a patient with cirrhosis using paroxetine and aspirin. In addition, they expressed a concern due to increased use of SSRIs in the elderly who frequently have pre-existing medical conditions that may increase their risk for UGI bleeding and are also frequently taking aspirin/NSAIDs.

Serebruany (2006) noted that while there is a preponderance of literature (120 Medline papers and more than 50,000 web pages) related to SSRIs and bleeding, there is no reliable incidence for bleeding events; however, he indicated that the "anecdotal evidence is alarming". He notes there is a "strong consensus that blockade of serotonin reuptake affects primary hemostasis."[19] , and concludes serotonin platelet and plasma levels most likely impact an array of factors during primary hemostasis. Serebruany highlighted the fact that all SSRIs have been associated with bleeding as well as antidepressants with partial serotonin inhibition such as venlafaxine.

[15] Turner et al., page 206-7.
[16] Halperin and Reber, page 56
[17] Halperin and Reber, page 56
[18] Yuan et al., page 719
[19] Serebruany, page 114

Duloxetine and Bleeding

The literature search for 'duloxetine and bleeding', and 'duloxetine and coagulation' resulted in two case reports. Glueck et al. described a patient, previously stable on warfarin, with an increased INR after initiation of duloxetine therapy, with the elevation continuing after warfarin was discontinued, and remaining elevated until duloxetine was discontinued. The patient's INR then returned to the normal range. Warfarin was restarted and the patient's INR remained stable and within the expected range. Balhara et al. described a case of bleeding with duloxetine and noted that the patient had not had a similar reaction to fluoxetine, escitalopram or amitryptiline. When given duloxetine, his gums became raw and oozed blood from the surface. No alternative cause of bleeding could be identified and coagulation tests were within normal limits. The bleeding resolved within one week of discontinuing duloxetine. Balhara et al. propose that the mechanism for duloxetine bleeding events may differ from the SSRIs, as the patient did not experience bleeding events with SSRIs.

Venlafaxine and Bleeding

Three case reports were identified in the literature for venlafaxine and bleeding. Horne et al. described a case report of a positive dechallenge and a positive rechallenge with venlafaxine resulting in generalized bruising. The patient's coagulation tests were normal with the exception of a prolonged bleeding time 8.5 at the initial presentation of bruising. Platelet aggregation studies were performed prior to the rechallenge and were normal but both platelet aggregation and ATP release were markedly depressed after the second presentation of generalized bruising. A second case report, detailed by Linnebur et al., described post-menopausal bleeding with venlafaxine including a positive dechallenge and positive rechallenge response. An abstract by Chakarian et al. reported onset of abdominal pain while on venlafaxine therapy with subsequent identification of a splenic hematoma in a patient with no recent injuries.

Disorders of Hemostasis

Harrison's[20] notes that patterns of bleeding are associated with different types of coagulation disorders. Bleeding into the joints, muscles, and body cavities hours or days after an injury is indicative of the congenital coagulation defects that result in a prolonged PT and/or PTT. Patients with hemostatic defects related to liver disease usually bleed from a present lesion such as a gastric ulcer or esophageal varices due to alterations in any or all of the following: PT, PTT, platelets and/or fibrinogen. [21]

A decrease in platelets (thrombocytopenia) may be drug induced by stimulating an autoimmune response and will usually resolve within seven to ten days after the drug is discontinued. Harrison's noted that once this response has been elicited, "only minute amounts of the drug are needed to set up subsequent reactions." [22] Platelet disorders include platelet dysfunction or a decrease in platelets and usually present with bleeding in the skin, mucous membranes and/or GI or genitourinary tract with petechiae as the hallmark presentation of thrombocytopenia. ACP Medicine[23] notes that purpura, gingival bleeding, menorrhagia, ecchymoses and recurrent

[20] Harrison's Principles of Internal Medicine – 16th Ed. (2005), Part 5, Section 3 – Disorders of Hemostasis
[21] Harrison's Principles of Internal Medicine – 16th Ed. (2005), Part 5, Section 3 – Disorders of Hemostasis
[22] Harrison Principles of Internal Medicine – Part 5, Section 3, 101. Disorders of the Platelets and Vessels, Drug-Induced Thrombocytopenia
[23] ACP Medicine (2007), XIII Platelet and Vascular Disorders

epistaxis, may also be seen with platelet disorders; however, Herkner et al.[24] reported that epistaxis may be associated with hypertension, particularly sustained arterial hypertension.

Several commonly used drugs interfere with hemostasis. Patients on warfarin may experience bleeding ranging from ecchymoses to more serious bleeding, mostly GI and genitourinary; however, intracranial and internal bleeding may also be seen as warfarin affects coagulation factors and prolongs the PT.[25] The drug class of platelet aggregation inhibitors, that includes clopidogrel and ticlopidine, alter platelet aggregation resulting in a prolonged bleeding time but do not prolong the PT.[26] Purpura and epistaxis were commonly seen in clinical trials. Patients on ASA or NSAIDS may experience easy bruising and occasionally prolonged oozing after surgery, particularly if the surgery involves the skin or mucous membranes. Both ASA and NSAIDS inhibit platelet release and aggregation and may prolong the PT. The most frequent adverse events for both the NSAIDs and ASA involve the GI tract and can include GI bleeding.[27] [28] [29]

3.3 AERS CASE SERIES

The search strategy resulted in the identification and retrieval of 225 reports from the AERS database from which 55 reports were excluded. The excluded cases met the following exclusion criteria (in decreasing order of frequency):

Table 2: Reasons for Case Exclusion

Exclusion Reason	Number
Duplicate	18
Injury from fall	11
Bleeding disorder present prior to starting duloxetine	9
Liver failure	5
Onset of bleeding after duloxetine discontinued	3
Self-induced cutting	2
Motor Vehicle Accident	2
Aneurysm	1
Mallory-Weiss Tear	2
Bleeding from scratching	1
Miscoded	1
Total	**55**

The final duloxetine case series included 170 unique cases. The outcomes of the 170 cases are placed into non-overlapping categories that include death, hospitalization, life-threatening, and

[24] H. Herkner, A.N. Laggner and M. Mullner et al., Hypertension in patients presenting with epistaxis, Ann. Emerg. Med. 35 (2000), pp. 126–130.
[25] AHFS Drug Information (2007), 20:12.04.08 Coumarin Derivatives, Warfarin
[26] AHFS Drug Information (2007), 20:12.18 Platelet-aggregation Inhibitors, clopidogrel.
[27] Harrison's Principles of Internal Medicine – 16th Ed. (2005), Part 5, Section 3 – Disorders of Hemostasis
[28] AHFS Drug Information (2007), 28:08.04.92 Other Nonsteroidal Anti-inflammatory Agents, diclofenac
[29] AHFS Drug Information (2007), 28:08.04.24 Salicylates, aspirin

required intervention such that each unique case is represented in a category. If a report is coded with more than one outcome, that report is placed in only one outcome category as determined by the outcome with the higher precedence. The outcome of death has a higher precedence than hospitalization, which is higher than life-threatening, which is higher than required intervention. For example, if a case is coded with hospitalization and life-threatening as outcomes, that case is assigned to the hospitalization category. Cases with non-serious outcomes or other serious outcomes that did not report death, hospitalization, life-threatening or required intervention are grouped together. When summed all outcomes equal the number of unique cases for the series.

The overall characteristics of the duloxetine case series are summarized in Table 3. Medical conditions and/or medications that might increase the risk for the reported bleeding event or platelet disorder were reported in 102 of the 170 cases. Thirty-nine of the patients reported concomitant use of anticoagulants, NSAIDs or ASA.

Table 3: Overall Characteristics of 170 Unique AERS Cases Reporting Bleeding Symptoms from Marketing to April 26, 2007

Location	US (131), Foreign (39)
Most Serious Outcome[30]	Death (6), Hospitalization (51), Life Threatening (2), Required Intervention (1), Other/Non-Serious (110)
Report Source	Expedited (100), Periodic (61), Direct (9)
Reporter	Health Care Provider (120), Consumer (50)
Gender	Male (49), Female (120), Unknown (1)
Age Range	Median (53 years), Range (17-88 years old), (n=148),
Peak Daily Dose	Median (60mg), Range (20-180mg), (n=152)
Onset Information	Median (14 days), Range (1-368 days), (n=73)
Offset Information	Median (5 days), Range (1-16 days), (n=9)
Indications for Use	Affective disorder (1), Anxiety (2), Bipolar disorder (1), Burn out syndrome (1), Chronic fatigue syndrome (1), Depression (78[31]), Fibromyalgia (5), Insomnia (1), Mood swing (1), Nervous system disorder (1), Neuropathy (14[32]), OCD[33] (1), Pain (8[34]), Phantom limb pain (1), Post herpetic neuralgia (1), PTSD[35] (1), Sciatica (1), Shingles (10), Stress (2), SUI[36] (5), Uncalm nerves (1)
Duloxetine Disposition	Discontinued (104), continued (44), unknown (22)
Positive Dechallenge	Without treatment (43), With treatment (17)
Positive Rechallenge	(4)

To facilitate analysis, the cases are further grouped by the System Organ Class as determined by MedDRA coding, and are ordered in descending frequency of reports. Cases with multiple sites of bleeding are grouped together.

[30] Unique cases with outcomes prioritized for serious as death, life threatening, hospitalization, required intervention, disability, congenital anomaly, other – Per Section B 2 of the Medwatch Form 3500
[31] Depression (71), Depressive episode (1), MDD (5), Mild depression (1)
[32] Diabetic neuropathy (2), DPNP (2), Facial neuropathy (1), Neuralgia (2), Neuropathic pain (1), Neuropathy (2), Neuropathy peripheral (4),
[33] OCD – obsessive-compulsive disorder
[34] Back pain (1), chronic pain (1), Pain (6)
[35] PTSD – post traumatic stress disorder
[36] SUI – Stress Urinary Incontinence

Gastrointestinal (GI) System Bleeding (n=54)

The AERS case series included 54 unique cases of GI bleeding, with almost half occurring in the upper GI tract. Thirty-one cases reported either medical conditions and/or concomitant medications that may have increased the potential for the reported GI system bleeding event. A history of previous GI bleeding was described in one case. Fifteen cases were concomitantly using anti-coagulants, NSAIDs and/or ASA; with the majority (12/16) experiencing upper GI bleeding, two lower GI bleeding, and one case both upper and lower GI bleeding. Twenty-three were age 61 or older.

Table 4: Overall Characteristics of Unique AERS cases reporting GI System Bleeding from Marketing through April 26, 2007 (n=54)

Location:	US (41), Foreign (13)
Outcome	Death (2), Hospitalized (23), Other/Non-Serious (29)
Age	Median (58), range (17-88), (n=50)
Gender	Female (39), Male (14), Unknown (1), (n=54)
Peak Daily Dose	60mg, Range (20-180), (n=48)
Onset	Median (21 days), Range (1-120 days), (n=23)
Offset	Median (3 days), Range (1-6 days), (n=3)
Coded Preferred Terms[37]	GI Haemorrhage (12), Haemorrhage[38] (2), Haemoptysis[39] (1), Lower GI haemorrhage[40] (19), Oral bleeding (3[41]) Upper GI haemorrhage[42] (25)
Concomitant Medication Drug Classes[43] - labeled for reported gastrointestinal bleeding-related symptoms or increased bleeding[44]	Antihistamine (1), Antihyperlipidemic agent (1), Anti-infective agent (1), Cardiovascular agent (1), CNS[45] agent (10), Endocrine and metabolic agent (3), Hematological agent (3), NSAID[46] (7), Renal and genitourinary agent (4), Salicylic acid (8), SSRI (3)
Co-morbid Relevant Medical Conditions[47]	Chronic constipation (1), Colitis (1), Colon resection (1), Duodenal ulcer (1), ETOH abuse (1), Gastritis (1), H-pylori (1), IBS[48] (2) Recurrent bleeding ulcers (1)
Identified Source of GI Bleeding	Bleeding ulcer (2), Diverticular bleeding (1), Duodenal bleeding (1), Duodenal ulcer (1), Gastric bleeding (1), Gastric ulcer (2), ulcer (1), Jejunal ulcer (1), Pan-colitis (1), Rectal ulcer (1), Sore in mouth (1)
Duloxetine Disposition:	Discontinued (37), Continued (9), Unknown or Not Reported (8)
Positive Dechallenge	Without treatment (13), With treatment (8)

[37] A report may contain multiple terms, and therefore the sum of the events exceed the number of cases
[38] GI blood loss (1), blood on pillow in morning (1)
[39] Reported symptom - spitting up blood
[40] Lower GI haemorrhage (1), intestinal haemorrhage (1), large intestinal haemorrhage (1), diverticulum intestinal haemorrhagic (1), rectal haemorrhage (8), haematochezia (7)
[41] Gingival bleeding (1), Mouth haemorrhage (1), Tongue haemorrhage (1)
[42] Upper GI haemorrhage (1), gastric haemorrhage (2), gastric ulcer haemorrhage (2), duodenal ulcer haemorrhage (1), gastric ulcer perforation (1), small intestine haemorrhage (1), ulcer haemorrhage (1), haematemesis (10), Melena (5), Faeces discoloured (1),
[43] Drug Classes from Facts & Comparison 4.0
[44] One case may contain multiple medications labeled for reported gastrointestinal system symptoms or increased bleeding
[45] CNS – Central nervous system
[46] NSAID – non-steroidal anti-inflammatory drug
[47] One case may contain multiple co-morbid conditions
[48] IBS – irritable bowel syndrome

Death
Two cases reported death. The first case (ISR # 5159352) was a report from the literature of accidental death, where multiple drug intoxication was given as the cause of death. The second case that reported the cause of death as secondary to GI hemorrhage is summarized below.

ISR # 4800401, Foreign, Death
A physician reported the case of an 84 year old male who was prescribed duloxetine 60mg daily. Forty-three days after starting duloxetine, the patient "collapsed with melena" and was hospitalized. One day after the patient collapsed, the patient died from "cardiac arrest, secondary to hypovolemic shock, secondary to GI hemorrhage." The patient was concomitantly taking multiple medications; however, the relevant medication for this assessment was diclofenac; although, the dose and duration of diclofenac were not provided. The patient's medical history included dementia, COPD, HTN and agitation; and was negative for GI bleeding, anticoagulant use and alcohol use. The physician considered the event to be causally related to duloxetine.

Hospitalization
Twenty-three[49] cases reported hospitalization as the most serious outcome with 21 hospitalized for a GI system bleeding event. The two remaining cases, although experiencing GI bleeding, were hospitalized for other reasons. Eighteen cases described either medical conditions and/or concomitant medications that may have increased the potential for the reported GI bleeding event, including three cases reporting use of warfarin and seven cases reporting use of NSAIDs and/or ASA[50]. Two representative cases are summarized below:

ISR # 4791183, Foreign, Hospitalization+Life Threatening, Positive Dechallenge
A health care professional reported a case of a 61 year-old male who started duloxetine 60mg daily to treat depression. Six weeks after initiation of treatment, the patient was hospitalized for GI bleeding. Duloxetine was discontinued. The patient was recovering at the time of the report. Valproate, a concomitant medication, is labeled for bleeding events.[51] The case did not report any relevant medical history. The reporter considered the event to be causally related to duloxetine.

ISR # 4852897, US, Hospitalization, Positive Dechallenge
A psychiatrist reported a case of a 54 year-old female who started duloxetine 180mg daily to treat anxiety and depression. After two to three weeks of therapy, the patient experienced severe stomach cramping and unexplained GI pain. Five days later, the patient was hospitalized for GI bleeding. Duloxetine was discontinued. The GI bleeding resolved. The patient's pain improved but had not resolved at the time of the report. No relevant medical history or concomitant medications were reported.

Elevated INR with concomitant use of Warfarin
The GI System included two cases of patients taking duloxetine and warfarin who experienced GI bleeding. ISR # 4777942 is temporally associated with warfarin, rather than duloxetine and

[49] Three hospitalization cases were also coded with a life-threatening outcome
[50] ASA - acetylsalicylic acid (aspirin).
[51] Valproic acid is labeled for thrombocytopenia, hemorrhage, bruising, and disorders of hemostasis/coagulation

did not include any laboratory values. The second case is temporally associated with duloxetine and is summarized below.

ISR # 4549439, US, Clinical Trial, Hospitalization, Positive Dechallenge
A physician reported the case of a 76 year old female concomitantly receiving warfarin and participating in a clinical trial, who started duloxetine 80mg daily to treat stress urinary incontinence (SUI). On Day 21, the patient woke up with bright red emesis on her night gown, pillow and bed sheets. No coffee ground substance was noted. The patient did not experience any nausea prior to the event. She was hospitalized and duloxetine was discontinued. Her INR was 10.2, and PT 93.4. Treatment included two units of fresh frozen plasma and one unit of blood. No evidence of active GI bleeding was identified. She was discharged on Day 24 with an INR of 1.0. The patient had a history of GERD, hepatitis C, and a bowel resection with a colostomy. Her history was negative for bleeding and vomiting blood. The patient was on additional multiple medications, which had not changed prior to the event.

Vascular System[52] (Organ and Tissue) Bleeding (n=38)
The AERS case series included 38 unique cases of vascular bleeding. The cases are included in the vascular system based on the coded MedDRA terms; however, the majority of the clinical presentations are internal bleeding or bleeding in the dermis. Twenty-four reported either medical conditions and/or concomitant medications that may have increased the potential for the reported vascular bleeding event. Four of the 38 cases were concomitantly using anti-coagulants, four ASA, and two NSAIDs. The most frequently reported symptom was ecchymosis and/or hematoma (24/38) with two cases presenting with petechiae and normal laboratory values. The characteristics of the vascular system group are summarized below.

Table 5: Overall Characteristics of Unique AERS cases reporting Vascular System Bleeding from Marketing through April 26, 2007 (n=38)

Location:	US (28), Foreign (10)
Outcome	Death (3), Hospitalized (14), Life threatening (2), Other/Non-serious (19)
Age	Median (57), Range (25-86), (n=33)
Gender	Female (23), Male (15)
Peak Daily Dose	Median (60 mg), Range (30-80), (n=36)
Onset	Median (22.5 days), Range (1-368 days), (n=20)
Offset	Median (7 days), Range (2-16 days), (n=3)
Coded Preferred Terms[53]	Catheter site haemorrhage (1), Cerebral haemorrhage (5), Cerebral vascular accident (2), Contusion (4), Cutaneous vasculitis purpura (1), Ecchymosis (6), Haemorrhage (4), Haematoma (5), Hepatic haemorrhage (1), Increased tendency to bruise (4), Injection site bruising (4), Injection site haemorrhage (1), Operative haemorrhage (1), Petechiae (2), Purpura (1), Skin haemorrhage (1), Skin ulcer haemorrhage (1), Subarachnoid haemorrhage (1), Subdural haematoma (2), Traumatic haematoma (1), Vasculitis allergica hemorrhagic necrotic type (1)
Concomitant Medication Drug Classes[54] - labeled for reported	Antihistamine (1), Antihyperlipidemic agent (2), Anti-infective agent (1), Biologic and immunological agent (1), Cardiovascular agent (2), CNS agent

[52] Organ and tissue bleeding, categorized as vascular bleeding by MedDRA PT terms
[53] A report may contain multiple terms, and therefore the sum of the events exceed the number of cases
[54] Drug Classes from Facts & Comparison 4.0

Table 5: Overall Characteristics of Unique AERS cases reporting Vascular System Bleeding from Marketing through April 26, 2007 (n=38)

vascular system bleeding-related symptoms or increased bleeding[55]	(5), Endocrine and metabolic agent (3), Hematological agent (4), NSAID (2), Renal and genitourinary agent (1), Salicylate (4), SSRI (1), Tricyclic (1)
Co-morbid Relevant Medical Conditions[56]	Aortic stenosis (1), Blood pressure increased (1), previous CVA (3), Endocarditis (1), Hypertension (1), ITP (1)
Duloxetine Disposition:	Discontinued (19), Continued (13), Unknown (6)
Positive Dechallenge	Without treatment (8), With treatment (2)

Death

Three cases in the vascular system group reported an outcome of death. One of the three cases (ISR # 4674574) described an 85 year-old female who experienced a cerebral hemorrhage and died one month after starting duloxetine. The case did not include concomitant medications or the patient's medical history. The second case (ISR # 4540780) reported vascular symptoms of petechial hemorrhage and ecchymosis on the extremities; however, the cause of death was listed as decompensated heart insufficiency with lung edema. The third case (ISR # 5260807) reported the cause of death as central pontine myelinosis due to rapid sodium level correction. The physician reported the patient experienced bleeding in an unspecified location "(not a stroke)" due to a low sodium level "which led to the seizure that caused the bleeding"

Hospitalization

Fifteen cases reported hospitalization, with seven of the hospitalizations reportedly due to the vascular system bleeding event. Intracranial bleeding was the most frequent location of vascular bleeding in the hospitalized patients. Eleven cases reported either medical conditions and/or concomitant medications that may have increased the potential for the reported vascular bleeding event, with one patient concomitantly using warfarin, and two ASA.

Positive Dechallenge

There were 11 cases in this group that reported positive dechallenge responses; eight of the dechallenge cases reported improvement and/or resolution with discontinuation of duloxetine only; and two cases reported improvement and/or resolution with discontinuation and medical treatment. Three representative positive dechallenge cases are described below.

ISR # 4682981, US, Positive Dechallenge

A physician reported the case of a 35 year-old male who started duloxetine 30mg daily. The patient experienced "big black and blue" ecchymosis without any related injury. The patient discontinued duloxetine after two weeks of therapy. The bruising resolved. The patient was not taking any concomitant medications.

ISR # 5036917, Foreign, Positive Dechallenge

A physician reported a case of a female who started on duloxetine 60mg daily for treatment of peripheral neuropathy. On Day 12, the patient experienced diffuse skin hemorrhage with large confluent purpuric lesions in the abdomen, legs and arms. All of the coagulation parameters

[55] One case may contain multiple medications labeled for reported vascular system symptoms or increased bleeding
[56] One case may contain multiple co-morbid conditions

were found to be normal. Duloxetine was discontinued on Day 12. The patient recovered. The reporting physician considered the event related to duloxetine.

ISR # 5120484, Foreign, Positive Dechallenge

A physician reported the case of a 42 year old male who started duloxetine 60mg daily for treatment of depression. On Day 4, the patient experienced pain in his arms and knees. The patient developed hematomas in many areas including upper arms, shoulders, elbows and knees. Duloxetine was discontinued. The hematomas abated two days after discontinuation of duloxetine therapy. The patient was not taking any concomitant medications but had experienced similar symptoms with benzoic acid chorothymol and salicylic acid thymol. The physician saw a causal relationship between the event and duloxetine.

Multi-system Bleeding (n=27)

The AERS case series included 27 unique cases with reports of multi-system bleeding. Fifteen of the 27 cases reported either medical conditions and/or concomitant medications that may have increased the potential for the reported bleeding event; with six cases concomitantly using anti-coagulants, and three ASA. Four patients presented with petechiae; one with normal laboratory values, two diagnosed with thrombocytopenia and one without laboratory results. The characteristics of the multi-system bleeding group are summarized below.

Table 6: Overall Characteristics of Unique AERS cases reporting Multi-system bleeding from Marketing through April 26, 2007 (n=27)

Outcome	Hospitalization (8), Life threatening (1), Required intervention (1), Other/Non-serious (17)
Age	Median (48), Range (33-83), (n=22)
Gender	Female (18), Male (9)
Peak Daily Dose	Median (60), Range (30-120), (n=23)
Onset	Median (16 days), Range (5-111 days), (n=9)
Offset	5 days, (n=1)
Coded Preferred Terms[57]	Activated PTT time prolonged (1), CVA (1), Coagulopathy (3), Contusion (3), Diarrhea hemorrhagic (1), Epistaxis (4), Faeces discoloured (2), GI haemorrhage (2), Gingival bleeding (2), Haematochezia (2), Haematemesis (1), Haematoma (3), Haematotympanum (1), Haemorrhage (2), Haemorrhage urinary tract (2), Injection site bruising (1), INR ratio increased (3), Intracranial haemorrhage (1), Metrorrhagia (1), Mouth haemorrhage (2), Mucosal haemorrhage (2), Occult blood positive (1), Petechiae (4), Platelet count decreased (4), Platelet disorder (1), Post procedural haemorrhage (1), PT prolonged (3), Purpura (1), Rectal haemorrhage (3), RBC urine positive (1), Scleral haemorrhage (1), Skin discolouration (1), Skin haemorrhage (1), Subdural haemorrhage (1), Thrombocytopenia (5), Vaginal haemorrhage (4), Vessel puncture site bruise (1),
Concomitant Medication Drug Classes[58] - labeled for reported bleeding related symptoms or	Anithyperlipidemic agent (1), CNS agent (6), Dietary supplement[60] (1), Endocrine and metabolic agent (1), Hematological agent (6), Renal and genitourinary agent (2), Salicylate (3)

[57] A report may contain multiple terms, and therefore the sum of the events exceed the number of cases
[58] Drug Classes from Facts & Comparison 4.0
[59] One case may contain multiple medications labeled for reported symptoms or increased bleeding

Table 6: Overall Characteristics of Unique AERS cases reporting Multi-system bleeding from Marketing through April 26, 2007 (n=27)

increased bleeding[59]	
Co-morbid Relevant Medical Conditions[61]	Congenital thrombocyte dysfunction (1), Hepatitis C (1), Infectious colitis (1), ITP (1), Possible cervical cancer (1), Possible leukemia (1)
Duloxetine Disposition:	Discontinued (18), Continued (6), Unknown (1)
Positive Dechallenge	Without treatment (7), With treatment (3)
Positive Rechallenge	2

Hospitalization

Eight cases reported hospitalization as the most serious outcome, including two positive rechallenges. Six cases reported either medical conditions and/or concomitant medications that may have increased the potential for the reported bleeding event, including two cases concomitantly using anti-coagulants, and one ASA. A positive rechallenge case is summarized below.

ISR # 4877819, US, Positive Dechallenge/Positive Rechallenge

A nurse practitioner reported the case of a 36 year old male who started duloxetine 30mg daily to treat depression. Three to five days later, the patient experienced bleeding from his nose, mouth, and anus and vomited blood. Duloxetine was discontinued. The bleeding stopped. A week later, duloxetine was restarted. The bleeding resumed. Duloxetine was discontinued. The patient was not taking any concomitant medications. The nurse practitioner considered the event related to duloxetine.

Platelet Disorders

Platelet disorders were the most frequently reported event (10/27) in the multi-system bleeding group, with five cases coded for thrombocytopenia, one a platelet disorder, and four a decreased platelet count. Six of the patients were hospitalized including four reporting thrombocytopenia, one a platelet disorder and one a decreased platelet count.

Four cases reported a decreased platelet count but did not include a diagnosis of thrombocytopenia and are described briefly. The first case reported a decreased platelet count in a 51 year-old patient concomitantly using warfarin and noted that "*the patient's platelet count was normally 40,000 and that it was only 34 upon admission to the hospital*." A platelet count of 10,000 was reported in the second case for a male of unknown age who experienced bleeding from his "*gums and nose*" during duloxetine therapy. The third case documented a platelet count of 145000cells/mm^3 in a patient with hemorrhagic diarrhea. The fourth case involved a 33 year-old female consumer who reported an increased frequency of menses with intermittent spotting and a low platelet count but did not include any specific laboratory results.

Five cases of thrombocytopenia were reported with two summarized in detail below. A brief description of the three remaining cases follows. The first case described a 40 year-old female

[60] COQ10
[61] One case may contain multiple co-morbid conditions

experienced thrombocytopenia (66,000) and elevated liver functions resulting in hospitalization after 35 days of duloxetine therapy. The second case involved a 64 year-old male patient with a history of idiopathic thrombocytopenia (ITP) who was hospitalized with spontaneous subdural bleeding after two weeks of duloxetine therapy and was found to have a thrombocyte count of 30 $X10^9$/L. In the third case, an 83 year-old female was hospitalized for dehydration, orthostatic hypotension, electrolyte imbalance and a urinary tract infection; however, her discharge diagnosis was a non-ST myocardial infarction, thrombocytopenia, infectious gastroenteritis and colitis and peptic ulcer. No laboratory results were provided. In addition to the two remaining thrombocytopenia cases, the single case reporting a platelet dysfunction is summarized below.

ISR # 4853476, Foreign, Hospitalization, Positive Dechallenge/Positive Rechallenge
A physician reported the case of a 33 year-old female who started duloxetine 60mg daily to treat a severe episode of depression. After 110 days of therapy, she experienced hematomas all over her body with generalized weakness, pruritis and later hematorrhea. "Basal blood clotting factors" were normal. Fibrinogen was in the middle range – 339 mg/dl. Bleeding time was at the upper limit of the normal range – 9.0 minutes. Aggregation was slightly constricted. Aggregation of thrombocytes with adenosine showed no reaction resulting in a diagnosis of medium thrombocyte dysfunction. Duloxetine was discontinued. The patient's hematomas were recovering when duloxetine was restarted. She developed new hematomas. Discontinuation of duloxetine was recommended. The physician saw a causal relationship between the event and duloxetine.

ISR # 4852906, US, Life Threatening + Hospitalization, Positive Dechallenge
A physician reported the case of a female patient who started duloxetine 60mg daily for treatment of post-herpetic neuralgia. After two weeks, the patient was hospitalized with severe thrombocytopenia and a platelet count of 6,000. A head CT revealed a left parietal cortical hemorrhage. The patient was treated with prednisone and discharged with an improved platelet count that had not returned to the normal range. Duloxetine was discontinued. The patient was not taking any medications and had a normal platelet count nine months prior to the duloxetine therapy. The physician considered the event possibly related to duloxetine.

ISR # 5300912, Foreign, Positive Dechallenge
A psychiatrist reported the case of a 46 year-old male who started duloxetine 60mg daily for treatment of depression. On Day 16, the patient experienced petechiae on his toes, night sweats and urination problems. On Day 30, a thrombocyte count of 49,350 was reported. Duloxetine was discontinued. The petechiae resolved. Eighteen days after stopping duloxetine, the platelet count had increased to 79,275. Three weeks later, a further increase was seen with a platelet count of 87,675. The psychiatrist considered the events possibly related to duloxetine.

Elevated INR
The multi-system bleeding group included four cases of elevated INR and one case with a decreased quick value after beginning duloxetine. Two representative cases are summarized below.

ISR # 5152905, US, Required Intervention
A pharmacist reported the case of a 74 year-old male who started duloxetine for treatment of sciatica. The patient experienced a slow rise in INR values over one month. Bleeding between his toes and at venipuncture and injection sites prompted the patient to seek treatment in the ER. The patient was treated with Vitamin K and the warfarin was held. The patient restarted the warfarin and his INR level rose again. Duloxetine was discontinued and the INR stabilized. The patient was on warfarin and Lovenox® concomitantly but his medications, diet and health issues were stable prior to the administration of duloxetine. The patient had normal liver functions and did not drink alcohol.

ISR # 4538855, US, Hospitalization
A nurse reported the case of a 53 year-old female who started duloxetine 60mg QD for depression. The patient was on concomitant warfarin therapy after a heart valve replacement. On Day 14, her INR was 1.81 and her PT was 18.3. On Day 49, the patient was hospitalized for severe bruising and rectal bleeding. Her PT was 141.1. Duloxetine was discontinued. The patient was treated with packed red blood cells and Vitamin K injections. She had not changed her dietary habits, had not taken any new medications, including over-the-counter medications and also had not experienced nausea, vomiting, or anorexia after initiating duloxetine therapy. The patient's PT levels had remained stable for at least a couple of months before starting duloxetine. Twenty-two days after discontinuing duloxetine, the patient's PT was 33.2; her INR was 3.43 with resolution of the bleeding and bruising. The nurse considered the event related to duloxetine as other causes had been ruled out.

Renal and Urinary System Bleeding (n=17)
The AERS case series included 17 unique cases with reports of bleeding in the renal and urinary system. Eleven of the 17 cases reported either medical conditions and/or concomitant medications that may have increased the potential for the reported renal and urinary system bleeding event. Three were concomitantly using ASA, and one an anti-coagulant. No abnormal PT or platelet values were reported for the renal and urinary system cases.

Table 7: Overall Characteristics of Unique AERS cases reporting Renal and Urinary System bleeding from Marketing through April 26, 2007 (n=17)

Outcome	Death (1), Hospitalization (2), Other/Non-serious (14)
Age	Median (52), Range (31-83), (n=14)
Gender	Female (12), Male (5), (n=17)
Peak Daily Dose	Median (60), range (30-80), (n=15)
Onset	Median (4 days), Range (1-45 days), (n=5)
Offset	Median (2), Range (1-2), (n=2)
Coded Preferred Terms[62]	Blood urine present (8), Haemorrhaging urinary tract (1), Hematuria (7), Renal haemorrhage (1), (n=17)
Concomitant Medication Drug Classes[63] - labeled for reported renal or urinary system related	Anti-infective agent (1), Cardiovascular agent (1), CNS agent (4), Hematological agent (1), Renal and genitourinary agent (1), Salicylate (3), SSRI (1)

[62] A report may contain multiple terms, and therefore the sum of the events exceed the number of cases
[63] Drug Classes from Facts & Comparison 4.0

Table 7: Overall Characteristics of Unique AERS cases reporting Renal and Urinary System bleeding from Marketing through April 26, 2007 (n=17)

bleeding symptoms or increased bleeding[64]	
Co-morbid Relevant Medical Conditions[65]	Chronic renal insufficiency (1), Chronic UTI (1), UTI (2)
Duloxetine Disposition:	Discontinued (9), Continued (5), Unknown (3)
Positive Dechallenge	Without treatment (4), with treatment (1)
Positive Rechallenge	1

Death

One case was coded with death. The patient was hospitalized due to Stevens Johnson Syndrome and pulmonary emboli with the cause of death reported as congestive heart failure. During the hospitalization, the patient developed bleeding in the kidneys that was reportedly related to heparin and resolved with adjusting the heparin dose.

Hospitalization

Two cases were coded with hospitalization as the most serious outcome with both concomitantly using ASA. The first case described a patient who was admitted with confusion, insomnia, anorexia and shortness of breath with the admitting urinalysis positive for blood. The second case (hospitalized for psychiatric reasons), also a positive dechallenge case, is summarized below.

ISR # 4821857, Foreign, Hospitalization, Positive Dechallenge

A physician reported the case of a male who started duloxetine 60mg daily for treatment of depression. During a psychiatric hospitalization, he experienced a "massive haematuria and a prolongation of hospitalization." Duloxetine was discontinued. The patient fully recovered from the haematuria. No relevant medical history was reported; however the patient was concomitantly using aspirin, although the dose and duration of use were not provided. The reporting physician saw a causal relationship between the event and duloxetine.

Positive Dechallenge/Positive Rechallenge

The renal and urinary system group included one positive dechallenge/positive rechallenge case, and five positive dechallenge cases. The dechallenge/rechallenge case is summarized below:

ISR # 5201156, US, Positive Dechallenge/Positive Rechallenge

A psychiatric nurse practitioner reported the case of a 47 year-old female who started duloxetine 60mg daily. The patient experienced frank urinary bleeding. Duloxetine was discontinued. The bleeding resolved. After re-starting duloxetine, the patient again experienced frank urinary bleeding. Duloxetine was discontinued and the bleeding again stopped. The patient did not have any relevant history and was taking clonazepam concomitantly. The nurse practitioner assessed the event as related to the duloxetine. Verbal follow-up with the reporter indicated that the patient was re-challenged a third time (starting at lower doses) without a recurrence of bleeding.

[64] One case may contain multiple medications labeled for reported renal and urinary symptoms or increased bleeding
[65] One case may contain multiple co-morbid conditions

The patient's primary care physician was unable to identify any alternative etiology for the frank urinary bleeding.

Reproductive System Bleeding (n=16)

The AERS case series included 16 unique cases with reports of increased or abnormal bleeding in the reproductive system. Seven of the sixteen cases reported either medical conditions and/or concomitant medications that may have increased the potential for the reproductive system bleeding event. No concomitant use of anti-coagulants, ASA or NSAIDs was reported.

Table 8: Overall Characteristics of Unique AERS cases reporting Reproductive System Bleeding from Marketing through April 26, 2007 (n=16)

Outcome	Hospitalization (1), life threatening (1), Other/Non-serious (14)
Age	Median (36.5), Range (17-58) (n=14)
Gender	Female (16)
Peak Daily Dose	50mg, Range (30-120), (n=16)
Onset	Median (9 days), range (1-32 days), (n=8)
Coded Preferred Terms[66]	Metrorrhagia (11), Polymenorrhea (1), Postmenopausal hemorrhage (1), Vaginal hemorrhage (4)
Concomitant Medication Drug Classes[67] - labeled for reported reproductive system related bleeding symptoms or increased bleeding[68]	CNS agent (5), SSRI (1)
Co-morbid Relevant Medical Conditions[69]	ETOH abuse (1), Hyperplastic uterus (1)
Duloxetine Disposition:	DC (7), Continued (8), Unknown (1)
Positive Dechallenge	Without treatment (5), With treatment (1)
Positive Rechallenge	1

Serious Outcomes

Two cases in this group reported serious outcomes unrelated to the bleeding event; one hospitalization and one life-threatening. The hospitalized patient was not taking any concomitant medications. The first case (hospitalization was related to thoracic pain) described post-menopausal bleeding after six months without menstruation. The second case (life-threatening outcome related to suicidal ideations) described vaginal bleeding that lasted for one month.

Positive Dechallenge

The reproductive system group included seven dechallenge cases, with six dechallenge cases reporting improvement and/or resolution with discontinuation of duloxetine only; and one case reporting improvement and/or resolution with discontinuation and medical treatment. A representative positive rechallenge case is summarized below:

[66] A report may contain multiple terms, and therefore the sum of the events exceed the number of cases
[67] Drug Classes from Facts & Comparison 4.0
[68] One case may contain multiple medications labeled for increased bleeding or reported reproductive system symptoms
[69] One case may contain multiple co-morbid conditions

ISR # 5150579, Foreign, Positive Dechallenge/Positive Rechallenge

A pharmacist reported the case of a 43 year-old female who started duloxetine 60mg daily for the treatment of depression. The patient had not experienced menstruation for two years. On Day 2, the patient experienced vaginal bleeding. The bleeding occurred on approximately 50% of the days the patient was taking duloxetine. The vaginal bleeding was confirmed by a gynecologist. Duloxetine was discontinued and the vaginal bleeding stopped. The patient restarted duloxetine and again experienced vaginal bleeding. At the time of the report, the patient was continuing duloxetine as the medication was effectively treating her depression. The patient's concomitant medications were prazepam for insomnia and levonorgestrel for contraception. The patient also took mirtazapine for 10 days concomitantly with duloxetine but did not experience vaginal bleeding while on mirtazapine. The pharmacist considered the event related to duloxetine.

Respiratory System Bleeding (n=10)

The AERS case series included 10 unique cases with reports of bleeding in the respiratory system. Six cases detailed either medical conditions and/or concomitant medications that may have increased the potential for the reported respiratory system bleeding event with one patient concomitantly using an NSAID. No concomitant use of anticoagulants or ASA was noted. In addition, no abnormal platelet counts or PT values were reported. Four cases reported increased blood pressure after beginning duloxetine therapy with two reporting a history of hypertension.

Table 9: Overall Characteristics of Unique AERS cases reporting Respiratory System Bleeding from Marketing through April 26, 2007 (n=10)

Location	US (7), Foreign (3)
Outcome	Hospitalized (1), Other/Non-serious (9)
Age	Median (60.5), Range (33-85), (n=7)
Gender	Female (6), Male (4)
Peak Daily Dose	60mg, Range (30-120), (n=8)
Onset	Median (1.5 days), Range (1-5 days), (n=4)
Offset	5 days, (n=1)
Coded Preferred Terms[70]	Epistaxis (9), Haemoptysis (1), (n=10)
Concomitant Medication Drug Classes[71] -labeled for reported respiratory symptoms related bleeding or increased bleeding[72]	CNS agent (1), Respiratory agent (2), NSAID (1)
Co-morbid Relevant Medical Conditions[73]	Arterial hypertension (1), asthma (1), hypertension (3), hypertensive crisis (1)
Duloxetine Disposition:	Discontinued(8), Continued (1), Unknown (1)
Positive Dechallenge	Without treatment (3), With treatment (1)

[70] A report may contain multiple terms, and therefore the sum of the events exceed the number of cases
[71] Drug Classes from Facts & Comparison 4.0
[72] One case may contain multiple medications labeled for reported respiratory system symptoms or increased bleeding
[73] One case may contain multiple co-morbid conditions

Hospitalization
The hospitalization was due to a hypertensive crisis with epistaxis in a patient with a reported history of well-controlled arterial hypertension with no concomitant use of anticoagulants, ASA or NSAIDs.

Positive Dechallenge
Four positive dechallenges were described; three dechallenge cases reporting improvement and/or resolution with discontinuation of duloxetine only; and one case reporting improvement and/or resolution with discontinuation and medical treatment. A representative positive dechallenge is summarized below.

ISR # 4683133, US, Positive Dechallenge
A 66 year-old female consumer reported starting duloxetine 30mg daily. She experienced bleeding from her nose as well as nausea, chest pain, constipation, exhaustion and increased pain in her legs. Duloxetine was discontinued and the nose bleeds stopped. The patient was also taking atenolol and simvastatin.

Otic and Ophthalmic Bleeding (n=8)
The AERS case series included 8 unique cases with reports of bleeding in the eye and/or ear but did not include any cases with serious outcomes. Although none of the cases reported use of anti-coagulants, ASA or NSAIDs, seven described either medical conditions and/or concomitant medications that may have increased the potential for the reported eye and/or ear bleeding event. Specific onset and offset were not reported for any of the cases in this group. One case reported both concomitant medications and co-existing medical condition that may have increased the risk of the reported eye hemorrhage; however, the case described a positive dechallenge response when the duloxetine was discontinued.

Table10: Overall Characteristics of Unique AERS Cases Reporting Otic and Ophthalmic Bleeding from Marketing through April 26, 2007 (n=8)

Location	US (8)
Outcomes	Other/Non-serious (8)
Age	Median (47.5), Range (26-65), (n=8)
Gender	Female (6), Male (2), (n=8)
Peak Daily Dose	Median (60), Range (30-60), (n=7)
Coded Preferred Terms[74]	Ear haemorrhage (1), Eye Haemorrhage (6), Retinal haemorrhage (1)
Concomitant Medication Drug Classes[75] - labeled increased bleeding[76]	CNS agent (1), Endocrine and metabolic agent (2)
Co-morbid Relevant Medical Conditions[77]	IDDM[78] (2), Hypertension (2)
Duloxetine Disposition:	Discontinued (4), Continued (2), Unknown (2)

[74] A report may contain multiple terms, and therefore the sum of the events exceed the number of cases
[75] Drug Classes from Facts & Comparison 4.0
[76] One case may contain multiple medications labeled for reported ear and eye symptoms or increased bleeding
[77] One case may contain multiple co-morbid conditions
[78] IDDM – insulin dependent diabetes mellitus

Table10: Overall Characteristics of Unique AERS Cases Reporting Otic and Ophthalmic Bleeding from Marketing through April 26, 2007 (n=8)

Positive Dechallenge	2

Summary Chart

A chart of the basic characteristics of the body system groups is summarized below.

Table 11. Summary of Characteristics of All Body System Groups

	Serious Outcomes death, hospitalization, life threatening	Median age	Median onset	Median offset	Positive Dechallenge	Positive Rechallenge	NSAID, ASA or anti-coagulants
GI (54)	25	58	21	3	21	0	15
Vascular (38)	19	60	22.5	7	10	0	11
Multi-System (27)	9	48	16	5	10	2	9
Renal (17)	3	52	4	2	5	1	4
Reproductive (16)	2	36.5	9	NA	6	1	0
Respiratory (10)	1	60.5	1.5	5	4	0	1
Otic & Ophthalmic (8)	0	47.5	NA	NA	2	0	0

Drug Use

The Duloxetine NME Postmarketing Review performed on March 13, 2007 included drug use information stratified by age and gender which are summarized in Tables 12 and 13 below:

Table 12. Duloxetine Adverse Event Reports in AERS Database by Age Category

Age Group	**Adverse Event Reports (%)** from August 2004 to February 2007	**Patients[79] (%)** from August 2004 to December 2006
0 – 5 years	16/5671 (0.3%)	1,354 (0.0%)
6 yrs – 16 yrs	39/5671 (0.7%)	24,696 (0.8%)
17 yrs – 30 yrs	399/5671 (7.0%)	314,749 (10.3%)
31 yrs – 40 yrs	697/5671 (12.3%)	519,301 (17.0%)
41 yrs – 50 yrs	937/5671 (16.5%)	823,357 (26.9%)
51 yrs – 60 yrs	929/5671 (16.4%)	756,469 (24.7%)
61 yrs – 70 yrs	549/5671 (9.7%)	367,467 (12.0%)
71 yrs +	583/5671 (10.3%)	329,656 (10.8%)
Unknown	1522/5671 (26.8%)	63,085 (2.1%)

[79] Verispan, LLC: Total Patient Tracker, Aug04-Dec06, Extracted Feb07. Files: TPT Cymbalta AUG04-DEC06 Aggregate Product Brand Report.xls, TPT Cymbalta aug04-dec06 Aggregate Gender Report.xls

Table 13. Duloxetine Adverse Event Reports in AERS Database by Gender

	Adverse Event % August 2004 to February 28, 2007	**Drug Use TRx[80] – Total Prescriptions %** from August 2004 through December 2006
Female	73% (4140/5671)	73% (10,198,586/14,016,887)
Male	26% (1474/5671)	26% (3,684,624/14,016,887)
Unknown	1% (57/5671)	1%

4 DISCUSSION

The duloxetine post-marketing case series included 170 unique cases with reports of bleeding. While GI system bleeding was the most frequently reported location of bleeding, bleeding was also reported in locations throughout the body and ranged in severity from bruising to a fatal GI hemorrhage. Medical conditions and/or concomitant medications that may increase the risk of bleeding were reported in 102 of the cases. Six reports of death were included in the case series. Four[81] of the deaths were unrelated to duloxetine; however, a role for duloxetine cannot be excluded in two of the deaths.[82] In addition, 33 of 51 hospitalizations were reportedly due to the bleeding event, with one death and 12 hospitalizations concomitantly using anti-coagulants, ASA and/or NSAIDS. The case series included 60 positive dechallenges, but most compelling were the four positive rechallenges.

Gastrointestinal bleeding was the most frequently reported event with 28% (15/54) concomitantly using NSAIDs, ASA and/or anticoagulants. Studies show that concomitant use of NSAIDs, anti-coagulants and/or ASA, and SSRIs resulted in an increased risk of upper GI bleeding that in some cases was more than the additive effect of the drugs. The SSRI labels address the concomitant use of NSAIDs, ASA and/or anticoagulants in the Drug Interactions and Patient Information sections. The duloxetine label does not mention the concomitant use of drugs that can affect hemostasis but does reference rare cases of hematochezia and melena under the clinical trials section.

Thirty-five post-marketing cases reported dermal or mucosal bleeding. The current labeling notes infrequent increased tendency to bruise and rare ecchymosis was seen in the clinical trials.

Thirteen cases of epistaxis were described with four cases also reporting a concurrent increase in blood pressure. Two of the four had a history of hypertension; one with arterial hypertension who described a hypertensive crisis after initiation of duloxetine. Duloxetine is currently labeled for hypertensive crisis in the postmarketing reports and increased blood pressure in Precautions but does not mention epistaxis.

[80] Verispan, LLC: Vector One®: National, Aug04-Dec06, Extracted March 2007. File: VONA 2007-69 Cymbalta NME Report TRx AgeGender.qry

[81] ISR # 4540780 – decompensated heart insufficiency with lung edema, ISR # 5260807 – central pontine myelinosis due to rapid sodium level correction, ISR # 5159352 – accidental death due to multiple drug intoxication, ISR # 4860668 – congestive heart failure

[82] ISR #4674574 – cerebral hemorrhage, ISR # 4800401 – cardiac arrest secondary to hypovolemic shock secondary to GI hemorrhage

Nine cases of decreased platelets and one case with platelet dysfunction were included in the case series. Additional cases of decreased platelets may be included in the post-marketing cases; however, the majority of the cases did not include laboratory values, or a diagnosis of thrombocytopenia. While a small portion of the cases (n=3) reported normal coagulation results with the presence of clinical symptoms such as petechiae, Halperin and Reber noted that hemostasis tests have a low sensitivity and approximately 50% of the bleeding cases they reviewed had normal coagulation tests. The current labeling includes a reference to rare cases of thrombocytopenia in clinical trials.

A possible drug interaction with warfarin was noted in five cases reporting increases in the PT/INR after initiating duloxetine, in addition to one case reporting a decreased quick time with use of phenproucomon. These cases point to an additional factor of hemostasis that may be affected by duloxetine. The current duloxetine label includes a section in Drug-Drug Interactions addressing the possibility of adverse events with highly protein bound drugs but does not specifically mention warfarin.

Coagulation is a complex process with serotonin playing an important though unexplained role. As the literature notes, serotonin may affect a number of factors during the hemostatic process. The OSE case series and the literature support that conclusion as a temporal association with altered platelet function, decreased platelets and increased PT levels was seen in the duloxetine post-marketing cases.

OSE previously evaluated a potential association between drugs that inhibit serotonin and an increased risk of bleeding. In May of 2000, OSE analyzed SSRI post-marketing reports and concluded that SSRI use "may contribute to an increased risk of bleeding in various body systems" and "may be associated with serious outcomes including death or disability."[83] DPP considered the evidence in the literature and the post-marketing reports sufficient[84] support of an increased risk for bleeding with serotonin inhibitors and requested SSRI class labeling for abnormal bleeding. The duloxetine post-marketing cases duloxetine and the literature for both duloxetine and venlafaxine continue to support a potential increased risk of bleeding with use of drugs that inhibit serotonin.

5 CONCLUSION

The duloxetine case series and the current literature are supportive of an increased risk of bleeding with drugs that inhibit serotonin, particularly in those patients using ASA, anticoagulants and/or NSAIDs. The literature has urged health care providers to use caution when prescribing a drug that inhibits serotonin to patients of advanced age, patients with a medical condition, that might affect hemostasis, and patients concomitantly using drugs that interfere with hemostasis. An increased risk may also be present for patients with an underlying hemostatic defect, either a coagulation defect or a platelet dysfunction. As of December 2006, over 3 million patients were prescribed duloxetine. Adding language similar to the SSRIs (see 1.3 Product Labeling) to the Precautions, Drug Interactions and Patient Information sections in

[83] OPDRA Postmarketing Safety Review, Hemorrhages with Serious Outcomes, Kathleen Phelan, May 8, 2000
[84] Hughes, Alice and Judith Racoosin, Review and Evaluation of Clinical Data, November 19, 2003

both SNRI labels, duloxetine and venlafaxine, will alert the practicing community and patients to potential bleeding complications with SNRI therapy.

RECOMMENDATIONS

1 Add the precaution for "abnormal bleeding" found in the SSRI labels to the SNRI (duloxetine and venlafaxine) labels. Also, add language describing duloxetine associated thrombocytopenia or platelet dysfunction.

2 Add the drug interaction language for warfarin and drugs that affect hemostasis (ASA, NSAIDS and anticoagulants) found in the SSRI labels to the SNRI labels.

3 Add patient information language regarding concomitant use of ASA, NSAIDs or anticoagulants found in the SSRI labels to the SNRI labels.

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APPENDICES

APPENDIX 1: DATA MINING DESCRIPTION

A data mining analysis of the Adverse Event Reporting System (AERS) database was performed for this review using WebVDME 6.0. The analysis uses the Multi-item Gamma Poisson Shrinker (MGPS)[85] [86] algorithm which analyzes the records contained in the AERS database. The algorithm then quantifies reported drug-event associations by producing a set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted EB05 and EB95 respectively.

EBGM values indicate the strength of the reporting relationship between a particular drug and event, as reported in AERS. For example, if EBGM=10 for a drug-event combination, then the drug-event occurred 10 times more frequently in the database than statistically expected when considering all other drugs and events in AERS database as a background, or expected. A drug-event combination having an EB05 $\geq$ 2 indicates 95% confidence that this drug-event combination occurs at least twice the expected rate when considering all other drugs and events in the database. A drug-event combination having an EB05 > 1 indicates 95% confidence that this drug-event combination occurs at least at a higher-than-expected rate considering all other drugs and events in the database.

The higher the EBGM score and accompanying EB05, EB95 confidence intervals for a particular drug-event, the higher the association is between that drug and event, given the database being analyzed. Note that this association is a result of the relative reporting for various events among all drugs in the database. The degree of this association in all patients exposed to the drug worldwide, however, cannot be elicited from an MGPS data mining analysis alone, because the association scores from such an analysis are generated from the specific database analyzed—in this case, AERS, which consists of spontaneous adverse events reports. Also, an elevated EBGM score of association for a particular drug-event combination does not prove causality or an increased relative risk of that drug-event. Similarly, the absence of an elevated EBGM score for a drug-event cannot be interpreted as a definite lack of toxicity for that drug-event. Finally, reporting and detection biases can occur and effects of concomitant illnesses or therapy cannot be fully controlled in data mining analyses using MGPS. Because of the spontaneous nature of reporting, the results should not be interpreted as a formal comparison of treatment groups or of their relative risks.

APPENDIX 2: LIMITATION OF AERS

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

APPENDIX 3: VERISPAN DRUG USE

VERISPAN, LLC

Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims, representing over 160 million unique patients.
The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

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VERISPAN, LLC
Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, physician offices and hospitals. Vector one receives over 1.8 billion prescription claims per year, which represents over 150 million patients tracked across time.

APPENDIX 4: MedDRA SMQ Preferred Terms for SMQ Haemorrhage (excluding laboratory terms)

SMQ Haemorrhage terms (excl laboratory terms)

Basal ganglia haemorrhage	Duodenitis haemorrhagic	Haemorrhagic transformation stroke	Operative haemorrhage	Skin haemorrhage
Abdominal haematoma	Dysfunctional uterine bleeding	Haemorrhagic tumour necrosis	Optic disc haemorrhage	Skin ulcer haemorrhage
Acute haemorrhagic leukoencephalitis	Ear haemorrhage	Haemorrhagic urticaria	Optic nerve sheath haemorrhage	Small intestinal haemorrhage
Adrenal haematoma	Ecchymosis	Haemorrhoidal haemorrhage	Oral mucosal petechiae	Small intestinal ulcer haemorrhage
Adrenal haemorrhage	Encephalitis haemorrhagic	Haemothorax	Osteorrhagia	Soft tissue haemorrhage
Anal haemorrhage	Enterocolitis haemorrhagic	Henoch-Schonlein purpura	Ovarian haematoma	Spermatic cord haemorrhage
Anal ulcer haemorrhage	Epistaxis	Hepatic haemangioma rupture	Ovarian haemorrhage	Spinal cord haemorrhage
Anastomotic haemorrhage	Exsanguination	Hepatic haematoma	Pancreatic haemorrhage	Spinal epidural haemorrhage
Anastomotic ulcer haemorrhage	Extradural haematoma	Hepatic haemorrhage	Pancreatitis haemorrhagic	Spinal haematoma
Aneurysm ruptured	Extravasation blood	Hereditary haemorrhagic telangiectasia	Papillary muscle haemorrhage	Splenic haematoma
Antepartum haemorrhage	Eye haemorrhage	Hyphaema	Parathyroid haemorrhage	Splenic haemorrhage
Aortic aneurysm rupture	Eyelid bleeding	Implant site bruising	Parotid gland haemorrhage	Splinter haemorrhages
Aortic rupture	Foetal-maternal haemorrhage	Implant site haematoma	Pelvic haematoma	Spontaneous haematoma
Application site bleeding	Gastric haemorrhage	Implant site haemorrhage	Pelvic haematoma obstetric	Stomatitis haemorrhagic
Application site bruising	Gastric ulcer haemorrhage	Incision site haematoma	Pelvic haemorrhage	Subarachnoid haemorrhage
Arterial haemorrhage	Gastric ulcer haemorrhage, obstructive	Incision site haemorrhage	Penile haemorrhage	Subarachnoid haemorrhage neonatal
Arteriovenous fistula site haematoma	Gastric ulcer perforation	Increased tendency to bruise	Peptic ulcer haemorrhage	Subcutaneous haematoma
Arteriovenous fistula site haemorrhage	Gastric varices haemorrhage	Induced abortion haemorrhage	Pericardial haemorrhage	Subdural haematoma
Arteriovenous graft site haematoma	Gastritis alcoholic haemorrhagic	Infusion site bruising	Perineal haematoma	Subdural haematoma evacuation
Arteriovenous graft site haemorrhage	Gastritis haemorrhagic	Infusion site haematoma	Periorbital haematoma	Subdural haemorrhage
Auricular haematoma	Gastroduodenal haemorrhage	Infusion site haemorrhage	Perirenal haematoma	Subdural haemorrhage neonatal
Bladder tamponade	Gastroduodenitis haemorrhagic	Injection site bruising	Peritoneal haematoma	Testicular haemorrhage
Bleeding peripartum	Gastrointestinal angiodysplasia haemorrhagic	Injection site haematoma	Peritoneal haemorrhage	Thalamus haemorrhage
Bleeding varicose vein	Gastrointestinal haemorrhage	Injection site haemorrhage	Petechiae	Third stage postpartum haemorrhage
Blood blister	Gastrointestinal ulcer haemorrhage	Intestinal haemorrhage	Pharyngeal haemorrhage	Thoracic haemorrhage
Blood urine	Genital haemorrhage	Intra-abdominal haemorrhage	Pituitary haemorrhage	Thrombocytopenic purpura
Blood urine present	Gingival bleeding	Intracerebral haematoma evacuation	Placenta praevia haemorrhage	Thrombotic thrombocytopenic purpura
Bloody discharge	Graft haemorrhage	Intracranial haematoma	Pleural haemorrhage	Thyroid haemorrhage
Brain stem haemorrhage	Haemarthrosis	Intracranial tumour haemorrhage	Polymenorrhagia	Tongue haematoma
Breast haematoma	Haematemesis	Intraventricular haemorrhage	Post abortion haemorrhage	Tongue haemorrhage
Breast haemorrhage	Haematochezia	Intraventricular haemorrhage neonatal	Post procedural haematoma	Tonsillar haemorrhage
Broad ligament haematoma	Haematoma	Iris haemorrhage	Post procedural haematuria	Tooth socket haemorrhage
Bronchial haemorrhage	Haematoma evacuation	Large intestinal haemorrhage	Post procedural	Tracheal haemorrhage

			haemorrhage	
Carotid aneurysm rupture	Haematoma infection	Large intestinal ulcer haemorrhage	Postmenopausal haemorrhage	Traumatic haematoma
Catheter site haematoma	Haematomyelia	Laryngeal haemorrhage	Postpartum haemorrhage	Traumatic haemorrhage
Catheter site haemorrhage	Haematosalpinx	Lip haematoma	Premature separation of placenta	Traumatic intracranial haemorrhage
Cephalhaematoma	Haematospermia	Lip haemorrhage	Proctitis haemorrhagic	Tumour haemorrhage
Cerebellar haematoma	Haematotympanum	Lower gastrointestinal haemorrhage	Prostatic haemorrhage	Ulcer haemorrhage
Cerebellar haemorrhage	Haematuria	Majocchi's purpura	Pulmonary alveolar haemorrhage	Umbilical cord haemorrhage
Cerebral aneurysm ruptured syphilitic	Haematuria traumatic	Mallory-Weiss syndrome	Pulmonary haematoma	Umbilical haemorrhage
Cerebral arteriovenous malformation haemorrhagic	Haemobilia	Mediastinal haematoma	Pulmonary haemorrhage	Upper gastrointestinal haemorrhage
Cerebral haematoma	Haemophilic arthropathy	Mediastinal haemorrhage	Puncture site haemorrhage	Ureteric haemorrhage
Cerebral haemorrhage	Haemopneumothorax	Melaena	Purpura	Urethral caruncle haemorrhage
Cerebral haemorrhage foetal	Haemoptysis	Melaena neonatal	Purpura neonatal	Urethral haemorrhage
Cerebral haemorrhage neonatal	Haemorrhage	Meningorrhagia	Purpura senile	Urinary bladder haemorrhage
Cerebral haemorrhage traumatic	Haemorrhage coronary artery	Menometrorrhagia	Putamen haemorrhage	Urogenital haemorrhage
Cervix haematoma uterine	Haemorrhage foetal	Menorrhagia	Rectal haemorrhage	Uterine haematoma
Cervix haemorrhage uterine	Haemorrhage intracranial	Metrorrhagia	Rectal ulcer haemorrhage	Uterine haemorrhage
Choroidal haemorrhage	Haemorrhage neonatal	Mouth haemorrhage	Renal haematoma	Vaginal haematoma
Chronic gastrointestinal bleeding	Haemorrhage subcutaneous	Mucosal haemorrhage	Renal haemorrhage	Vaginal haemorrhage
Ciliary body haemorrhage	Haemorrhage subepidermal	Muscle haemorrhage	Respiratory tract haemorrhage	Varicose vein ruptured
Coital bleeding	Haemorrhage urinary tract	Myocardial haemorrhage	Respiratory tract haemorrhage neonatal	Vascular pseudoaneurysm ruptured
Colonic haematoma	Haemorrhagic anaemia	Naevus haemorrhage	Retinal haemorrhage	Vascular purpura
Conjunctival haemorrhage	Haemorrhagic arteriovenous malformation	Nail bed bleeding	Retinopathy haemorrhagic	Vascular rupture
Corneal bleeding	Haemorrhagic ascites	Nephritis haemorrhagic	Retroperitoneal haematoma	Venous haemorrhage
Cullen's sign	Haemorrhagic cerebral infarction	Nipple exudate bloody	Retroperitoneal haemorrhage	Vessel puncture site haematoma
Cystitis haemorrhagic	Haemorrhagic diathesis	Occult blood positive	Retroplacental haematoma	Vessel puncture site haemorrhage
Diarrhoea haemorrhagic	Haemorrhagic disease of newborn	Ocular retrobulbar haemorrhage	Ruptured cerebral aneurysm	Vitreous haemorrhage
Disseminated intravascular coagulation	Haemorrhagic disorder	Oesophageal haemorrhage	Scleral haemorrhage	Vulval haematoma
Diverticulitis intestinal haemorrhagic	Haemorrhagic infarction	Oesophageal ulcer haemorrhage	Scrotal haematocoele	Vulval haematoma evacuation
Diverticulum intestinal haemorrhagic	Haemorrhagic ovarian cyst	Oesophageal varices haemorrhage	Scrotal haematoma	Vulval haemorrhage
Duodenal ulcer haemorrhage	Haemorrhagic stroke	Oesophagitis haemorrhagic	Shock haemorrhagic	Wound haemorrhage

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