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REVLIMID® (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1–risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

REVLIMID is not indicated and not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

HELPING YOU SHAPE **TRANSFUSION INDEPENDENCE** in patients with del 5q MDS

CLINICAL TRIAL RESULTS

67%* of patients **achieved RBC transfusion independence** with REVLIMID in the MDS clinical trial. (99/148; 95% CI, 59-74).

TRIAL DESIGN[1]

- In a multicenter, single-arm, open-label study
- This major study enrolled 148 patients who had RBC transfusion dependent anemia† with a del 5q cytogenetic abnormality
- Patients received REVLIMID 10 mg once daily or 10 mg once daily for 21 days every 28 days. Sequential dose reductions to 5 mg daily and 5 mg every other day, as well as dose delays, were allowed for toxicity
- 80% of patients in the trial had at least one dose interruption or reduction, and 34% underwent a second dose interruption
- G-CSF was permitted for patients who developed neutropenia or fever associated with neutropenia

*Frequency of RBC transfusion independence was assessed using criteria modified from the International Working Group (IWG) response criteria.

†RBC transfusion dependence was defined as having received ≥2 units of RBCs within 8 weeks prior to study treatment.

Study not designed or powered to prospectively compare efficacy of 2 dosing regimens.

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS THROMBOEMBOLISM

See full prescribing information for complete boxed warning.

EMBRYO-FETAL TOXICITY

- **Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.**
- **Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.**

REVLIMID is available only through a restricted distribution program called the REVLIMID REMS™ program (formerly known as the "RevAssist® program").

HEMATOLOGIC TOXICITY. REVLIMID can cause significant neutropenia and thrombocytopenia.

- **For patients with del 5q myelodysplastic syndromes, monitor complete blood counts weekly for the first 8 weeks and monthly thereafter.**

VENOUS THROMBOEMBOLISM

- **Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma receiving REVLIMID with dexamethasone.**

For more information, please visit www.REVLIMID.com.

REVLIMID is only available through a restricted distribution program, REVLIMID REMS™.

Please see Important Safety Information, including Boxed WARNINGS, and Brief Summary of full Prescribing Information, on the following pages.

Celgene

Revlimid® (lenalidomide) capsules
2.5 · 5 · 10 · 15 · 20 · 25 mg

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS THROMBOEMBOLISM

Embryo-Fetal Toxicity

Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS™ program (formerly known as the "RevAssist®" program).

Information about the REVLIMID REMS™ Program is available at www.celgeneriskmanagement.com or by calling the manufacturer's toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q MDS had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

Venous Thromboembolism

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with MM who were treated with REVLIMID and dexamethasone therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID may lessen the potential for venous thromboembolism. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

CONTRAINDICATIONS

Pregnancy:

- REVLIMID can cause fetal harm when administered to a pregnant female. Lenalidomide is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus

Allergic Reactions:

- REVLIMID is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity:

- REVLIMID is an analogue of thalidomide, a known human teratogen that causes life-threatening human birth defects or embryo-fetal death. An embryo-fetal development study in monkeys indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy
- Females of Reproductive Potential: Must avoid pregnancy for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy. Must obtain 2 negative pregnancy tests prior to initiating therapy
- Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm
- Blood Donation: Patients must not donate blood during treatment with REVLIMID and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID

REVLIMID REMS Program

Because of embryo-fetal risk, REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) the **REVLIMID REMS** Program (**formerly known as the "RevAssist®" Program**). Prescribers and pharmacies must be certified with the program and patients must sign an agreement form and comply with the requirements. Further information about the **REVLIMID REMS** program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436

Hematologic Toxicity Myelodysplastic Syndromes: REVLIMID can cause significant neutropenia and thrombocytopenia. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Please see the Black Box Warnings for further information

Please see Brief Summary of full Prescribing Information on the following pages.

Venous Thromboembolism: Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients with MDS treated with lenalidomide monotherapy. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID may lessen the potential for venous thromboembolism

Increased Mortality in Patients With CLL: In a clinical trial in the first line treatment of patients with CLL, single agent REVLIMID therapy increased the risk of death as compared to single agent chlorambucil. In an interim analysis, there were 34 deaths among 210 patients on the REVLIMID treatment arm compared to 18 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 [95% CI: 1.08-3.41] consistent with a 92% increase in risk of death. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in the REVLIMID treatment arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials

Second Primary Malignancies: Patients with MM treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide. Monitor patients for the development of second malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide

Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered

Allergic Reactions: Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. REVLIMID interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. REVLIMID capsules contain lactose. Risk-benefit of REVLIMID treatment should be evaluated in patients with lactose intolerance

Tumor Lysis Syndrome: Fatal instances of tumor lysis syndrome (TLS) have been reported during treatment with lenalidomide. The patients at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken

Tumor Flare Reaction: Tumor flare reaction has occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials

ADVERSE REACTIONS

Myelodysplastic Syndromes

- Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events observed in the del 5q MDS population
- Grade 3 and 4 adverse events reported in ≥5% of patients with del 5q MDS were neutropenia (53%), thrombocytopenia (50%), pneumonia (7%), rash (7%), anemia (6%), leukopenia (5%), fatigue (5%), dyspnea (5%), and back pain (5%)
- Other adverse events reported in ≥15% of del 5q MDS patients (REVLIMID): diarrhea (49%), pruritus (42%), rash (36%), fatigue (31%), constipation (24%), nausea (24%), nasopharyngitis (23%), arthralgia (22%), pyrexia (21%), back pain (21%), peripheral edema (20%), cough (20%), dizziness (20%), headache (20%), muscle cramp (18%), dyspnea (17%), pharyngitis (16%), epistaxis (15%), asthenia (15%), upper respiratory tract infection (15%)

DRUG INTERACTIONS

Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in MM patients taking concomitant warfarin. Erythropoietic agents, or other agents, that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution in MM patients receiving lenalidomide with dexamethasone

USE IN SPECIFIC POPULATIONS

Pregnancy: If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID must be reported to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436

Nursing Mothers: It is not known whether REVLIMID is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established

Geriatric Use: Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function

Renal Impairment: Since REVLIMID is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate (CLcr 30-60 mL/min) or severe renal impairment (CLcr <30 mL/min) and in patients on dialysis

REVLIMID is only available through a restricted distribution program, REVLIMID REMS™.

Reference: 1. Revlimid [package insert]. Summit, NJ: Celgene Corp; 2013.

REVLIMID [lenalidomide] capsules, for oral use

The following is a brief summary for myelodysplastic syndrome; refer to full prescribing information for complete product information

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS THROMBOEMBOLISM

Embryo-Fetal Toxicity

Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID® treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment [*see Warnings and Precautions (5.1), and Medication Guide (17)*]. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS™ program (formerly known as the "RevAssist®" program) (5.2).

Information about the REVLIMID REMS™ program is available at www.celgeneriskmanagement.com or by calling the manufacturer's toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors [*see Dosage and Administration (2.2)*].

Venous Thromboembolism

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma who were treated with REVLIMID and dexamethasone therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID may lessen the potential for venous thromboembolism. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors [*see Warnings and Precautions (5.4)*].

1 INDICATIONS AND USAGE

1.2 Myelodysplastic Syndromes

REVLIMID is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

1.4 Limitations of Use:

REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials [*see Warnings and Precautions (5.5)*].

2 DOSAGE AND ADMINISTRATION

REVLIMID should be taken orally at about the same time each day, either with or without food. REVLIMID capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed.

2.2 Myelodysplastic Syndromes

The recommended starting dose of REVLIMID is 10 mg daily. Treatment is continued or modified based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During MDS Treatment

Patients who are dosed initially at 10 mg and who experience thrombocytopenia should have their dosage adjusted as follows:

Platelet counts

If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS

If baseline ≥100,000/mcL	
When Platelets	**Recommended Course**
Fall to <50,000/mcL	Interrupt REVLIMID treatment
Return to ≥50,000/mcL	Resume REVLIMID at 5 mg daily
If baseline <100,000/mcL	
When Platelets	**Recommended Course**
Fall to 50% of the baseline value	Interrupt REVLIMID treatment
If baseline ≥60,000/mcL and returns to ≥50,000/mcL	Resume REVLIMID at 5 mg daily
If baseline <60,000/mcL and returns to ≥30,000/mcL	Resume REVLIMID at 5 mg daily

If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Platelets	**Recommended Course**
<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt REVLIMID treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID at 5 mg daily

Patients who experience thrombocytopenia at 5 mg daily should have their dosage adjusted as follows:

If thrombocytopenia develops during treatment at 5 mg daily in MDS

When Platelets	**Recommended Course**
<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt REVLIMID treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID at 2.5 mg daily

Patients who are dosed initially at 10 mg and experience neutropenia should have their dosage adjusted as follows:

Absolute Neutrophil counts (ANC)

If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS

If baseline ANC ≥1,000/mcL	
When Neutrophils	**Recommended Course**
Fall to <750/mcL	Interrupt REVLIMID treatment
Return to ≥1,000/mcL	Resume REVLIMID at 5 mg daily
If baseline ANC <1,000/mcL	
When Neutrophils	**Recommended Course**
Fall to <500/mcL	Interrupt REVLIMID treatment
Return to ≥500/mcL	Resume REVLIMID at 5 mg daily

If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Neutrophils	**Recommended Course**
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID treatment
Return to ≥500/mcL	Resume REVLIMID at 5 mg daily

Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as follows:

If neutropenia develops during treatment at 5 mg daily in MDS

When Neutrophils	**Recommended Course**
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID treatment
Return to ≥500/mcL	Resume REVLIMID at 2.5 mg daily

Other Grade 3 / 4 Toxicities in MDS

For other Grade 3/4 toxicities judged to be related to REVLIMID, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to ≤ Grade 2.

Starting Dose Adjustment for Renal Impairment in MDS:

See Section 2.4.

2.4 Starting Dose for Renal Impairment in MDS

Since REVLIMID is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Based on a pharmacokinetic study in patients with renal impairment due to non-malignant conditions, REVLIMID starting dose adjustment is recommended for patients with CLcr < 60 mL/min. Non-dialysis patients with creatinine clearances less than 11 mL/min and dialysis patients with creatinine clearances less than 7 mL/min have not been studied. The recommendations for initial starting doses for patients with MM, MDS or MCL are as follows:

Table 1: Starting Dose Adjustments for Patients with Renal Impairment in MDS

Category	Renal Function (Cockcroft-Gault)	Dose in MDS
Moderate Renal Impairment	CLcr 30-60 mL/min	5 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	2.5 mg Every 24 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	2.5 mg Once daily. On dialysis days, administer the dose following dialysis.

After initiation of REVLIMID therapy, subsequent REVLIMID dose modification is based on individual patient treatment tolerance, as described elsewhere (see section 2).

4 CONTRAINDICATIONS

4.1 Pregnancy

REVLIMID can cause fetal harm when administered to a pregnant female. Limb abnormalities were seen in the offspring of monkeys that were dosed with lenalidomide during organogenesis. This effect was seen at all doses tested. Due to the results of this developmental monkey study, and lenalidomide's structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in females who are pregnant [*see Boxed Warning*]. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [*see Warnings and Precautions (5.1, 5.2), Use in Special Populations (8.1), (8.6)*].

4.2 Allergic Reactions

REVLIMID is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide [*see Warnings and Precautions (5.8)*].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

REVLIMID is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes life-threatening human birth defects or embryo-fetal death [*see Use in Specific Populations (8.1)*]. An embryo-fetal development study in monkeys indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy.

REVLIMID is only available through the REVLIMID REMS™ program (formerly known as the "RevAssist® program") [*see Warnings and Precautions (5.2)*].

Females of Reproductive Potential

Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy.

Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing REVLIMID therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles [*see Use in Specific Populations (8.6)*].

Males

Lenalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm [*see Use in Specific Populations (8.6)*].

Blood Donation

Patients must not donate blood during treatment with REVLIMID and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID.

5.2 REVLIMID REMS™ program

Because of the embryo-fetal risk [*see Warnings and Precautions (5.1)*], REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the **REVLIMID REMS™** program **(formerly known as the "RevAssist®" program).**

Required components of the **REVLIMID REMS™** program include the following:

- Prescribers must be certified with the **REVLIMID REMS™** program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Prescriber agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements [*see Use in Specific Populations (8.6)*] and males must comply with contraception requirements [*see Use in Specific Populations (8.6)*].
- Pharmacies must be certified with the **REVLIMID REMS™** program, must only dispense to patients who are authorized to receive REVLIMID and comply with REMS requirements.

Further information about the **REVLIMID REMS™** program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436.

5.3 Hematologic Toxicity

REVLIMID can cause significant neutropenia and thrombocytopenia. Patients taking REVLIMID for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. Patients taking REVLIMID for MM should have their complete blood counts monitored every 2 weeks for the first 12 weeks and then monthly thereafter. Patients taking REVLIMID for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction [*see Dosage and Administration (2.1,* 2.2, 2.3*)*].

Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the MDS study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days [*see Boxed Warning and Dosage and Administration (2.2)*].

In the pooled MM trials Grade 3 and 4 hematologic toxicities were more frequent in patients treated with the combination of REVLIMID and dexamethasone than in patients treated with dexamethasone alone [*see Adverse Reactions (6.1)*].

In the MCL trial, Grade 3 or 4 neutropenia was reported in 43% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients.

5.4 Venous Thromboembolism

Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients with multiple myeloma treated with lenalidomide combination therapy [see Boxed Warning] and patients with MDS or MCL treated with lenalidomide monotherapy. A significantly increased risk of DVT and PE was observed in patients with multiple myeloma who were treated with REVLIMID and dexamethasone therapy in a clinical trial [*see Boxed Warning*]. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID may lessen the potential for venous thromboembolism. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

5.5 Increased Mortality in Patients with CLL

In a prospective randomized (1:1) clinical trial in the first line treatment of patients with chronic lymphocytic leukemia, single agent REVLIMID therapy increased the risk of death as compared to single agent chlorambucil. In an interim analysis, there were 34 deaths among 210 patients on the REVLIMID treatment arm compared to 18 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 [95% CI: 1.08 – 3.41], consistent with a 92% increase in the risk of death. The trial was halted for safety in July 2013.

Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in the REVLIMID treatment arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

5.6 Second Primary Malignancies

Patients with multiple myeloma treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide. Monitor patients for the development of second malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

5.7 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestatic and mixed characteristics); 2% of patients with multiple myeloma and 1% of patients with myelodysplasia had serious hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

5.8 Allergic Reactions

Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. REVLIMID interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected and should not be resumed following discontinuation for these reactions.

REVLIMID capsules contain lactose. Risk-benefit of REVLIMID treatment should be evaluated in patients with lactose intolerance.

5.9 Tumor Lysis Syndrome

Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

5.10 Tumor Flare Reaction

Tumor flare reaction has occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Monitoring and evaluation for tumor flare reaction (TFR) is recommended in patients with MCL. Tumor flare reaction may mimic progression of disease (PD). In the MCL trial, 13/134 (10%) of subjects experienced TFR; all reports were Grade 1 or 2 in severity. All of the events occurred in cycle 1 and one patient developed TFR again in cycle 11. Lenalidomide may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion. Patients with Grade 1 and 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1. Patients with Grade 3 or 4 TFR may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other labeling sections:

- Neutropenia and thrombocytopenia [*see Boxed Warnings, Warnings and Precautions (5.3)*]
- Deep vein thrombosis and pulmonary embolism [*see Boxed Warnings, Warnings and Precautions (5.4)*]
- Increased Mortality in Patients with CLL [*see Warnings and Precautions (5.5)]*
- Second Primary Malignancies [*see Warnings and Precautions (5.6)*]
- Hepatotoxicity [*see Warnings and Precautions (5.7)*]
- Allergic Reactions [*see Warnings and Precautions (5.8)*]
- Tumor lysis syndrome [*see Warnings and Precautions (5.9)*]
- Tumor flare reactions [*see Warnings and Precautions (5.10)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.2 Clinical Trials Experience in Myelodysplastic Syndromes

A total of 148 patients received at least 1 dose of 10 mg REVLIMID in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of REVLIMID. The most frequently reported adverse events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions.

Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 5 summarizes the adverse events that were reported in ≥ 5% of the REVLIMID treated patients in the del 5q MDS clinical study. Table 6 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with REVLIMID. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease.

Table 5: Summary of Adverse Events Reported in ≥5% of the REVLIMID Treated Patients in del 5q MDS Clinical Study

System organ class/Preferred term [a]	10 mg Overall (N=148)	
Patients with at least one adverse event	148	(100.0)
Blood and Lymphatic System Disorders		
Thrombocytopenia	91	(61.5)
Neutropenia	87	(58.8)
Anemia	17	(11.5)
Leukopenia	12	(8.1)
Febrile Neutropenia	8	(5.4)
Skin and Subcutaneous Tissue Disorders		
Pruritus	62	(41.9)
Rash	53	(35.8)
Dry Skin	21	(14.2)
Contusion	12	(8.1)
Night Sweats	12	(8.1)
Sweating Increased	10	(6.8)
Ecchymosis	8	(5.4)
Erythema	8	(5.4)
Gastrointestinal Disorders		
Diarrhea	72	(48.6)
Constipation	35	(23.6)
Nausea	35	(23.6)
Abdominal Pain	18	(12.2)
Vomiting	15	(10.1)
Abdominal Pain Upper	12	(8.1)
Dry Mouth	10	(6.8)
Loose Stools	9	(6.1)
Respiratory, Thoracic and Mediastinal Disorders		
Nasopharyngitis	34	(23.0)
Cough	29	(19.6)
Dyspnea	25	(16.9)
Pharyngitis	23	(15.5)
Epistaxis	22	(14.9)
Dyspnea Exertional	10	(6.8)
Rhinitis	10	(6.8)
Bronchitis	9	(6.1)
General Disorders and Administration Site Conditions		
Fatigue	46	(31.1)
Pyrexia	31	(20.9)
Edema Peripheral	30	(20.3)
Asthenia	22	(14.9)
Edema	15	(10.1)
Pain	10	(6.8)
Rigors	9	(6.1)
Chest Pain	8	(5.4)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	32	(21.6)
Back Pain	31	(20.9)
Muscle Cramp	27	(18.2)
Pain in Limb	16	(10.8)
Myalgia	13	(8.8)
Peripheral Swelling	12	(8.1)

(continued)

Table 5: Summary of Adverse Events Reported in ≥5% of the REVLIMID Treated Patients in del 5q MDS Clinical Study

System organ class/Preferred term [a]	10 mg Overall (N=148)	
Nervous System Disorders		
Dizziness	29	(19.6)
Headache	29	(19.6)
Hypoesthesia	10	(6.8)
Dysgeusia	9	(6.1)
Peripheral Neuropathy	8	(5.4)
Infections and Infestations		
Upper Respiratory Tract Infection	22	(14.9)
Pneumonia	17	(11.5)
Urinary Tract Infection	16	(10.8)
Sinusitis	12	(8.1)
Cellulitis	8	(5.4)
Metabolism and Nutrition Disorders		
Hypokalemia	16	(10.8)
Anorexia	15	(10.1)
Hypomagnesemia	9	(6.1)
Investigations		
Alanine Aminotransferase Increased	12	(8.1)
Psychiatric Disorders		
Insomnia	15	(10.1)
Depression	8	(5.4)
Renal and Urinary Disorders		
Dysuria	10	(6.8)
Vascular Disorders		
Hypertension	9	(6.1)
Endocrine Disorders		
Acquired Hypothyroidism	10	(6.8)
Cardiac Disorders		
Palpitations	8	(5.4)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Table 6: Most Frequently Observed Grade 3 and 4 Adverse Events [1] Regardless of Relationship to Study Drug Treatment

Preferred term [2]	10 mg (N=148)	
Patients with at least one Grade 3/4 AE	131	(88.5)
Neutropenia	79	(53.4)
Thrombocytopenia	74	(50.0)
Pneumonia	11	(7.4)
Rash	10	(6.8)
Anemia	9	(6.1)
Leukopenia	8	(5.4)
Fatigue	7	(4.7)
Dyspnea	7	(4.7)
Back Pain	7	(4.7)
Febrile Neutropenia	6	(4.1)
Nausea	6	(4.1)
Diarrhea	5	(3.4)
Pyrexia	5	(3.4)
Sepsis	4	(2.7)
Dizziness	4	(2.7)
Granulocytopenia	3	(2.0)
Chest Pain	3	(2.0)
Pulmonary Embolism	3	(2.0)
Respiratory Distress	3	(2.0)
Pruritus	3	(2.0)
Pancytopenia	3	(2.0)
Muscle Cramp	3	(2.0)
Respiratory Tract Infection	2	(1.4)

(continued)

Table 6: Most Frequently Observed Grade 3 and 4 Adverse Events [1] Regardless of Relationship to Study Drug Treatment

Preferred term [2]	10 mg (N=148)	
Upper Respiratory Tract Infection	2	(1.4)
Asthenia	2	(1.4)
Multi-organ Failure	2	(1.4)
Epistaxis	2	(1.4)
Hypoxia	2	(1.4)
Pleural Effusion	2	(1.4)
Pneumonitis	2	(1.4)
Pulmonary Hypertension	2	(1.4)
Vomiting	2	(1.4)
Sweating Increased	2	(1.4)
Arthralgia	2	(1.4)
Pain in Limb	2	(1.4)
Headache	2	(1.4)
Syncope	2	(1.4)

[1] Adverse events with frequency ≥1% in the 10 mg Overall group. Grade 3 and 4 are based on National Cancer Institute Common Toxicity Criteria version 2.

[2] Preferred Terms are coded using the MedDRA dictionary. A patient with multiple occurrences of an AE is counted only once in the Preferred Term category.

In other clinical studies of REVLIMID in MDS patients, the following serious adverse events (regardless of relationship to study drug treatment) not described in Table 5 or 6 were reported:

Blood and lymphatic system disorders: warm type hemolytic anemia, splenic infarction, bone marrow depression, coagulopathy, hemolysis, hemolytic anemia, refractory anemia

Cardiac disorders: cardiac failure congestive, atrial fibrillation, angina pectoris, cardiac arrest, cardiac failure, cardio-respiratory arrest, cardiomyopathy, myocardial infarction, myocardial ischemia, atrial fibrillation aggravated, bradycardia, cardiogenic shock, pulmonary edema, supraventricular arrhythmia, tachyarrhythmia, ventricular dysfunction

Ear and labyrinth disorders: vertigo

Endocrine disorders: Basedow's disease

Gastrointestinal disorders: gastrointestinal hemorrhage, colitis ischemic, intestinal perforation, rectal hemorrhage, colonic polyp, diverticulitis, dysphagia, gastritis, gastroenteritis, gastroesophageal reflux disease, obstructive inguinal hernia, irritable bowel syndrome, melena, pancreatitis due to biliary obstruction, pancreatitis, perirectal abscess, small intestinal obstruction, upper gastrointestinal hemorrhage

General disorders and administration site conditions: disease progression, fall, gait abnormal, intermittent pyrexia, nodule, rigors, sudden death

Hepatobiliary disorders: hyperbilirubinemia, cholecystitis, acute cholecystitis, hepatic failure

Immune system disorders: hypersensitivity

Infections and infestations infection bacteremia, central line infection, clostridial infection, ear infection, *Enterobacter* sepsis, fungal infection, herpes viral infection NOS, influenza, kidney infection, *Klebsiella* sepsis, lobar pneumonia, localized infection, oral infection, *Pseudomonas* infection, septic shock, sinusitis acute, sinusitis, *Staphylococcal* infection, urosepsis

Injury, poisoning and procedural complications: femur fracture, transfusion reaction, cervical vertebral fracture, femoral neck fracture, fractured pelvis, hip fracture, overdose, post procedural hemorrhage, rib fracture, road traffic accident, spinal compression fracture

Investigations: blood creatinine increased, hemoglobin decreased, liver function tests abnormal, troponin I increased

Metabolism and nutrition disorders: dehydration, gout, hypernatremia, hypoglycemia

Musculoskeletal and connective tissue disorders: arthritis, arthritis aggravated, gouty arthritis, neck pain, chondrocalcinosis pyrophosphate

Neoplasms benign, malignant and unspecified: acute leukemia, acute myeloid leukemia, bronchoalveolar carcinoma, lung cancer metastatic, lymphoma, prostate cancer metastatic

Nervous system disorders: cerebrovascular accident, aphasia, cerebellar infarction, cerebral infarction, depressed level of consciousness, dysarthria, migraine, spinal cord compression, subarachnoid hemorrhage, transient ischemic attack

Psychiatric disorders: confusional state

Renal and urinary disorders: renal failure, hematuria, renal failure acute, azotemia, calculus ureteric, renal mass

Reproductive system and breast disorders: pelvic pain

Respiratory, thoracic and mediastinal disorders: bronchitis, chronic obstructive airways disease exacerbated, respiratory failure, dyspnea exacerbated, interstitial lung disease, lung infiltration, wheezing

Skin and subcutaneous tissue disorders: acute febrile neutrophilic dermatosis

Vascular system disorders: deep vein thrombosis, hypotension, aortic disorder, ischemia, thrombophlebitis superficial, thrombosis

6.4 Postmarketing Experience

The following adverse drug reactions have been identified from the worldwide post-marketing experience with REVLIMID: Allergic conditions (angioedema, SJS, TEN), tumor lysis syndrome (TLS) and tumor flare reaction (TFR), pneumonitis, hepatic failure, including fatality, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis and transient abnormal liver laboratory tests. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure [*see Warnings and Precautions Section (5.5 to 5.8)*].

Cases of hypothyroidism and hyperthyroidism have also been reported. Optimal control of thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

7 DRUG INTERACTIONS

Results from human in vitro studies show that REVLIMID is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions.

In vitro studies demonstrated that REVLIMID is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1 or OATP2), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

In vitro, lenalidomide is a substrate, but is not an inhibitor of P-glycoprotein (P-gp).

7.1 Digoxin

When digoxin was co-administered with multiple doses of REVLIMID (10 mg/day) the digoxin C_{max} and $AUC_{0-\infty}$ were increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID.

7.2 Warfarin

Co-administration of multiple dose REVLIMID (10 mg) with single dose warfarin (25 mg) had no effect on the pharmacokinetics of total lenalidomide or R- and S-warfarin. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant REVLIMID administration. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

7.3 Concomitant Therapies That May Increase the Risk of Thrombosis

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone [*see Warnings and Precautions (5.4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [*see Boxed Warnings and Contraindications (4.1)*]

Risk Summary

REVLIMID can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy. REVLIMID is a thalidomide analogue.

Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants.

Lenalidomide caused thalidomide-type limb defects in monkey offspring. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID must be reported to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436.

Animal data

In an embryo-fetal developmental toxicity study in monkeys, teratogenicity, including thalidomide-like limb defects, occurred in offspring when pregnant monkeys received oral lenalidomide during organogenesis. Exposure (AUC) in monkeys at the lowest dose was 0.17 times the human exposure at the maximum recommended human dose (MRHD) of 25 mg. Similar studies in pregnant rabbits and rats at 20 times and 200 times the MRHD respectively, produced embryo lethality in rabbits and no adverse reproductive effects in rats.

In a pre- and post-natal development study in rats, animals received lenalidomide from organogenesis through lactation. The study revealed a few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg (approximately 200 times the human dose of 25 mg based on body surface area). The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gains during gestation when bred to male offspring. As with thalidomide, the rat model may not adequately address the full spectrum of potential human embryo-fetal developmental effects for lenalidomide.

8.3 Nursing mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from lenalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric use

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

8.5 Geriatric use

REVLIMID has been used in multiple myeloma (MM) clinical trials in patients up to 86 years of age.

Of the 703 MM patients who received study treatment in Studies 1 and 2, 45% were age 65 or over while 12% of patients were age 75 and over. The percentage of patients age 65 or over was not significantly different between the REVLIMID/dexamethasone and placebo/dexamethasone groups. Of the 353 patients who received REVLIMID/dexamethasone, 46% were age 65 and over. In both studies, patients > 65 years of age were more likely than patients ≤ 65 years of age to experience DVT, pulmonary embolism, atrial fibrillation, and renal failure following use of REVLIMID. No differences in efficacy were observed between patients over 65 years of age and younger patients.

REVLIMID has been used in del 5q MDS clinical trials in patients up to 95 years of age.

Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and over, while 33% were age 75 and over. Although the overall frequency of adverse events (100%) was the same in patients over 65 years of age as in younger patients, the frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (54% vs. 33%). A greater proportion of patients over 65 years of age discontinued from the clinical studies because of adverse events than the proportion of younger patients (27% vs.16%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

REVLIMID has been used in a mantle cell lymphoma (MCL) clinical trial in patients up to 83 years of age. Of the 134 patients with MCL enrolled in the MCL trial, 63% were age 65 and over, while 22% of patients were age 75 and over. The overall frequency of adverse events was similar in patients over 65 years of age and in younger patients (98% vs. 100%). The overall incidence of grade 3 and 4 adverse events was also similar in these 2 patient groups (79% vs. 78%, respectively). The frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (55% vs. 41%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function.

8.6 Females of Reproductive Potential and Males

REVLIMID can cause fetal harm when administered during pregnancy [*see Use in Specific Populations (8.1)*]. Females of reproductive potential must avoid pregnancy 4 weeks before therapy, while taking REVLIMID, during dose interruptions and for at least 4 weeks after completing therapy.

Females

Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control simultaneously (one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings or implants) or partner's vasectomy and one additional effective contraceptive method – male latex or synthetic condom, diaphragm or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

Females of reproductive potential must have 2 negative pregnancy tests before initiating REVLIMID. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. REVLIMID treatment must be discontinued during this evaluation.

Males

Lenalidomide is present in the semen of males who take REVLIMID. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID, during dose interruptions and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm

8.7 Renal Impairment

Since lenalidomide is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate (CLcr 30-60 mL/min) or severe renal impairment (CLcr < 30 mL/min) and in patients on dialysis [*see Dosage and Administration (2.4)*].

8.8 Hepatic Impairment

No dedicated study has been conducted in patients with hepatic impairment. The elimination of unchanged lenalidomide is predominantly by the renal route.

10 OVERDOSAGE

There is no specific experience in the management of lenalidomide overdose in patients; although in dose-ranging studies, some patients were exposed to up to 150 mg and in single-dose studies, some patients were exposed to up to 400 mg.

In studies, the dose-limiting toxicity was essentially hematological. In the event of overdose, supportive care is advised.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity studies with lenalidomide have not been conducted.

Lenalidomide was not mutagenic in the bacterial reverse mutation assay (Ames test) and did not induce chromosome aberrations in cultured human peripheral blood lymphocytes, or mutations at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells. Lenalidomide did not increase morphological transformation in Syrian Hamster Embryo assay or induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats.

A fertility and early embryonic development study in rats, with administration of lenalidomide up to 500 mg/kg (approximately 200 times the human dose of 25 mg, based on body surface area) produced no parental toxicity and no adverse effects on fertility.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient labeling (Medication Guide)

Embryo-Fetal Toxicity

Advise patients that REVLIMID is contraindicated in pregnancy [*see Contraindications (4.1)*]. REVLIMID is a thalidomide analog and can cause serious birth defects or death to a developing baby. [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

- Advise females of reproductive potential that they must avoid pregnancy while taking REVLIMID and for at least 4 weeks after completing therapy.
- Initiate REVLIMID treatment in females of reproductive potential only following a negative pregnancy test.
- Advise females of reproductive potential of the importance of monthly pregnancy tests and the need to use two different forms of contraception including at least one highly effective form simultaneously during REVLIMID therapy, during dose interruption and for 4 weeks after she has completely finished taking REVLIMID. Highly effective forms of contraception other than tubal ligation include IUD and hormonal (birth control pills, injections, patch or implants) and a partner's vasectomy. Additional effective contraceptive methods include latex or synthetic condom, diaphragm and cervical cap.
- Instruct patient to immediately stop taking REVLIMID and contact her doctor if she becomes pregnant while taking this drug, if she misses her menstrual period, or experiences unusual menstrual bleeding, if she stops taking birth control, or if she thinks FOR ANY REASON that she may be pregnant.
- Advise patient that if her doctor is not available, she can call 1-888-668-2528 for information on emergency contraception [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].
- Advise males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy.
- Advise male patients taking REVLIMID that they must not donate sperm [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].
- All patients must be instructed to not donate blood while taking REVLIMID, during dose interruptions and for 1 month following discontinuation of REVLIMID [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].

REVLIMID REMS™ program

Because of the risk of embryo-fetal toxicity, REVLIMID is only available through a restricted program called the REVLIMID REMS™ program **(formerly known as the "RevAssist®" program)** [*see Warnings and Precautions (5.2)*].

- Patients must sign a Patient-Prescriber agreement form and comply with the requirements to receive REVLIMID. In particular, females of reproductive potential must comply with the pregnancy testing, contraception requirements and participate in monthly telephone surveys. Males must comply with the contraception requirements [*see Use in Specific Populations (8.6)*].
- REVLIMID is available only from pharmacies that are certified in REVLIMID REMS™ program. Provide patients with the telephone number and website for information on how to obtain the product.

Hematologic Toxicity
Inform patients that REVLIMID is associated with significant neutropenia and thrombocytopenia [*see Boxed Warnings and Warnings and Precautions (5.3)*].

Venous Thromboembolism
Inform patients that REVLIMID/dexamethasone has demonstrated significant increased risk of DVT and PE in patients with multiple myeloma [see *Boxed Warnings and Warning and Precautions (5.4)*].

Increased Mortality in Patients with CLL
Inform patients that REVLIMID had increased mortality in patients with CLL and serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure [*see Warning and Precautions (5.5)*].

Second Primary Malignancies
Inform patients of the potential risk of developing second primary malignancies during treatment with REVLIMID.

Hepatotoxicity
Inform patients of the risk of hepatotoxicity, including hepatic failure and death, and to report any signs and symptoms associated with this event to their healthcare provider for evaluation.

Allergic Reactions
Inform patients of the potential for allergic reactions including hypersensitivity, angioedema, Stevens Johnsons Syndrome, or toxic epidermal necrolysis if they had such a reaction to THALOMID and report symptoms associated with these events to their healthcare provider for evaluation.

Tumor Lysis Syndrome
Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation.

Tumor Flare Reaction
Inform patients of the potential risk of tumor flare reaction and to report any signs and symptoms associated with this event to their healthcare provider for evaluation.

Dosing Instructions
Inform patients to take REVLIMID once daily at about the same time each day, either with or without food. The capsules should not be opened, broken, or chewed. REVLIMID should be swallowed whole with water.

Instruct patients that if they miss a dose of REVLIMID, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take REVLIMID at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

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EDITORIAL

James V. Felicetta, MD, *Editor-in-Chief*

Did Niacin Get a Bum Rap?

I had thought that my long-standing romance with niacin was finally over. Although it was a very early love of mine, reluctantly I had gone along with the mainstream consensus. It seemed that niacin had been sent into near-permanent pharmaceutical exile by the devastating one-two punches of the AIM HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) and the HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) studies. I had even stopped taking my own self-prescribed niacin 2,500 mg twice a day, which I had been religiously consuming for over 2 decades. But before long, I found that I had real difficulty divorcing myself completely from the charms of this lipid-lowering Lorelei. Now, after agonizing over the issue for some time, I'm here to tell you that niacin almost certainly did get a bum rap and should be restored as an important tool in your therapeutic armamentarium.

A recent report that niacin seems to function partially as an inhibitor of the PCSK-9 enzyme accelerated my reconsideration. The inhibition of PCSK-9, an enzyme that removes low-density lipoprotein cholesterol (LDL-C) receptors from hepatocytes, is the hot new way of dropping LDL-C levels. And I mean *really* dropping LDL-C levels. Studies conducted with investigational compounds developed by Amgen and Pfizer have shown truly dramatic drops in LDL-C levels by as much as 80%—often down to ridiculously low levels (around 25 mg/dL).

Of course, we are still waiting for outcome trials, which will answer the critical question: Are these dramatic falls in LDL-C levels actually associated with meaningful reductions in the occurrence rates for cardiovascular events such as myocardial infarction and stroke? For now, inhibiting PCSK-9 seems to be a good way to change the lipid profile dramatically. Even if niacin is not nearly as potent an inhibitor of the PCSK-9 enzymes as some newer compounds, the fact that it has measurable inhibiting activity seems enough to earn it a second look.

The concerns over niacin derive almost entirely from the results of the AIM HIGH study and the HPS2-THRIVE trials. Thus, any effort to rehabilitate niacin will require a reckoning with each of these major trials.

I was one of the original AIM HIGH investigators, but our study site at the Phoenix VA eventually was removed from the trial because of poor enrollment. Nonetheless, I had a front-row seat to observe the conduct of the trial, and it seemed less than optimal. The relatively infrequent monitor visits for this study probably contributed to the finding that the lipid differences between the 2 study groups were considerably smaller than they could have been. It was my impression that study sites did not have their feet held to the fire when niacin compliance became problematic for subjects randomized to the larger dose of niacin.

The study design also contributed to blunting the difference between the 2 study groups. Subjects in the control group actually received 200 mg of immediate-release niacin to help blind the study by ensuring that all subjects experienced a niacin flush. The statin dose wound up being higher in the control group, and the use of the add-on lipid-lowering agent ezetimibe was also greater (22% vs 10%) in the control group. All these factors would tend to blunt the differences between the 2 groups, and indeed lipid levels did improve significantly in both groups.

To add insult to injury, the trial was stopped after just 3 years. A number of other lipid trials that were ultimately positive had not yet reached a statistically significant separation between the control and the experimental groups after that relatively brief study interval. Although these study flaws are hardly fatal, when taken together, they suggest the need to maintain an open mind. If niacin is like Brylcreem and "a little dab'll do ya," then the small dusting received by the control subjects might have been cardioprotective enough to blunt any differences in event rates between the 2 groups, especially over the truncated period of the actual trial.

What about the much larger HPS2-THRIVE study; surely there can't be similar flaws in that study as well? Well, a critical review identifies a number of significant shortcomings. Although conducted by British academics through the Medical Research Council, the trial was funded and largely designed by Merck, which had hoped it would demonstrate the clinical utility of its new combination of extended-release niacin and an anti-flushing agent called laropiprant, a prostaglandin-inhibiting compound. One has only to remember the fiasco with the cyclo-oxygenase-2 inhibitor celecoxib to recognize the potential

increase in cardiovascular events of any agent that blocks prostaglandins. Any failure of the niacin/laropiprant arm to show a reduced cardiovascular event rate on top of baseline statin therapy might have been because the laropiprant was increasing events enough to cancel any reductions the niacin might have produced.

A fair trial of the potential effectiveness of a niacin preparation on top of statin therapy should test niacin in a clinical setting in which it is typically prescribed. I'm not going far out on a limb by asserting that the majority of niacin prescriptions are written for patients who have low levels of high-density lipoprotein cholesterol (HDL-C), typically < 40 mg/dL but often much lower than that. Yet the mean HDL-C in the HPS2-THRIVE study was a robust 44 mg/dL, and the mean LDL-C level was a well-controlled 63 mg/dL. The subjects who were randomized to receive either placebo or niacin/laropiprant on top of their preexisting statin therapy were simply not the typical patients who would normally be started on niacin.

The supposedly airtight case against niacin isn't really so strong after all. Where does this leave us? Let's not forget that there is a sizable population of individuals who cannot or will not take statins. Surely these individuals would be better off on niacin therapy than on no therapy, particularly if they have a combination of low HDL-C levels, elevated triglyceride levels, and elevated LDL-C levels.

I currently prescribe this combination in patients who have persistently elevated triglyceride levels even after their statins have been maxed out, because I believe that lowering triglycerides in such patients may well translate into lower cardiovascular risk. Some recent evidence suggests that the epidemiologic association of low HDL-C levels with cardiovascular events may not be due so much to the low HDL-C levels per se, but rather to the very frequent association of elevated triglyceride levels—the true culprit, with low HDL-C levels. So if you have a need to lower either triglyceride levels or LDL-C levels in a patient already taking as much statin as they can tolerate, niacin would be a very reasonable drug to consider. My romance with niacin has been rekindled, and perhaps you'll want to give it a second look as well. ●

Author disclosures

The author reports no actual or potential conflicts of interest with regard to this article.

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The Cost of Unused Medications

Jennifer L. Schuh, PharmD, BCPS, BCPP, CGP; and Andrew J. Hewuse, CPhT

This quality improvement project evaluated the cost of patient medication returns and explores additional sources of waste in the prescribing and dispensing processes at a military community hospital.

Studies analyzing the causes of and patterns associated with polypharmacy have increased over the past decade.[1-3] Disadvantages to polypharmacy include but are not limited to higher risk of drug-drug interactions, greater potential for adverse effects (AEs), higher risk of nonadherence, and higher costs for the patient and health care systems.[1] Compounding the disadvantages associated with polypharmacy, medication storage and disposal are areas of environmental concern. A recent study by Wieczorkiewicz and colleagues examined how patients use, store, and dispose of medications and found that "almost all respondents had excess and leftover medications in their homes."[4] The authors concluded that both overprescribing and poor medication adherence contribute to excess medications at home.

As health care systems become more fiscally responsible, it is beneficial to review prescribing and dispensing patterns, which contribute to polypharmacy and excess medications in patient homes. One of the specific areas that came to the attention of the authors was the number of medication returns received at Evans Army Community Hospital (EACH). As Wiesczorkiewicz and colleagues discovered, it is common that medicine cabinets are filled with expired drugs or medications no longer in use. Although some of these medications can be disposed of in the trash or toilets, some facilities take back unused drugs.[5]

In an attempt to keep patients and the environment safe, EACH takes back unused medications daily for destruction. These patient returns must be destroyed for both legal and ethical reasons, because there is the potential that medications that have left the system may have been adulterated. The purpose of this quality improvement (QI) project was to evaluate the cost of patient medication returns and explore any additional sources of waste in the prescribing and dispensing processes.

METHODS

As a QI project assessing current prescribing and dispensing processes and improving patient-centered performance, Institutional Review Board approval was not required. The QI project and manuscript submission did receive approval from the EACH Command Team. Patient prescription returns were collected at the main and outlying hospital pharmacies between December 16, 2012, and April 5, 2013. Patients were encouraged to bring all medications to clinic visits, and if it was determined that the patient was no longer taking the medication or that the medication was discontinued, the clinician would bring the medication(s) to the patient return collection bin for destruction.

Patients also presented medications no longer used to the pharmacy for the patient return collection bin. A pharmacy technician recorded the medication name, strength, original amount prescribed, and the number of tablets/capsules remaining in the vial. Quantities dispensed greater than the quantities prescribed were later segregated for additional analysis. The brand name of the product was recorded only when the brand name was dispensed. The cost per unit was obtained from the pharmaceutical distributor and recorded to quantify the total cost of each prescription and the total cost of the medications returned. Medications that were classified as hazardous waste were assessed, as were all other medications, and then were segregated to the hospital's satellite accumulation point for disposal by the Directorate of Public Works Environmental Division. Partial creams and ointments were excluded from the analysis, because the total amount returned was not easily quantifiable.

RESULTS

The total value of the medications collected from December 16, 2012,

Dr. Schuh was a clinical medication safety pharmacist at the time of the manuscript submission, and **Mr. Hewuse** is currently a pharmacy technician, both at Evans Army Community Hospital in Fort Carson, Colorado.

through April 5, 2013, was $63,183 (1,174 prescriptions). Furthermore, there was the cost of the vials; printer ink; labels; labor to pay pharmacists to process, check, and dispense the medications; and the time of technician staff to fill the prescriptions and later sort the medications to look for hazardous waste and controlled substances. These additional expenses were not quantified and therefore were not included in the aforementioned value.

A subanalysis was conducted after it was observed that several prescriptions had greater quantities dispensed than the quantity prescribed (Table). An excess of $102.41 was dispensed and later collected during the study period. Of the 26 prescriptions that were overfilled, 10 were not due to human error but were intentionally overfilled as evidenced by sealed manufacturer bottles; the cost of the medications overfilled for these 10 prescriptions was $70.26.

The top returned drugs in descending order were lisinopril (42), bupropion (32), prazosin (28), gabapentin (27), and ondansetron (26). The top classifications of medications returned in descending order were antidepressants (198), antihypertensives (185), anticonvulsants (61), antilipemics (60), antibiotics (57), and antipsychotics (57). Also noteworthy is that a total of 91 prescriptions (7.8%) for over-the-counter (OTC) products were returned.

DISCUSSION

As suggested by Wieczorkiewicz and colleagues, prescribing and dispensing patterns may be contributing to the accumulation of unwanted and unused medications.[4] Patient feedback would also give insight to this problem. Furthermore, the data highlighted improvement opportunities related to back order/shortage and high-dollar medications. Additional exploration into prescribing, dispensing, and consumer patterns as well as potential cost-saving strategies addressing the aforementioned processes is warranted.

Prescribing Patterns

An editorial by Ruef addressed overprescribing patterns and hypothesized that prescribers may be more cautious and prescribe antibiotics (without laboratory confirmation), because if medications are not prescribed, patients with a potentially serious, quickly developing infection may experience an adverse outcome.[6] Additionally, there is the anticipation and pressure from patients to receive a medication. Although only 60 of the 1,174 prescriptions were antibiotics or antifungals, one could easily insert other indications into this rationale.

During the collection period, the problem of polypharmacy stemming from the emergency department (ED), independent of this QI project, was brought to the authors' attention. Consequently, data were collected from patients who presented for what was perceived (by both the patient and the pharmacy) as a high number of prescriptions from the ED. The data were reviewed and analyzed to determine whether there were any correlations between perceived excessive prescribing and the patient medication return data.

This study found that of 54 patient visits, there were a total of 324 prescriptions with a median of 6 prescriptions per person. The majority (56%) of these prescriptions were for OTC medications. The top 5 medications prescribed were ibuprofen, acetaminophen, ondansetron, oxymetazoline, and pseudoephedrine; 4 of which are OTC medications. The top 5 classifications of medications were decongestants, nonsteroidal anti-inflammatory drugs, analgesics, antibiotics, and antiemetics.

In contrast to the patient return data with 5 of the 6 top medications

prescribed for chronic conditions, it is no surprise that the top 5 ED medications were prescribed for acute conditions. Ondansetron, which costs up to $0.37 per tablet, was one of the top prescribed medications from the ED and one of the most frequently returned medications. One might question whether this was a misuse of ED resources, considering patients were seen in this costly setting and received OTC medications. Further study of misappropriation of resources in the ED and trends from other clinic areas are needed.

Dispensing Patterns

In addition, it was observed that the pharmacy was overfilling prescriptions. Inaccurate quantities dispensed may have been due to human error and also due to staff belief that it would cost more (in staff time) to count the exact quantity prescribed for medications supplied in a manufacturer bottle near the amount needed for the prescription. It has been noted by pharmacy staff that deviation from exact counts is only done with medications that do not have a significant cost per tablet or capsule. The cost of medications intentionally overfilled was $70.26—not an insignificant source of waste.

Medications returned to stock (because patients never picked up the prescription) were not used for future prescriptions but rather placed in the patient return collection for destruction. After this practice was noted, these returned-to-stock products were segregated to evaluate the value of the medications that could have been used for future prescriptions. Seventy-six prescriptions could have been dispensed, and the value of these unused medications was $3,049. Whereas civilian retail settings would not allow the practice of destroying medications that can otherwise be dispensed, this practice was permitted at EACH.

Consumer Patterns

It was hypothesized in this study that patients were returning medications because the prescriber switched the medication, the patient ultimately did not need the medication because symptoms resolved on their own, the patient may have had an AE or tolerance issues, the patient died, the dose was adjusted, or the patient had duplicate prescriptions. Further exploration regarding patients' perspectives should be considered.

Back Orders and Shortages

Similar to many other institutions across the country, EACH has been affected by drug product shortages. There are a number of contributing factors to these shortages, including raw and bulk material unavailability, manufacturer difficulties and regulatory issues, voluntary recalls, change in product formulation or manufacturer, unexpected increases in demand, and shifts in clinical practice.[7]

An example of a recently recalled medication is atorvastatin. Historical data indicate that EACH paid $0.08 per tablet ($6.77 for a 90-day supply). After the generic manufacturer recalled atorvastatin, the brand-name product needed to be ordered, which cost $1.93 per tablet (or $173.70 for a 90-day supply). During the study, 370 atorvastatin tablets were returned, 90 of which were the brand-name tablets. It was unfortunate that this quantity was dispensed, considering these tablets were destroyed. If it is possible to limit quantities dispensed on manufacturer recall/back order products until the price is more reasonable, without a significant disruption in patient care, pharmacies may consider policy changes.

High-Dollar Medications

Although the cost of a number of generic medications may be negligible, a number of medications continue to have a significant associated cost. Of the prescriptions returned, 170 cost > $100. Of these, 16 prescriptions cost > $500, and the total was > $13,000.

The U.S. Air Force had a high dollar program, in which patients were limited to a 30-day supply if the 30-day supply cost > $500 for treatment of a chronic condition. The staff burden and difficulty of maintaining such a program is unknown; however, the program is thought-provoking. Specifically, instead of dispensing 90-day supplies, the facility might consider limiting expensive prescriptions to ≤ 30 days for medications with additional refills if needed. Quantity limitations are already implemented for medications such as sildenafil, migraine medications, and opioids.

There is clearly a financial burden that needs to be addressed, and as this study evaluated the waste involved in patient returns, additional sources of waste were illuminated. Lean Six Sigma highlights several forms of waste: transportation, inventory, motion, waiting, overprocessing, overproduction, and defects/errors.[8,9] This study found that there were several forms of waste in the prescribing and dispensing processes. Specifically, the authors found inventory mismanagement, overprocessing (overprescribing), overproduction (dispensing more than prescribed), possible misuse of costly resources, and defects/errors.

LIMITATIONS

The results of this QI project were limited to unused medications that patients returned to the facility. Returning unused medications is neither requested nor mandatory. Therefore, it is estimated that the

Table. The Cost of Overfilled Medications Collected Between December 16, 2012, and April 5, 2013[a,b]

Drug	Quantity Dispensed	Quantity Prescribed	$/tablet	Total Cost, $	Extra Tablets Dispensed	Cost of Extra Medication, $
Metformin ER 500 mg	200	180	0.0487	9.74	20	0.97
Metformin ER 500 mg	100	90	0.0487	4.87	10	0.49
Skelaxin 800 mg	100	90	2.374	237.40	10	23.74
Skelaxin 800 mg	100	90	2.374	237.40	10	23.74
Lithobid ER 300 mg	100	90	1.0716	107.16	10	10.72
Alfuzosin ER 10 mg	100	90	0.473	47.30	10	4.73
Felodipine ER 5 mg	100	90	0.232	23.20	10	2.32
Klor-Con ER 10 mEq	100	90	0.17549	17.55	10	1.75
Chlorpromazine 25 mg	100	90	0.1395	13.95	10	1.40
Lisinopril 2.5 mg	100	90	0.04	4.00	10	0.40
Seroquel 50 mg	34	30	0.975	33.15	4	3.90
Amlodipine 2.5 mg	93	90	0.008	0.74	3	2.22
Valtrex 500 mg	33	30	4.688	154.70	3	14.06
Nexium 40 mg	63	60	0.404	25.45	3	1.21
Cephalexin 500 mg	17	15	0.094	1.60	2	0.19
Keppra 250 mg	182	180	1.47	267.54	2	2.94
Lisinopril 5 mg	92	90	0.0126	1.16	2	0.03
Mirtazapine 15 mg	92	90	0.497	45.72	2	0.99
Pramipexole 0.5 mg	62	60	0.85	52.70	2	1.70
Sertraline 50 mg	32	30	0.175	5.60	2	0.35
Sertraline 50 mg	32	30	0.175	5.60	2	0.35
Lisinopril 10 mg	31	30	0.0946	2.93	1	0.09
Lisinopril/HCTZ 20/25 mg	91	90	0.06	5.46	1	0.06
Mirtazapine 15 mg	31	30	0.497	15.41	1	0.50
Ondansetron 4 mg	16	15	0.258	4.13	1	0.26
Olanzapine 20 mg	8	7	3.296	26.37	1	3.30

Abbreviations: ER, extended release; HCTZ, hydrochlorothiazide.
[a]Each table row represents a unique returned prescription.
[b]Brand name used when brand name was dispensed.

true amount of unused medications that could be returned for destruction is vastly greater than the brief collection obtained in this data set. Furthermore, this collection is only a snapshot at one military treatment facility. With multiple facilities within the DoD, the total amount and value of unused medications is likely to be immensely greater than the $63,000 collected in this study.

Additionally, the cost to discard hazardous waste medications was not quantified. Evans Army Community Hospital pays $1.95 per lb for disposal of hazardous waste medications (eg, fluticasone/salmeterol, albuterol,

warfarin, insulins), but this financial burden was not addressed in this QI project.

RECOMMENDATIONS

There are a number of behaviors that could be addressed to reduce the waste observed in this study:

- Prescribers should reevaluate prescribing habits to assess whether they are overprescribing medications. They may consider asking the patient whether they plan to take the medication prior to writing the prescription. If the patient is not agreeable to the treatment plan, then the treatment plan may need to be reevaluated.
- Facilities may consider a policy that allows no more than a 30-day supply for new medication prescriptions. Patients should have a follow-up to determine whether the treatment is effective or whether there are AEs, and a new maintenance prescription may be written at that time.
- Pharmacies should ensure that pharmacists fill the quantity prescribed. Prescriptions that have overfills in quantities are considered misbranded.
- Pharmacies should enforce policies for returning to stock the prescriptions that were prepared but never dispensed to patients.
- For medications that are on back order or in short supply, prescribers should consider changing the quantity dispensed to a 30-day supply (or less as appropriate) with refills.
- Pharmacies should consider limiting quantities of high-dollar medications and adding refills for any additional therapy needed.
- Hospitals should evaluate patient use of emergency resources. Other local health treatment facilities outline clearly for patients what constitutes an emergency and what does not. A similar policy change should be considered at EACH.

SUMMARY

Polypharmacy is an increasing problem in today's medical field. Consequently, unwanted and unused medications accumulate in patients' homes. In an attempt to keep patients and the environment safe, EACH takes back unused medications every day for destruction. During the collection period of patient returns from December 16, 2012, through April 5, 2013, > $63,000 of unused medications were returned for destruction, which did not include the cost of labor or additional supplies. These data illuminated possible prescribing and dispensing patterns contributing to this waste and inspired further exploration of additional sources of waste, such as overprocessing, overproduction, inventory mismanagement, misuse of resources, and defects/errors. This study highlighted a number of strategies that, if implemented, may significantly reduce the deficit burden and reduce costs associated with polypharmacy.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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Abraxane®
for Injectable Suspension

(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

ignited we stand with 3 indications

MBC

ABRAXANE is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

NSCLC

ABRAXANE is indicated for the first-line treatment of locally advanced or metastatic non–small cell lung cancer (NSCLC), in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

MPAC

ABRAXANE is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas (MPAC), in combination with gemcitabine.

Important Safety Information

WARNING - NEUTROPENIA

- **Do not administer ABRAXANE therapy to patients who have baseline neutrophil counts of less than 1500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE**
- **Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS**

CONTRAINDICATIONS

Neutrophil Counts

- ABRAXANE should not be used in patients who have baseline neutrophil counts of <1500 cells/mm^3

Hypersensitivity

- Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug

WARNINGS AND PRECAUTIONS

Hematologic Effects

- Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of ABRAXANE. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC), 47% of patients with non–small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer

Please see additional Important Safety Information and Brief Summary for ABRAXANE, including Boxed WARNING, on following pages.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Monitor for myelotoxicity by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC) and Days 1, 8, and 15 (for NSCLC and for pancreatic cancer)
- Do not administer ABRAXANE to patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/mm^3
- In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of ABRAXANE therapy, reduce the dose of ABRAXANE in subsequent courses in patients with either MBC or NSCLC
- In patients with MBC, resume treatment with every-3-week cycles of ABRAXANE after ANC recovers to a level >1500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3
- In patients with NSCLC, resume treatment if recommended at permanently reduced doses for both weekly ABRAXANE and every-3-week carboplatin after ANC recovers to at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an ANC of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle
- In patients with adenocarcinoma of the pancreas, withhold ABRAXANE and gemcitabine if the ANC is less than 500 cells/mm^3 or platelets are less than 50,000 cells/mm^3 and delay initiation of the next cycle if the ANC is less than 1500 cells/mm^3 or platelet count is less than 100,000 cells/mm^3 on Day 1 of the cycle. Resume treatment with appropriate dose reduction if recommended

Nervous System

- Sensory neuropathy is dose- and schedule-dependent
- The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification
- If ≥ Grade 3 sensory neuropathy develops, withhold ABRAXANE treatment until resolution to Grade 1 or 2 for MBC or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses of ABRAXANE

Sepsis

- Sepsis occurred in 5% of patients with or without neutropenia who received ABRAXANE in combination with gemcitabine
- Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis
- If a patient becomes febrile (regardless of ANC), initiate treatment with broad-spectrum antibiotics
- For febrile neutropenia, interrupt ABRAXANE and gemcitabine until fever resolves and ANC ≥1500 cells/mm^3, then resume treatment at reduced dose levels

Pneumonitis

- Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving ABRAXANE in combination with gemcitabine
- Monitor patients for signs and symptoms and interrupt ABRAXANE and gemcitabine during evaluation of suspected pneumonitis
- Permanently discontinue treatment with ABRAXANE and gemcitabine upon making a diagnosis of pneumonitis

Hypersensitivity

- Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported
- Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with this drug

Hepatic Impairment

- Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of ABRAXANE in patients with hepatic impairment should be performed with caution
- For MBC and NSCLC, the starting dose should be reduced for patients with moderate or severe hepatic impairment
- For pancreatic adenocarcinoma, ABRAXANE is not recommended for patients with moderate or severe hepatic impairment

Albumin (Human)

- ABRAXANE contains albumin (human), a derivative of human blood

Use in Pregnancy: Pregnancy Category D

- ABRAXANE can cause fetal harm when administered to a pregnant woman
- If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus
- Women of childbearing potential should be advised to avoid becoming pregnant while receiving ABRAXANE

Use in Men

- Men should be advised not to father a child while receiving ABRAXANE

ADVERSE REACTIONS

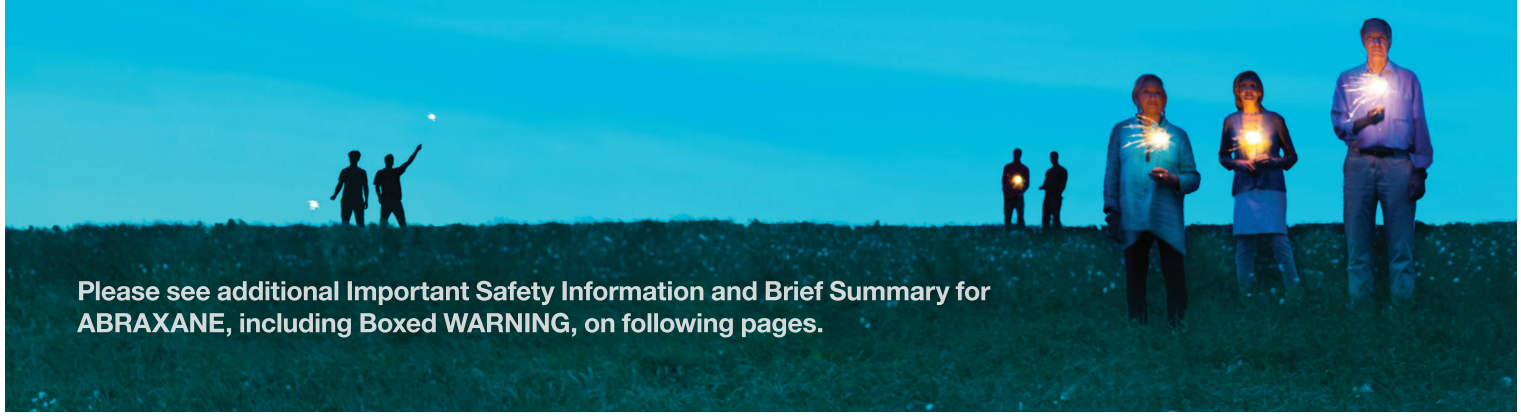
Randomized Metastatic Breast Cancer (MBC) Study

- The most common adverse reactions (≥20%) with single-agent use of ABRAXANE vs paclitaxel injection in the MBC study are alopecia (90%, 94%), neutropenia (all cases 80%, 82%; severe 9%, 22%), sensory neuropathy (any symptoms 71%, 56%; severe 10%, 2%), abnormal ECG (all patients 60%, 52%; patients with normal baseline 35%, 30%), fatigue/asthenia (any 47%, 39%; severe 8%, 3%), myalgia/arthralgia (any 44%, 49%; severe 8%, 4%), AST elevation (any 39%, 32%), alkaline phosphatase elevation (any 36%, 31%), anemia (any 33%, 25%; severe 1%, <1%), nausea (any 30%, 22%; severe 3%, <1%), diarrhea (any 27%, 15%; severe <1%, 1%) and infections (24%, 20%), respectively
- Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients
- Other adverse reactions of note with the use of ABRAXANE vs paclitaxel injection included vomiting (any 18%, 10%; severe 4%, 1%), fluid retention (any 10%, 8%; severe 0%, <1%), mucositis (any 7%, 6%; severe <1%, 0%), hepatic dysfunction (elevations in bilirubin 7%, 7%), hypersensitivity reactions (any 4%, 12%; severe 0%, 2%), thrombocytopenia (any 2%, 3%; severe <1%, <1%), neutropenic sepsis (<1%, <1%), and injection site reactions (<1%, 1%), respectively. Dehydration and pyrexia were also reported
- Renal dysfunction (any 11%, severe 1%) was reported in patients treated with ABRAXANE (n=229)
- In all ABRAXANE-treated patients (n=366), ocular/visual disturbances were reported (any 13%; severe 1%)
- Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients and included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension
- Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported

Please see next page for adverse events in the NSCLC study.

Pancreatic Adenocarcinoma Study

- Among the most common (≥20%) adverse reactions in the phase III study, those with a ≥5% higher incidence in the ABRAXANE/gemcitabine group compared with the gemcitabine group are neutropenia (73%, 58%), fatigue (59%, 46%), peripheral neuropathy (54%, 13%), nausea (54%, 48%), alopecia (50%, 5%), peripheral edema (46%, 30%), diarrhea (44%, 24%), pyrexia (41%, 28%), vomiting (36%, 28%), decreased appetite (36%, 26%), rash (30%, 11%), and dehydration (21%, 11%)
- Of these most common adverse reactions, those with a ≥2% higher incidence of Grade 3-4 toxicity in the ABRAXANE/gemcitabine group compared with the gemcitabine group, respectively, are neutropenia (38%, 27%), fatigue (18%, 9%), peripheral neuropathy (17%, 1%), nausea (6%, 3%), diarrhea (6%, 1%), pyrexia (3%, 1%), vomiting (6%, 4%), decreased appetite (5%, 2%), and dehydration (7%, 2%)
- Thrombocytopenia (all grades) was reported in 74% of patients in the ABRAXANE/gemcitabine group vs 70% of patients in the gemcitabine group



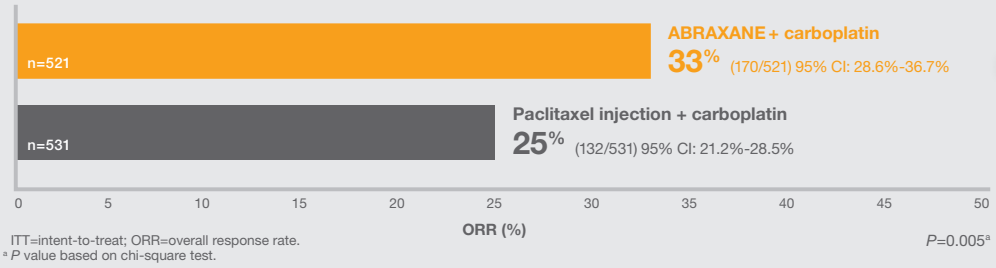
Please see additional Important Safety Information and Brief Summary for ABRAXANE, including Boxed WARNING, on following pages.

ABRAXANE® is indicated for the first-line treatment of locally advanced or metastatic non–small cell lung cancer (NSCLC), in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

Abraxane®
for Injectable Suspension
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

significantly superior ORR in first-line ITT population with advanced NSCLC

Primary end point: First-line ABRAXANE + carboplatin significantly improved ORR in the phase 3 NSCLC trial (ITT population)



ITT=intent-to-treat; ORR=overall response rate.
[a] *P* value based on chi-square test.

There was no statistically significant difference in overall survival between the 2 study arms.

CATEGORY 1

A National Comprehensive Cancer Network® (NCCN®) Category 1 recommendation[1,2,b,c]

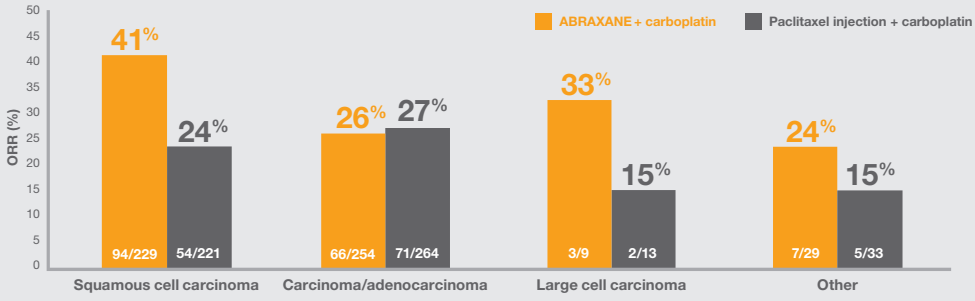
[b] First-line albumin-bound paclitaxel (ABRAXANE) + carboplatin is recommended for PS 0-1 patients with advanced NSCLC of negative or unknown *EGFR* mutation and *ALK* status.

[c] Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

ALK=anaplastic lymphoma kinase; *EGFR*=epidermal growth factor receptor; PS=performance status.

41% ORR in squamous patients

ORR by histology in the phase 3 NSCLC trial



STUDY DESIGN

- Multicenter 1:1 randomized, phase 3 study comparing ABRAXANE (100 mg/m² IV; Days 1, 8, and 15 of each 21-day cycle) + carboplatin (AUC=6 mg•min/mL IV, Day 1 of each 21-day cycle) with paclitaxel injection (200 mg/m² IV, Day 1 of each 21-day cycle) + carboplatin (AUC=6 mg•min/mL IV, Day 1 of each 21-day cycle) in 1052 chemonaïve patients with advanced NSCLC

Adverse events in the NSCLC study

- The most common adverse reactions (≥20%) of ABRAXANE in combination with carboplatin are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue
- The most common serious adverse reactions of ABRAXANE in combination with carboplatin for NSCLC are anemia (4%) and pneumonia (3%)
- The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%)
- The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (24%), thrombocytopenia (13%), and anemia (6%)
- The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%)
- The following common (≥10% incidence) adverse reactions were observed at a similar incidence in ABRAXANE plus carboplatin–treated and paclitaxel injection plus carboplatin–treated patients: alopecia (56%), nausea (27%), fatigue (25%), decreased appetite (17%), asthenia (16%), constipation (16%), diarrhea (15%), vomiting (12%), dyspnea (12%), and rash (10%); incidence rates are for the ABRAXANE plus carboplatin treatment group
- Adverse reactions with a difference of ≥2%, Grade 3 or higher, with combination use of ABRAXANE and carboplatin vs combination use of paclitaxel injection and carboplatin in NSCLC are anemia (28%, 7%), neutropenia (47%, 58%), thrombocytopenia (18%, 9%), and peripheral neuropathy (3%, 12%), respectively
- Adverse reactions with a difference of ≥5%, Grades 1-4, with combination use of ABRAXANE and carboplatin vs combination use of paclitaxel injection and carboplatin in NSCLC are anemia (98%, 91%), thrombocytopenia (68%, 55%), peripheral neuropathy (48%, 64%), edema peripheral (10%, 4%), epistaxis (7%, 2%), arthralgia (13%, 25%), and myalgia (10%, 19%), respectively
- Neutropenia (all grades) was reported in 85% of patients who received ABRAXANE and carboplatin vs 83% of patients who received paclitaxel injection and carboplatin

Important Safety Information (cont'd)

ADVERSE REACTIONS (cont'd)

- The most common serious adverse reactions of ABRAXANE (with a ≥1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%), and vomiting (4%)
- The most common adverse reactions resulting in permanent discontinuation of ABRAXANE were peripheral neuropathy (8%), fatigue (4%), and thrombocytopenia (2%)
- The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (10%) and peripheral neuropathy (6%)
- The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%), and diarrhea (5%)
- Other selected adverse reactions with a ≥5% higher incidence for all-grade toxicity in the ABRAXANE/gemcitabine group compared to the gemcitabine group, respectively, are asthenia (19%, 13%), mucositis (10%, 4%), dysgeusia (16%, 8%), headache (14%, 9%), hypokalemia (12%, 7%), cough (17%, 7%), epistaxis (15%, 3%), urinary tract infection (11%, 5%), pain in extremity (11%, 6%), arthralgia (11%, 3%), myalgia (10%, 4%), and depression (12%, 6%)
- Other selected adverse reactions with a ≥2% higher incidence for Grade 3-4 toxicity in the ABRAXANE/gemcitabine group compared to the gemcitabine group are thrombocytopenia (13%, 9%), asthenia (7%, 4%), and hypokalemia (4%, 1%)

Postmarketing Experience With ABRAXANE and Other Paclitaxel Formulations

- Severe and sometimes fatal hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied
- There have been reports of congestive heart failure, left ventricular dysfunction and atrioventricular block with ABRAXANE, primarily among individuals with underlying cardiac history or prior exposure to cardiotoxic drugs
- There have been reports of extravasation of ABRAXANE. Given the possibility of extravasation, it is advisable to monitor closely the ABRAXANE infusion site for possible infiltration during drug administration

DRUG INTERACTIONS

- Caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4

USE IN SPECIFIC POPULATIONS

Nursing Mothers

- It is not known whether paclitaxel is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

Pediatric

- The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated

Geriatric

- No toxicities occurred notably more frequently among patients ≥65 years of age who received ABRAXANE for MBC
- Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients ≥65 years of age treated with ABRAXANE and carboplatin in NSCLC
- Diarrhea, decreased appetite, dehydration, and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old who received ABRAXANE and gemcitabine in adenocarcinoma of the pancreas

Renal Impairment

- The use of ABRAXANE has not been studied in patients with renal impairment

DOSAGE AND ADMINISTRATION

- For MBC and NSCLC, dose adjustment is recommended for patients with moderate and severe hepatic impairment. Withhold ABRAXANE if AST >10 x ULN or if bilirubin >5 x ULN
- For adenocarcinoma of the pancreas, withhold ABRAXANE if bilirubin ≥1.26 x ULN or if AST >10 x ULN
- Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicity
- Monitor patients closely

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.3.2014. © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed April 16, 2014. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc. **2.** Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®): Non-Small Cell Lung Cancer V.3.2014. © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed April 16, 2014. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Please see Brief Summary for ABRAXANE, including Boxed WARNING, on following pages.

For more information, please visit www.abraxane.com.

Celgene

Abraxane®
for Injectable Suspension
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

ABRAXANE® for Injectable Suspension
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

WARNING: NEUTROPENIA

- **Do not administer ABRAXANE therapy to patients who have baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE *[see Contraindications (4), Warnings and Precautions (5.1) and Adverse Reactions (6.1, 6.2, 6.3)]*.**
- **Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.**

1 INDICATIONS AND USAGE

1.1 Metastatic Breast Cancer

ABRAXANE is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

1.2 Non-Small Cell Lung Cancer

ABRAXANE is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

1.3 Adenocarcinoma of the Pancreas

ABRAXANE is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

2 DOSAGE AND ADMINISTRATION

2.1 Metastatic Breast Cancer

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

2.2 Non-Small Cell Lung Cancer

The recommended dose of ABRAXANE is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. Administer carboplatin on Day 1 of each 21 day cycle immediately after ABRAXANE *[see Clinical Studies (14.2)]*.

2.3 Adenocarcinoma of the Pancreas

The recommended dose of ABRAXANE is 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle. Administer gemcitabine immediately after ABRAXANE on Days 1, 8 and 15 of each 28-day cycle *[see Clinical Studies (14.3)]*.

2.4 Dosage in Patients with Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate and severe hepatic impairment treated with ABRAXANE may be at increased risk of toxicities known to paclitaxel. Withhold ABRAXANE if AST >10 x ULN or bilirubin > 5 x ULN. Recommendations for dosage adjustment for the first course of therapy are shown in Table 1.

For metastatic breast cancer, the dose of ABRAXANE can be increased from 130 mg/m^2 up to 200 mg/m^2 in patients with severe hepatic impairment in subsequent cycles based on individual tolerance.

For non-small cell lung cancer, reduce the dose of ABRAXANE to 50 mg/m^2 in patients with severe hepatic impairment. In subsequent cycles, the dose of ABRAXANE may be increased to 75 mg/m^2 as tolerated.

Monitor patients closely *[see Warnings and Precautions (5.6), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Table 1: Recommendations for Starting Dose in Patients with Hepatic Impairment

	SGOT (AST) Levels		Bilirubin Levels	ABRAXANE Dose[a]		
				MBC	NSCLC[c]	Pancreatic[c] Adenocarcinoma
Mild	< 10 x ULN	AND	> ULN to ≤ 1.25 x ULN	260 mg/m^2	100 mg/m^2	125 mg/m^2
Moderate	< 10 x ULN	AND	1.26 to 2 x ULN	200 mg/m^2	75 mg/m^2	not recommended
Severe	< 10 x ULN	AND	2.01 to 5 x ULN	130 mg/m^2 [b]	50 mg/m^2	not recommended
	> 10 x ULN	OR	> 5 x ULN	not recommended	not recommended	not recommended

MBC = Metastatic Breast Cancer; NSCLC = Non-Small Cell Lung Cancer.

[a] Dosage recommendations are for the first course of therapy. The need for further dose adjustments in subsequent courses should be based on individual tolerance.

[b] A dose increase to 200 mg/m^2 in subsequent courses should be considered based on individual tolerance.

[c] Patients with bilirubin levels above the upper limit of normal were excluded from clinical trials for pancreatic or lung cancer.

2.5 Dose Reduction/Discontinuation Recommendations

Metastatic Breast Cancer

Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. For Grade 3 sensory neuropathy hold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE *[see Contraindications (4), Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*.

Non-Small Cell Lung Cancer

- Do not administer ABRAXANE on Day 1 of a cycle until absolute neutrophil count (ANC) is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3 *[see Contraindications (4), Warnings and Precautions (5.1) and Adverse Reactions (6.2)]*.
- In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce ABRAXANE and carboplatin doses as outlined in Table 2.
- Withhold ABRAXANE for Grade 3-4 peripheral neuropathy. Resume ABRAXANE and carboplatin at reduced doses (see Table 2) when peripheral neuropathy improves to Grade 1 or completely resolves *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.

Table 2: Permanent Dose Reductions for Hematologic and Neurologic Adverse Drug Reactions in NSCLC

Adverse Drug Reaction	Occurrence	Weekly ABRAXANE Dose (mg/m^2)	Every 3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic Fever (ANC less than 500/mm^3 with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm^3 OR ANC less than 500/mm^3 for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment	
Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

Adenocarcinoma of the Pancreas

Dose level reductions for patients with adenocarcinoma of the pancreas, as referenced in Tables 4 and 5, are provided in Table 3.

Table 3: Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas

Dose Level	ABRAXANE (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia for patients with adenocarcinoma of the pancreas are provided in Table 4.

Table 4: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	ABRAXANE / Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: IF Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: IF Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

Abbreviations: ANC = Absolute Neutrophil Count.

Recommended dose modifications for other adverse drug reactions in patients with adenocarcinoma of the pancreas are provided in Table 5.

Table 5: Dose Modifications for Other Adverse Drug Reactions in Patients with Adenocarcinoma of the Pancreas

Adverse Drug Reaction	ABRAXANE	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

4 CONTRAINDICATIONS

- ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm^3.
- Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug.

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Effects

Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of ABRAXANE. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC), 47% of patients with non-small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer.

Monitor for myelotoxicity by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC) and Days 1, 8, and 15 (for NSCLC and for pancreatic cancer). Do not administer ABRAXANE to patients with baseline absolute neutrophil counts (ANC) of less than 1,500 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of ABRAXANE therapy, reduce the dose of ABRAXANE in subsequent courses in patients with either MBC or NSCLC.

In patients with MBC, resume treatment with every-3-week cycles of ABRAXANE after ANC recovers to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3.

In patients with NSCLC, resume treatment if recommended (see Dosage and Administration, Table 2) at permanently reduced doses for both weekly ABRAXANE and every-3-week carboplatin after ANC recovers to at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an ANC of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle *[see Dosage and Administration (2.5)]*.

In patients with adenocarcinoma of the pancreas, withhold ABRAXANE and gemcitabine if the ANC is less than 500 cells/mm^3 or platelets are less than 50,000 cells/mm^3 and delay initiation of the next cycle if the ANC is less than 1500 cells/mm^3 or platelet count is less than 100,000 cells/mm^3 on Day 1 of the cycle. Resume treatment with appropriate dose reduction if recommended *[see Dosage and Administration (2.5)]*.

5.2 Nervous System

Sensory neuropathy is dose- and schedule-dependent *[see Adverse Reactions (6.1, 6.2, 6.3)]*. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification. If ≥ Grade 3 sensory neuropathy develops, withhold ABRAXANE treatment until resolution to Grade 1 or 2 for metastatic breast cancer or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses of ABRAXANE *[see Dosage and Administration (2.5)]*.

5.3 Sepsis

Sepsis occurred in 5% of patients with or without neutropenia who received ABRAXANE in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis. If a patient becomes febrile (regardless of ANC) initiate treatment with broad spectrum antibiotics. For febrile neutropenia, interrupt ABRAXANE and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels *[see Dosage and Administration (2.5)]*.

5.4 Pneumonitis

Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving ABRAXANE in combination with gemcitabine. Monitor patients for signs and symptoms of pneumonitis and interrupt ABRAXANE and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with ABRAXANE and gemcitabine.

5.5 Hypersensitivity

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged with this drug.

5. 6 Hepatic Impairment

Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of ABRAXANE in patients with hepatic impairment should be performed with caution. The starting dose should be reduced for patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.4), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

5.7 Albumin (Human)

ABRAXANE contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

5.8 Use in Pregnancy

ABRAXANE can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats during pregnancy at doses lower than the maximum recommended human dose, based on body surface area, caused embryofetal toxicities, including intrauterine mortality, increased resorptions, reduced numbers of live fetuses, and malformations.

There are no adequate and well-controlled studies in pregnant women receiving ABRAXANE. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving ABRAXANE *[see Use in Specific Populations (8.1)]*.

5.9 Use in Men

Men should be advised not to father a child while receiving ABRAXANE *[see Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions (≥ 20%) with single-agent use of ABRAXANE in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea *[see Adverse Reactions (6.1)]*.

The most common adverse reactions (≥ 20%) of ABRAXANE in combination with carboplatin for non-small cell lung cancer are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue *[see Adverse Reactions (6.2)]*. The most common serious adverse reactions of ABRAXANE in combination with carboplatin for non-small cell lung cancer are anemia (4%) and pneumonia (3%). The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%). The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (24%), thrombocytopenia (13%), and anemia (6%). The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%).

In a randomized open-label trial of ABRAXANE in combination with gemcitabine for pancreatic adenocarcinoma [*see Clinical Studies (14.3)*], the most common (≥ 20%) selected (with a ≥ 5% higher incidence) adverse reactions of ABRAXANE are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The most common serious adverse reactions of ABRAXANE (with a ≥ 1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%) and vomiting (4%). The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are peripheral neuropathy (8%), fatigue (4%) and thrombocytopenia (2%). The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (10%) and peripheral neuropathy (6%). The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%) and diarrhea (5%).

6.1 Clinical Trials Experience in Metastatic Breast Cancer

Table 6 shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent ABRAXANE or paclitaxel injection for the treatment of metastatic breast cancer.

Table 6: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Metastatic Breast Cancer Study on an Every-3-Weeks Schedule

	Percent of Patients	
	ABRAXANE 260 mg/m² over 30 min (n=229)	**Paclitaxel Injection 175 mg/m² over 3 h[b] (n=225)**
Bone Marrow		
Neutropenia		
< 2.0 x 10^9/L	80	82
< 0.5 x 10^9/L	9	22
Thrombocytopenia		
< 100 x 10^9/L	2	3
< 50 x 10^9/L	<1	<1
Anemia		
< 11 g/dL	33	25
< 8 g/dL	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Neutropenic Sepsis	<1	<1
Bleeding	2	2
Hypersensitivity Reaction[c]		
All	4	12
Severe[d]	0	2
Cardiovascular		
Vital Sign Changes During Administration		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[d]	3	4
Abnormal ECG		
All Patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms[d]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[d]	8	4
Asthenia		
Any Symptoms	47	39
Severe Symptoms[d]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[d]	0	<1
Gastrointestinal		
Nausea		
Any Symptoms	30	22
Severe Symptoms[d]	3	<1
Vomiting		
Any Symptoms	18	10
Severe Symptoms[d]	4	1

(continued)

Table 6: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Metastatic Breast Cancer Study on an Every-3-Weeks Schedule

	Percent of Patients	
	ABRAXANE 260 mg/m² over 30 min (n=229)	**Paclitaxel Injection 175 mg/m² over 3 h[b] (n=225)**
Gastrointestinal		
Diarrhea		
Any Symptoms	27	15
Severe Symptoms[d]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[d]	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

[a] Based on worst grade by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 2.
[b] Paclitaxel injection patients received premedication.
[c] Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.
[d] Severe events are defined as at least grade 3 toxicity.

Adverse Event Experiences by Body System

Hematologic Disorders
Neutropenia was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm³ (Grade 4) in 9% of the patients treated with a dose of 260 mg/m² compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m². Pancytopenia has been observed in clinical trials.

Infections
Infectious episodes were reported in 24% of the patients treated with ABRAXANE. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications.

Hypersensitivity Reactions (HSRs)
Grade 1 or 2 HSRs occurred on the day of ABRAXANE administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular
Hypotension, during the 30-minute infusion, occurred in 5% of patients. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients. These events included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory
Dyspnea (12%), cough (7%), and pneumothorax (<1%) were reported after treatment with ABRAXANE.

Neurologic
The frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients. Twenty-four patients (10%) treated with ABRAXANE developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of ABRAXANE and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No Grade 4 sensory neuropathies were reported. Only one incident of motor neuropathy (Grade 2) was observed in either arm of the controlled trial.

Vision Disorders
Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients who received higher doses than those recommended (300 or 375 mg/m²). These effects generally have been reversible.

Arthralgia/Myalgia
The symptoms were usually transient, occurred two or three days after ABRAXANE administration, and resolved within a few days.

Hepatic
Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with ABRAXANE and 10% of patients treated with paclitaxel injection in the randomized trial.

Renal
Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Other Clinical Events
Nail changes (changes in pigmentation or discoloration of nail bed) have been reported. Edema occurred in 10% of patients; no patients had severe edema. Dehydration and pyrexia were also reported.

6.2 Clinical Trials Experience in Non-Small Cell Lung Cancer
Adverse reactions were assessed in 514 ABRAXANE/carboplatin-treated patients and 524 paclitaxel injection/carboplatin-treated patients receiving first-line systemic treatment for locally advanced (stage IIIB) or metastatic (IV) non-small cell lung cancer (NSCLC) in a multicenter, randomized, open-label trial. ABRAXANE was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m² on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m², following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of ABRAXANE/paclitaxel infusion.

The differences in paclitaxel dose and schedule between the two arms limit direct comparison of dose- and schedule-dependent adverse reactions. Among patients evaluable for adverse reactions, the median age was 60 years, 75% were men, 81% were White, 49% had adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1. Patients in both treatment arms received a median of 6 cycles of treatment.

The following common (≥ 10% incidence) adverse reactions were observed at a similar incidence in ABRAXANE plus carboplatin-treated and paclitaxel injection plus carboplatin-treated patients: alopecia 56%, nausea 27%, fatigue 25%, decreased appetite 17%, asthenia 16%, constipation 16%, diarrhea 15%, vomiting 12%, dyspnea 12%, and rash 10% (incidence rates are for the ABRAXANE plus carboplatin treatment group).

Table 7 provides the frequency and severity laboratory-detected abnormalities which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 toxicity between ABRAXANE plus carboplatin-treated patients or paclitaxel injection plus carboplatin-treated patients.

Table 7: Selected Hematologic Laboratory-Detected Abnormalities With a Difference of ≥ 5% for grades (1-4) or ≥ 2% for Grade 3-4 Toxicity Between Treatment Groups

	ABRAXANE (100 mg/m² weekly) plus carboplatin		Paclitaxel Injection (200 mg/m² every 3 weeks) plus carboplatin	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Anemia[1,2]	98	28	91	7
Neutropenia [1,3]	85	47	83	58
Thrombocytopenia[1,3]	68	18	55	9

[1] 508 patients assessed in ABRAXANE/carboplatin-treated group
[2] 514 patients assessed in paclitaxel injection/carboplatin-treated group
[3] 513 patients assessed in paclitaxel injection/carboplatin-treated group

Table 8 provides the frequency and severity of adverse reactions, which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 between either treatment group for the 514 ABRAXANE plus carboplatin-treated patients compared with the 524 patients who received paclitaxel injection plus carboplatin.

Table 8: Selected Adverse Reactions with a Difference of ≥5% for All Grade Toxicity or ≥2% for Grade 3-4 Toxicity Between Treatment Groups

System Organ Class	MedDRA v 12.1 Preferred Term	ABRAXANE (100 mg/m² weekly) + carboplatin (N=514)		Paclitaxel Injection (200 mg/m² every 3 weeks) + carboplatin (N=524)	
		Grade 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)	Grades 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)
Nervous system disorders	Peripheral neuropathy[a]	48	3	64	12
General disorders and administration site conditions	Edema peripheral	10	0	4	<1
Respiratory thoracic and mediastinal disorders	Epistaxis	7	0	2	0
Musculoskeletal and connective tissue disorders	Arthralgia	13	<1	25	2
	Myalgia	10	<1	19	2

[a] Peripheral neuropathy is defined by the MedDRA Version 14.0 SMQ neuropathy (broad scope).

For the ABRAXANE plus carboplatin treated group, 17/514 (3%) patients developed Grade 3 peripheral neuropathy and no patients developed Grade 4 peripheral neuropathy. Grade 3 neuropathy improved to Grade 1 or resolved in 10/17 patients (59%) following interruption or discontinuation of ABRAXANE.

6.3 Clinical Trials Experience in Adenocarcinoma of the Pancreas

Adverse reactions were assessed in 421 patients who received ABRAXANE plus gemcitabine and 402 patients who received gemcitabine for the first-line systemic treatment of metastatic adenocarcinoma of the pancreas in a multicenter, multinational, randomized, controlled, open-label trial. Patients received a median treatment duration of 3.9 months in the ABRAXANE/gemcitabine group and 2.8 months in the gemcitabine group. For the treated population, the median relative dose intensity for gemcitabine was 75% in the ABRAXANE/gemcitabine group and 85% in the gemcitabine group. The median relative dose intensity of ABRAXANE was 81%.

Table 9 provides the frequency and severity of laboratory-detected abnormalities which occurred at a higher incidence for Grades 1-4 (≥ 5%) or for Grade 3-4 (≥ 2%) toxicity in ABRAXANE plus gemcitabine-treated patients.

Table 9: Selected Hematologic Laboratory-Detected Abnormalities with a Higher Incidence (≥ 5% for Grades 1-4 or ≥ 2% for Grades 3-4 Events) in the ABRAXANE/Gemcitabine Arm

	ABRAXANE(125 mg/m²)/ Gemcitabine[d]		Gemcitabine	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Neutropenia[a,b]	73	38	58	27
Thrombocytopenia[b,c]	74	13	70	9

[a] 405 patients assessed in ABRAXANE/gemcitabine-treated group
[b] 388 patients assessed in gemcitabine-treated group
[c] 404 patients assessed in ABRAXANE/gemcitabine-treated group
[d] Neutrophil growth factors were administered to 26% of patients in the ABRAXANE/gemcitabine group.

Table 10 provides the frequency and severity of adverse reactions which occurred with a difference of ≥ 5% for all grades or ≥ 2% for Grade 3 or higher in the ABRAXANE plus gemcitabine-treated group compared to the gemcitabine group.

Table 10: Selected Adverse Reactions with a Higher Incidence (≥5% for All Grade Toxicity or ≥2% for Grade 3 or Higher Toxicity) in the ABRAXANE/Gemcitabine Arm

System Organ Class	Adverse Reaction	ABRAXANE (125 mg/m²) and gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
General disorders and administration site conditions	Fatigue	248 (59%)	77 (18%)	183 (46%)	37 (9%)
	Peripheral edema	194 (46%)	13 (3%)	122 (30%)	12 (3%)
	Pyrexia	171 (41%)	12 (3%)	114 (28%)	4 (1%)
	Asthenia	79 (19%)	29 (7%)	54 (13%)	17 (4%)
	Mucositis	42 (10%)	6 (1%)	16 (4%)	1 (<1%)
Gastrointestinal disorders	Nausea	228 (54%)	27 (6%)	192 (48%)	14 (3%)
	Diarrhea	184 (44%)	26 (6%)	95 (24%)	6 (1%)
	Vomiting	151 (36%)	25 (6%)	113 (28%)	15 (4%)
Skin and subcutaneous tissue disorders	Alopecia	212 (50%)	6 (1%)	21 (5%)	0
	Rash	128 (30%)	8 (2%)	45 (11%)	2 (<1%)
Nervous system disorders	Peripheral neuropathy[a]	227 (54%)	70 (17%)	51 (13%)	3 (1%)
	Dysgeusia	68 (16%)	0	33 (8%)	0
	Headache	60 (14%)	1 (<1%)	38 (9%)	1 (<1%)
Metabolism and nutrition disorders	Decreased appetite	152 (36%)	23 (5%)	104 (26%)	8 (2%)
	Dehydration	87 (21%)	31 (7%)	45 (11%)	10 (2%)
	Hypokalemia	52 (12%)	18 (4%)	28 (7%)	6 (1%)
Respiratory, thoracic and mediastinal disorders	Cough	72 (17%)	0	30 (7%)	0
	Epistaxis	64 (15%)	1 (<1%)	14 (3%)	1 (<1%)
Infections and infestations	Urinary tract infections[b]	47 (11%)	10 (2%)	20 (5%)	1 (<1%)
Musculoskeletal and connective tissue disorders	Pain in extremity	48 (11%)	3 (1%)	24 (6%)	3 (1%)
	Arthralgia	47 (11%)	3 (1%)	13 (3%)	1 (<1%)
	Myalgia	44 (10%)	4 (1%)	15 (4%)	0
Psychiatric disorders	Depression	51 (12%)	1 (<1%)	24 (6%)	0

[a] Peripheral neuropathy is defined by the MedDRA Version 15.0 Standard MedDRA Query neuropathy (broad scope).
[b] Urinary tract infections includes the preferred terms of: urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, and urinary tract infection enterococcal.

Additional clinically relevant adverse reactions that were reported in < 10% of the patients with adenocarcinoma of the pancreas who received ABRAXANE/gemcitabine included:

Infections & infestations: oral candidiasis, pneumonia
Vascular disorders: hypertension
Cardiac disorders: tachycardia, congestive cardiac failure
Eye disorders: cystoid macular edema

Peripheral Neuropathy
Grade 3 peripheral neuropathy occurred in 17% of patients who received ABRAXANE/gemcitibine compared to 1% of patients who received gemcitabine only; no patients developed grade 4 peripheral neuropathy. The median time to first occurrence of Grade 3 peripheral neuropathy in the ABRAXANE arm was 140 days. Upon suspension of ABRAXANE dosing, the median time to improvement from Grade 3 peripheral neuropathy to ≤ Grade 1 was 29 days. Of ABRAXANE-treated patients with Grade 3 peripheral neuropathy, 44% resumed ABRAXANE at a reduced dose.

Sepsis
Sepsis occurred in 5% of patients who received ABRAXANE/gemcitabine compared to 2% of patients who received gemcitabine alone. Sepsis occurred both in patients with and without neutropenia. Risk factors for sepsis included biliary obstruction or presence of biliary stent.

Pneumonitis
Pneumonitis occurred in 4% of patients who received ABRAXANE/gemcitabine compared to 1% of patients who received gemcitabine alone. Two of 17 patients in the ABRAXANE arm with pneumonitis died.

6.4 Post-Marketing Experience with ABRAXANE and other Paclitaxel Formulations
Unless otherwise noted, the following discussion refers to the adverse reactions that have been identified during post-approval use of ABRAXANE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In some instances, severe events observed with paclitaxel injection may be expected to occur with ABRAXANE.

Hypersensitivity Reactions
Severe and sometimes fatal hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular
There have been reports of congestive heart failure, left ventricular dysfunction, and atrioventricular block with ABRAXANE. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

Respiratory
There have been reports of pneumonitis, interstitial pneumonia and pulmonary embolism in patients receiving ABRAXANE and reports of radiation pneumonitis in patients receiving concurrent radiotherapy. Reports of lung fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety and may also be observed with ABRAXANE.

Neurologic
Cranial nerve palsies and vocal cord paresis have been reported, as well as autonomic neuropathy resulting in paralytic ileus.

Vision Disorders
Reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection suggest persistent optic nerve damage. These may also be observed with ABRAXANE.

Reduced visual acuity due to cystoid macular edema (CME) has been reported during treatment with ABRAXANE as well as with other taxanes. After cessation of treatment, CME improves and visual acuity may return to baseline.

Hepatic
Reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment.

Gastrointestinal (GI)
There have been reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis following ABRAXANE treatment. There have been reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, occurring in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction
There have been reports of extravasation of ABRAXANE. Given the possibility of extravasation, it is advisable to monitor closely the ABRAXANE infusion site for possible infiltration during drug administration.

Severe events such as phlebitis, cellulitis, induration, necrosis, and fibrosis have been reported as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., “recall”, has been reported.

Other Clinical Events
Skin reactions including generalized or maculopapular rash, erythema, and pruritus have been observed with ABRAXANE. There have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

There have been reports of conjunctivitis, cellulitis, and increased lacrimation with paclitaxel injection.

6.5 Accidental Exposure
No reports of accidental exposure to ABRAXANE have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

7 DRUG INTERACTIONS
The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category D *[see Warnings and Precautions (5.9)]*.

There are no adequate and well-controlled studies in pregnant women using ABRAXANE. Based on its mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving ABRAXANE.

Administration of paclitaxel protein-bound particles to rats during pregnancy, on gestation days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryofetal toxicities, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

8.3 Nursing Mothers
It is not known whether paclitaxel is excreted in human milk. Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

8.5 Geriatric Use
Of the 229 patients in the randomized study who received ABRAXANE for the treatment of metastatic breast cancer, 13% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among patients who received ABRAXANE.

Of the 514 patients in the randomized study who received ABRAXANE and carboplatin for the first-line treatment of non-small cell lung cancer, 31% were 65 years or older and 3.5% were 75 years or older. Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years old. No overall difference in effectiveness, as measured by response rates, was observed between patients 65 years or older compared to patients younger than 65 years old.

Of the 431 patients in the randomized study who received ABRAXANE and gemcitabine for the first-line treatment of pancreatic adenocarcinoma, 41% were 65 years or older and 10% were 75 years or older. No overall differences in effectiveness were observed between patients who were 65 years of age or older and younger patients. Diarrhea, decreased appetite, dehydration and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old. Clinical studies of ABRAXANE did not include sufficient number of patients with pancreatic cancer who were 75 years and older to determine whether they respond differently from younger patients.

8.6 Patients with Hepatic Impairment
Because the exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment, the administration of ABRAXANE should be performed with caution in patients with hepatic impairment *[see Dosage and Administration (2.4), Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*. Abraxane has not been studied in combination with gemcitabine for the treatment of pancreatic cancer in patients with a bilirubin greater than the upper limit of normal.

8.7 Patients with Renal Impairment
The use of ABRAXANE has not been studied in patients with renal impairment.

10 OVERDOSAGE
There is no known antidote for ABRAXANE overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
Product No.: 103450

NDC No.: 68817-134-50	100 mg of paclitaxel in a single-use vial, individually packaged in a carton.

16.2 Storage
Store the vials in original cartons at 20°C to 25°C (68° F to 77°F). Retain in the original package to protect from bright light.

16.3 Handling and Disposal
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling

- ABRAXANE injection may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Women of childbearing potential should use effective contraceptives while receiving ABRAXANE *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)]*.
- Advise men not to father a child while receiving ABRAXANE *[see Warnings and Precautions (5.9)]*.
- Patients must be informed of the risk of low blood cell counts and severe and life-threatening infections and instructed to contact their physician immediately for fever or evidence of infection. *[see Warnings and Precautions (5.1), (5.3)]*.
- Patients should be instructed to contact their physician for persistent vomiting, diarrhea, or signs of dehydration.
- Patients must be informed that sensory neuropathy occurs frequently with ABRAXANE and patients should advise their physicians of numbness, tingling, pain or weakness involving the extremities *[see Warnings and Precautions (5.2)]*.
- Explain to patients that alopecia, fatigue/asthenia, and myalgia/arthralgia occur frequently with ABRAXANE
- Instruct patients to contact their physician for signs of an allergic reaction, which could be severe and sometimes fatal *[see Warnings and Precautions (5.5)]*.
- Instruct patients to contact their physician immediately for sudden onset of dry persistent cough, or shortness of breath *[see Warnings and Precautions (5.4)]*.

Manufactured for: Celgene Corporation
Summit, NJ 07901

U.S. Patent Numbers: See www.celgene.com.

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Weight Loss Promotes Nonbariatric Surgery Medical Clearance

Julie L. Kurtz, MS, RD, CDE; Ashley M. Bremer, RD, CDE; Diane J. Parrington, PhD, RD; and Dawn C. Schwenke, PhD, MS

A liquid-based weight-loss program had a high success rate among obese veterans, was cost-effective, and reduced the need for surgery.

The prevalence of overweight and obesity has continued to increase over the past several decades.[1,2] Data specific to the veteran population indicates prevalence rates are considerably higher than that of the general population, with overweight or obese veteran women and men at 68.4% and 73%, respectively.[3-6]

Traditional weight-loss programs (> 1,200 calories per day) fail to produce the degree of weight loss required to reduce surgical risk to a safe level for individuals with a body mass index (BMI) > 35. In contrast, intensive weight-loss programs using very low calorie diets (< 800 calories per day) combined with lifestyle modifications have been effective in generating considerable weight loss. These intensive weight-loss programs have also improved comorbid conditions such as insulin resistance, diabetes, hypertension, hyperlipidemia, and hypertriglyceridemia.[7-10] Additionally, these programs have reduced surgical risks by decreasing operative time and reducing hospital length of stay.[11,12] Weight loss not only improves surgical risk, but also impacts health care resource allocation.

Very low calorie diets have proven to be safe for preoperative weight loss. One prospective study evaluated the safety of a weight-reduction program with 30 patients with morbid obesity and whose elective surgery had been postponed due to patient's weight status.[13] Study participants lost ≥ 15% of their body weight. Subsequently, only 15 patients underwent surgery. Surgery was no longer indicated for 4 participants, 9 did not have surgery for reasons that were unreported, and 2 discontinued the diet. The authors suggested a very low calorie diet program is suitable for preoperative weight reduction in morbid obesity without significant complications.

Most investigations of preoperative very low calorie diets included only those patients awaiting bariatric surgery. These studies confirmed bariatric preoperative weight loss correlates with reduced postoperative complications.[11,14,15] Additionally, the National Surgery Quality Improvement Program analysis of bariatric outcomes identified superobesity (defined as > 350 pounds) as a preoperative risk factor associated with postoperative complications.[16]

Obesity-related intra- and postoperative complications during elective surgeries are concerning because of the increasing number of obese surgical patients. With a growing aging population and rising rates of obesity, the number of total knee arthroplasties (TKAs) are increasing and now surpass total hip arthoplasties.[17] The risk of intra-operative surgical complications is higher in patients with an elevated BMI than in those without, including higher blood transfusion requirements as a result of operative blood loss, difficulty in identifying anatomy leading to iatrogenic damage, or malalignment of the prosthesis.[18-20]

The risk of postoperative complications in obese patients is reported with rates as high as 32% and is primarily caused by superficial and deep surgical site infections and postoperative venous thromboembolic complications.[18,19,21,22] One retrospective study evaluated prevalence, pattern, and severity of 7,721 postoperative complications in obese and nonobese surgical patients occurring within 30 days of surgery.[23] Obese patients had significantly higher rates of postoperative myocardial infarction, wound infection, nerve injury, and urinary tract infections. The evidence

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suggests a higher risk of intra- and postoperative complications of TKA in obese patients, but there remains continued controversy in this area. Furthermore, there is a paucity of data regarding actual postponement or cancellation rate in elective procedures related to obesity. There is a lack of literature evaluating the impact of significant preoperative weight loss by nonsurgical interventions on outcomes of subsequent elective surgery

The primary aim of this study was to determine whether a medically supervised, very low calorie weight loss program (Optifast, Nestlé Health Science) could safely and effectively produce the weight loss necessary to achieve surgical clearance at the Phoenix VA Health Care System (PVAHCS). The secondary aim was to determine whether a decrease in medication utilization during the diet intervention would offset the cost of the nutrition intervention.

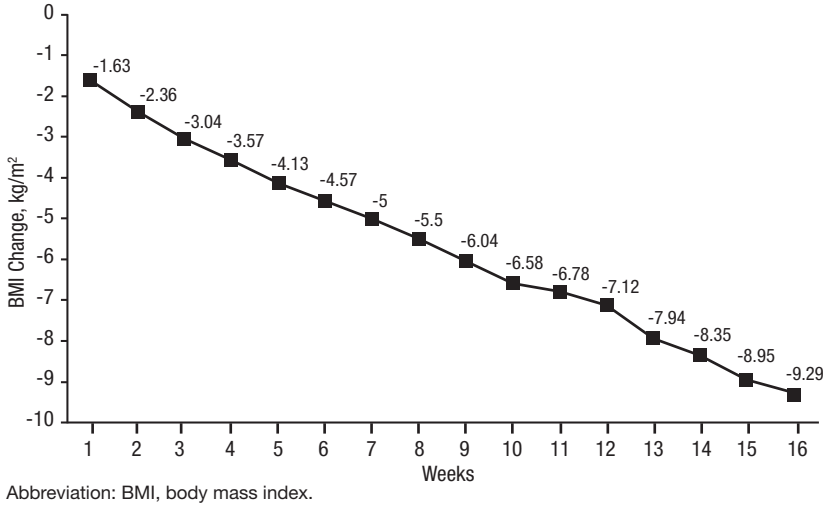
METHODS

This was a prospective, theory-based pilot study exploring weight status in response to a very low calorie diet, utilizing a quasi-experimental design. The PVAHCS Institutional Review Board approved the study.

Subjects participated in a medically supervised weight-loss program, including a liquid-meal replacement and weekly education administered by a registered dietitian. Twenty male and female veterans with obesity who had been denied medically indicated nonbariatric elective surgery due to obesity/morbid obesity and who met the study's inclusion criteria were recruited.

Inclusion criteria included veterans aged 18 to 70 years, BMI > 30, and a nutritional consult for weight loss prior to elective (nonbariatric) surgery. The exclusion criteria included active medical conditions for which weight loss would be contraindicated, active alcohol or substance abuse, and psychological issues that could prevent compliance.

Figure 1. Average Change in BMI in all Particpants[a]



Abbreviation: BMI, body mass index.
[a]Values are ± standard error of the mean.

Screening Measures

A complete metabolic panel and prealbumin levels were assessed at baseline and used as indicators of overall electrolyte, hydration, and nutritional status. A complete blood count and thyroid stimulating test were used to rule out anemia, infections, and thyroid disorders. Because rapid weight loss may precipitate serious ventricular arrhythmias, an electrocardiogram was performed at baseline and after each 50 pounds of weight loss.

Intervention

Subjects consumed 5 Optifast packets per day (each mixed with 6-10 ounces of water), providing 800 calories per day (34% protein, 49% carbohydrate, and 17% fat; with 100% of the Dietary Reference Intake for vitamins and minerals). Participants were enrolled in the program for a minimum of 6 weeks and a maximum of 16 weeks.

The research dietitian provided participants with weekly modules focused on lifestyle and education plans developed by Nestlé (eTable 1, available at www.fedprac.com). Concentrating initially on behavior modification techniques and later introducing concepts dealing with food minimized distracting stimuli for participants. Subjects were required to consume an additional 2 quarts of noncaloric liquid to maintain hydration and were educated not to consume any liquids or solids containing calories. Subjects were required to maintain a diary on timing of Optifast and fluid consumption. Caffeine intake was limited (< 200 mg per day) because of its effects on fluid loss, cardiac stimulation, and irritation to the gastric mucosa. Participants served as their own controls.

Three weeks prior to completing the liquid diet, patients were instructed on a 3-week dietary transition plan, incorporating solid foods into their meal plan. Transition guidelines used the plate method, based on recommendations from the Dietary Guidelines for Americans to assist individuals in making healthy food choices, as patients were transitioned

Table 1. Baseline Demographics and Clinical Characteristics

	All	Completers	Withdrawals
Mean, y ± SD (range)	55.1 ± 7.9 (43-68)	56.1 ± 8.1 (43-68)	52.8 ±7.3 (45-59)
Gender, no.			
Male	18	14	4
Female	2	2	0
Race/ethnicity, no.			
Non-Hispanic white	18	15	3
African American	2	1	1
Comorbid conditions, no.			
Diabetes/prediabetes	12	8	4
Hypertension	16	12	4
Hyperlipidemia	12	9	3
Mental health diagnoses, no.			
Depression			
Obsessive compulsive disorder	11	7	4
Posttraumatic stress disorder	1	0	1
Panic disorder	2	2	0
	1	1	0
Elective surgery referrals, no.			
Hip	1	1	0
Hernia	2	1	1
Knee	17	14	3

from the liquid to solid food.[24] During transition week 1, subjects consumed 4 shakes per day and 1 meal (885 kcal per day); the second transition week consisted of 3 shakes and 2 meals (1,030 kcal per day); and the final transition week included 1 shake and 3 meals (1,080 kcal per day).

Outcome Measurements

Subjects were weighed weekly. To assess dietary compliance, participants were given a log to record daily intake of the liquid diet, additional liquids consumed, and physical activity. Bioelectrical impedance analysis was used pre- and postintervention to determine body composition, including body fat percentile.

Biochemical outcome measures affected by very low calorie diets (lipids, hemoglobin A_{1c}, fasting glucose) were measured at baseline and every 4 weeks, and clinical outcomes were measured weekly. A BodyGem handheld indirect calorimeter measured resting energy expenditure (REE) to monitor caloric needs during weight loss and to guide the transition to solid food. Medication use related to obesity was recorded weekly, and the total medication costs were calculated pre- and postintervention.

Medication Management

Blood pressure was monitored weekly. If a patient was prescribed warfarin, the primary care provider and pharmacist were alerted, because it was anticipated that dosages would change with weight loss. Patients on insulin had a 50% reduction on week 1, and subsequent adjustments were made at the discretion of the provider based on glucose monitoring. Oral hypoglycemic agent adjustments were also made based on glucose monitoring.

All patients were prescribed ursodeoxycholic acid 300 mg twice a day to reduce the risk of gallstone formation.[25] Psyllium was provided to prevent constipation, a commonly reported adverse event (AE) of Optifast. Over-the-counter lactase additives were recommended for patients with known lactose intolerance. As recommended by the Optifast program, patients were instructed to avoid nonsteroidal anti-inflammatory drugs, aspirin and laxatives, amphetamines/stimulants, pseudoephedrine, and sugar-containing medications. Medications were adjusted according to clinical practices.

Statistical Analysis

Distributions of continuous measurements at the beginning (baseline) and end (follow-up) of the study and changes in these measurements (follow-up minus baseline) were tested for normality using the Shapiro-Wilk test. Where both baseline and follow-up values of a given measurement were distributed normally, both baseline and follow-up values are shown as mean ± SD (Table 1). If ≥ 1 baseline and follow-up measurements were not normally distributed, both baseline and follow-up measurements are shown as median with interquartile range. Changes in measurements are either shown as mean ± SD or median and interquartile range as appropriate. Significance of the former changes was evaluated with a paired *t* test; whereas the latter changes were evaluated with a Wilcoxon signed rank test.

RESULTS

A total of 65 veterans were referred to the program. Eighteen male and 2 female veterans ranging from ages 43 to

Table 2. Clinical Measures Before and After Intervention

Measure[a]	N (Baseline/ Follow-up)	Baseline	Follow-up	Change, %	*P* Value
Weight, lbs.	20/20	320 ± 50	269 ± 45	-16 ± 8	< .0001
Body fat, lbs.	20/16	124 ± 25	92 ± 19	-26 ± 9	< .0001
Fat-free mass, lbs.	20/16	194 (172, 225)	168 (141, 192)	-14 ± 5	< .0001
Body fat, %	20/16	38.0 (36.1, 39.6)	34.6 (33.4, 35.1)	9 ± 4	< .0001
BMI, kg/m^2	20/20	44.9 ± 6.3	37.7 ± 5.7	-16 ± 8	< .0001
Systolic BP, mm Hg	20/16	126 (118, 138)	112 (108, 116)	-14 ± 11	< .0001
Diastolic BP, mm Hg	20/16	79 (78, 86)	74 (69, 78)	-8 ± 13	.029
Plasma cholesterol, mg/dL	20/16	169 (154, 198)	140 (124, 170)	-21 (-28, 4)	.0042
LDL-C, mg/dL	20/16	93 (77, 122)	81 (62, 108)	-19 (-37, 3)	.065
HDL-C, mg/dL	19/16	39 ± 8	38 ± 7	-4 (-22, 10)	.52
Plasma triglyceride, mg/dL	20/16	194 (105, 266)	94 (78, 140)	-37 (-49, -21)	.0052
Fasting plasma glucose, mg/dL	20/16	106 (98, 137)	96 (88, 102)	-13 ± 15	.0047
A_{1c}, %	20/16	6.2 (5.9, 6.7)	5.4 (5.2, 5.8)	-10 ± 7	< .0001
Prealbumin	20/16	28.5 (24.0, 31.5)	23.0 (20.0, 31.0)	-11 ± 18	.029
Resting energy expenditure, calories/d	20/15	2,595 (1,980, 2,825)	1,920 (1,530, 2,150)	-24 ± 11	< .0001
Resting energy expenditure per kg fat-free mass, calories/kg/d	20/15	12.6 ± 1.4	11.3 ± 1.6	-11 ± 10	.0005

Abbreviations: BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]Values are mean ± SD or median (25th percentile, 75th percentile). *P* values are by paired *t* test for changes distributed normally, shown as mean ± SD and by Wilcoxon signed rank test for changes not normally distributed shown as median (25th percentile, 75th percentile).

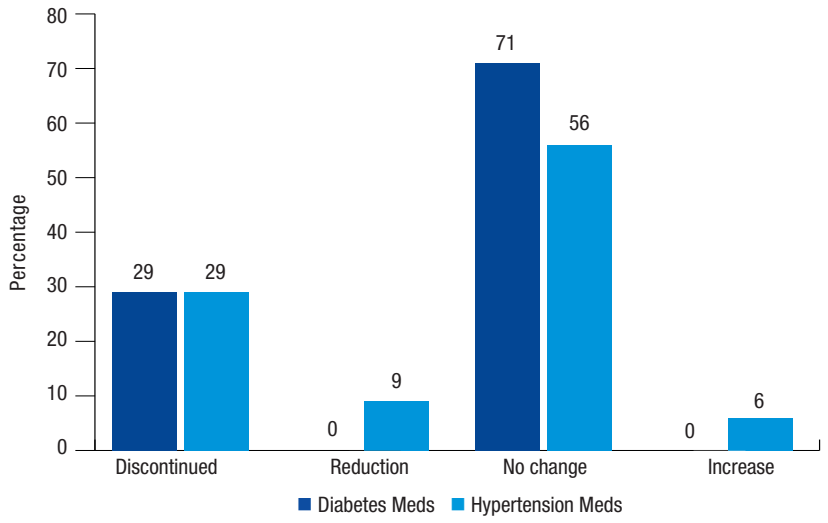
68 years, with a mean age of 55 years (SD ± 7.9) consented to participate; 16 (80%) completed the study. Four subjects dropped out; 1 due to lactose intolerance uncontrolled by lactase, 1 due to exacerbation of obsessive compulsive disorder, 1 moved out of state, and 1 opted out before beginning the dietary intervention. Comorbidities included psychiatric diagnoses (80%), hypertension (80%), diabetes (60%), and hyperlipidemia (60%). Baseline characteristics were not different between those who withdrew and those who completed the study (Table 1). Study outcomes based on intent-to-treat analysis are presented in Table 2.

BMI decreased linearly during the intervention (Figure 1). In 10 subjects, the change in BMI postintervention was both statistically (-16 ± 8%, $P < .0001$) and clinically significant and sufficient for surgical clearance. Eight (40%) had surgery and 2 (10%) no longer needed surgery due to self-reported improved quality of life and decreased pain. Despite the clinically and statistically significant weight loss, 14.5% of the weight lost was fat-free mass; decrease in body fat was 9% ± 4% ($P < .0001$).

All study subjects consumed 5 Optifast packets per day for at least 10 weeks and no longer than 16 weeks. Of the participants who completed the intervention, the majority elected to continue the intervention time to 16 weeks; however 1 participant went to week 10 and 2 participants completed through week 13. Nonadherence in this protocol was defined as > 2 weeks of weight gain. Two participants gained weight for 6 and 7 weeks, respectively.

Mean systolic blood pressure, plasma triglyceride and fasting glucose levels, A_{1c}, and REE levels decreased significantly postintervention. Additionally, patients experienced either dose reduction or discontinuation of diabetes or hypertension medication use postintervention (Figure 2). Discontinued diabetes

Figure 2. Effect of Weight Loss on Medication Utilization



medications included rosiglitazone (n = 1), glyburide (n = 1), and metformin (n = 2). Discontinued or reduced antihypertensives included furosemide (n = 1), thiazides (n = 3), beta blockers (n = 1), angiotensin-converting enzyme inhibitors (n = 4), calcium channel blockers (n = 2), and angiotensin II receptor antagonists (n = 2).

DISCUSSION

To the authors' knowledge, this was the first study using a low calorie liquid diet to achieve weight loss to qualify for nonbariatric elective surgery. This diet provides an alternative intervention for individuals who would otherwise be denied elective surgery due to extreme obesity. Eighty percent of participants completed 10 to 16 weeks of the 800 calorie liquid diet plan with significant weight loss of 16 BMI ± 8%. The intervention was well tolerated without significant AEs.

It is difficult to compare these results to prior studies, as the target populations differ. Previous studies utilizing calorie levels < 800 calories per day included mostly women and consequently, their preintervention weights were lower than in the current study population.[10] This study population was predominately older males with a high prevalence of comorbid medical and psychiatric conditions. Despite these demographic and clinical differences, improvements in biochemistries were similar to those demonstrated previously.[8-10] The observations for beneficial changes in cardiovascular and glycemic risk factors and reduced medication use related to weight loss and calorie control are consistent with previous results.[8-10]

To the authors' knowledge, REE has not been reported in earlier investigations of very low calorie diet interventions. This study found significant decreases in REE, which was measured pre- and postintervention. Participants were given postintervention REE value and individualized meal plans were developed from this number. An interesting and unexpected finding was that this number seemed to provide useful reinforcement for patients as they transitioned to solid food. This may have helped improve adherence to meal plans. Despite concerns regarding possible weight gain, the weight loss continued at a similar rate during the transition, demonstrating that continued weight loss can occur with a combination of food and liquid diet.

The need for elective surgery may have increased motivation to adhere to this weight-loss program. The dropout rate was 20%; lower than previous studies using very low calorie diets and substantially better than traditional weight-loss programs.[8,9]

An unexpected finding was that 10% of participants who qualified for knee replacement surgery chose to postpone surgery due to decreased pain and improved quality of life. Over the past 20 years, the estimated cost of 1 TKA was $15,000 with an estimated $9 billion spent annually for this procedure in the U.S.[26] Importantly, obesity increases the risk of TKA revision surgeries, which are both expensive (average cost of Medicare-covered TKA revision surgeries is $73,696) and projected to increase 66% over the next 25 years.[27] Weight loss prior to surgery not only may decrease risk for revisions of TKA, but in some cases also may delay or eliminate the need for surgery.

Although there are significant costs associated with certain weight loss programs, the savings associated with reducing the need for surgery would be substantially greater than that associated with the dietary intervention. The estimated private sector cost of an 18-week weight-loss program (12-week liquid with 6-week transition) is $3,500 per participant. This study program was estimated to cost $2,400 per participant for the 16-week (13-week liquid diet and 3-week transition) program. Patients with obesity awaiting orthopedic, gastrointestinal, or neurosurgery were often referred for bariatric surgery to obtain weight loss. Bariatric surgery averages $17,000 to $26,000, which is more expensive than this diet program.[28]

The majority of AEs observed in this intervention were expected and similar to other studies.[10] Among the 20 participants, 18 experienced a total of 60 AEs, of which 38 (63%) were considered to be study-related. Although constipation was a known AE, 25% of participants subjectively complained of decrease in frequency of bowel movements. The 2 most frequent and unanticipated AEs were increased blood urea nitrogen/creatinine (n = 9) and reduced sodium (n = 7).

Nonadherence was often related but not limited to the following: inappropriate social cues for eating, lack of social support, sabotage by family or peers, filling an emotional void with food, and/or psychological eating related to depression and posttraumatic stress disorder. Prior to starting a similar intervention, a complete mental health assessment for individuals with known or suspected mental health diagnoses seems warranted.

CONCLUSION

The study limitations are its small and predominantly male sample size and lack of a randomized control. Nonetheless, this study demonstrated the feasibility of the medically supervised weight loss program to obtain the necessary weight loss in 50% of the veterans (with higher comorbidities and more advanced age). Because of the results of this investigation, the authors have initiated a randomized controlled trial utilizing this intervention. The Optifast program had a high success rate, was cost-effective, and may obviate the need for surgery. ●

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Estimating Fall Risk in Veterans With Atrial Fibrillation

Eric J. Del Giacco, MD

Using the modified Morse Fall Scale prior to hospital discharge may be a simple and productive way to help physicians determine proper anticoagulation therapy in patients with atrial fibrillation who are at risk for falls.

Atrial fibrillation (AF) is the most common chronic cardiac rhythm disturbance and increases an individual's risk of stroke 5-fold.[1] Anticoagulation therapy reduces the risk of stroke by > 60% in patients with AF.[2] The risk of AF increases with age, yet the perceived risk of fall in elderly patients taking warfarin reduces the use of this therapy.[3]

A single-institution study in 2000 revealed that 49% of veterans with AF were not receiving anticoagulation therapy. In 13% of cases, warfarin was withheld due to the perceived fall risk.[4] Some studies of anticoagulation therapy for AF, in keeping with recommendations of the Medicare Health Care Quality Improvement Program National Stroke Project, have excluded patients who are deemed at high risk for falls.[5] Although fall risk is being used in both research and clinical settings to determine the safety of prescribing warfarin for AF, how to determine such a patient's fall risk has not been defined.

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Although several rules for predicting falls in community dwellers have been published, none are routinely assessed during a patient's hospital stay.[6] Research shows the Morse Fall Scale (MFS) is a widely used, validated tool for assessing fall risk among hospitalized patients and indicates VA patients to be at high risk for falls.[7,8] All patients hospitalized at the John L. McClellan Memorial Veterans Hospital (JLMMVH) in Little Rock, Arkansas, receive a MFS score at admission. If the MFS score is predictive of the postdischarge risk of a veteran with AF falling, the score would assist in determining which patients can be safely discharged while taking anticoagulation therapy.

The present study is a retrospective chart review of all patients with AF discharged from the JLMMVH during 2006 and their subsequent risk of falls requiring acute medical care. Based on CDC data indicating the risk for nonfatal falls by persons aged > 65 years to be more than twice that of younger persons and the established fall risk ranges of the MFS, it was hypothesized that AF patients aged ≥ 65 years with a modified MFS score (MMS) ≥ 55 would be at a significantly greater risk of fall requiring acute medical care following hospital discharge than would those of the same age with lower scores.

METHODS

This study was approved by the JLMMVH Institutional Review Board. The electronic medical records (EMRs) of all veterans with a diagnosis of AF discharged from the JLMMVH during 2006 were manually reviewed for study inclusion. The year 2006 was chosen in order to ensure adequate subject follow-up time.

Inclusion criteria consisted of discharge from an acute care unit and the patient's most recent electrocardiogram (ECG) prior to the index discharge, showing AF or atrial flutter; or the most recent ECG prior to the index discharge, showing a fully paced rhythm consistent with an underlying rhythm of AF and documentation of previously diagnosed chronic AF for which a permanent pacemaker was placed.

Exclusion criteria consisted of discharge due to patient death; transient (persisting < 24 hours) AF associated with an acute medical illness or surgical procedure; index hospitalization representing transfer temporarily from another VAMC for the sole purpose of performing a procedure; hospitalization lasting < 24 hours (not coded as a hospital admission); mechanical heart valve; index admission for a neurosurgical procedure, hemorrhagic stroke, or bleeding esophageal/gastric

varices; anticoagulation therapy recommended by the physician at the time of discharge but declined by the patient; incomplete or missing MFS score in the EMR; and lack of follow-up after the index discharge. Temporary transfers from outside facilities were excluded, due to anticipated difficulty in performing follow-up. Individuals for whom anticoagulation therapy was either inappropriate (eg, bleeding varices) or absolutely required (eg, mechanical heart valve) also were excluded.

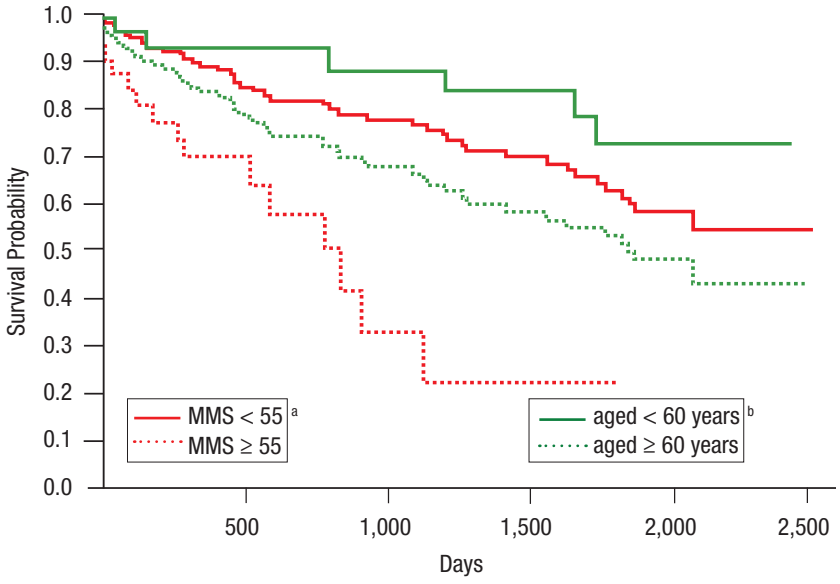
Data Collection

Each EMR was reviewed, and the following data were abstracted: (1) patient age; (2) date of first hospital discharge during 2006; (3) final MFS score and subscores recorded during the index hospitalization; (4) date of the first fall requiring acute medical evaluation; (5) severe bleeding associated with the fall; (6) date of the subject's death; and (7) date of the last recorded follow-up. The occurrence of a postdischarge fall and of fall-associated severe bleeding was determined by review of all hospitalizations, clinic visits, emergency department (ED) visits, outside records scanned into the EMR, and visiting nurse reports. The MFS score was converted to a MMS by subtracting points given for the presence of an IV line during the hospitalization, as such a fall risk would end at discharge.

Endpoints

The primary endpoint for the study was the occurrence of a fall following hospital discharge, resulting in evaluation of the subject in an outpatient clinic or ED within 24 hours. The primary comparison was between subjects aged ≥ 65 years with a MMS ≥ 55 and subjects aged ≥ 65 years with a MMS < 55.

Figure 1. Subject Time to First Fall (Survival)



Abbreviation: MMS, modified Morse Fall Scale score.
[a]*P* < .0001.
[b]*P* = .0215.

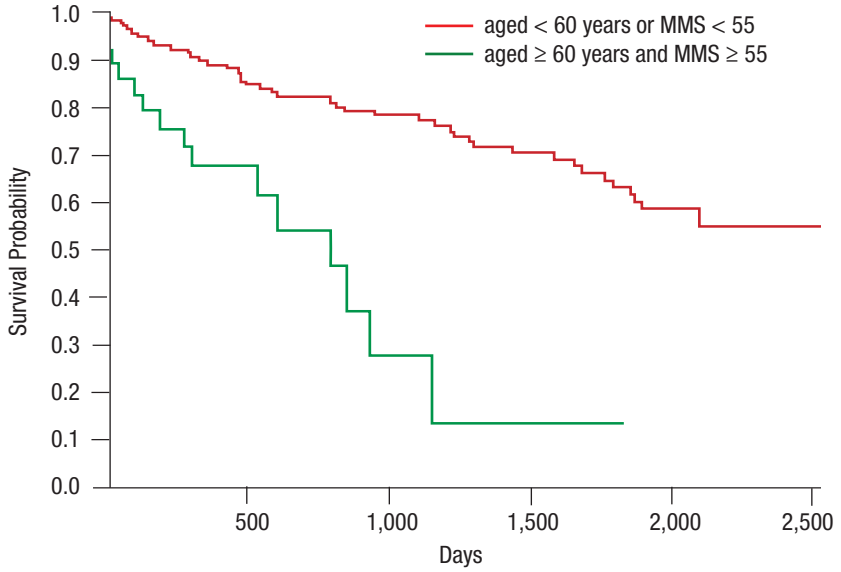
A secondary endpoint was the occurrence of severe bleeding associated with a fall. Severe bleeding was defined as fatal bleeding; and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a fall in hemoglobin level of ≥ 2 g/dL or leading to transfusion of ≥ 2 units of whole blood or red blood cells.[9]

Statistical Analysis

An estimated analyzable sample size (df = 1, α = 0.05, and a critical value for $\chi 2$ of 3.841) of 180 subjects was based on CDC age-related fall rates, MFS-related fall rates, and published sensitivity and specificity values of the MFS.[7,10,11] An estimated exclusion rate of 25% to 30% based on published rates of AF-related hospital mortality; transient (persisting < 24 hours) AF; patients with AF declining recommended anticoagulation therapy; and hospital admissions lasting < 24 hours (coded as observations) yielded a total estimated study sample size of 240 to 257 subjects.

Life-table analysis (time until fall) was performed using the LIFETEST procedure (SAS Institute Inc.; Cary, NC). Subject death and end of follow-up in EMRs were treated as censored events. Comparison of survival curves was accomplished using the log-rank statistic. To generate a user-friendly predictive rule, intervals of 5-year age cutoff values (eg, aged 55, aged 60, aged 65 years) were used for survival comparisons. The MMS is calculated in multiples of 5, hence, all possible score cutoffs were considered in survival comparisons. The 2-sample t test was performed for comparison of mean age and MMS between groups and reported as mean ± SD. A P value < .05 was considered statistically significant. Statistical analysis was performed using SAS Enterprise Guide 5.1.

Figure 2. Subject Time to First Fall (Survival) Grouped by Age and MMS[a]



Abbreviation: MMS, modified Morse Fall Scale score.
[a]$P < .0001$.

RESULTS

A search of JCMMVH EMRs yielded 270 patients with a diagnosis of AF discharged from the hospital during 2006. Seventy-seven patients were excluded from analysis for the following reasons: dead at time of discharge, 28; transient (persisting < 24 hours) AF associated with an acute medical illness, 12; referred solely for a procedure, 19; mechanical heart valve, 2; patient declined to take anticoagulation therapy, 2; hemorrhagic stroke, 1; bleeding esophageal varices, 1; lacking MFS documentation, 10; and no post-discharge follow-up documented, 2. All subjects except 1 were male. Both the age and MMS of subjects represented non-normal distributions (Anderson-Darling statistic 1.8, $P < .001$; and 6.7, $P < .005$). The median subject age was 74 years; the median MMS was 25.

During the approximately 7-year follow-up period (follow-up range 2-2,545 days), 59 of the 193 subjects (31%) fell. No fall resulted in severe bleeding or death. The mean age of subjects who fell was 73.0 ± 10.3 years compared with 71.6 ± 10.5 years for nonfallers ($P = .40$). Likewise, the mean MMS for subjects who fell was 34.1 ± 22.3 compared with 30.3 ± 19.9 for nonfallers ($P = .24$). The mean time until first fall (mean survival) was 725 ± 642 days; whereas the mean length of follow-up for people who did not fall (including those censored due to death) was 1,050 ± 869 days. Subject age and MMS were positively correlated, though weakly (Pearson $r = 0.36$; Spearman $r = 0.37$).

Grouping subjects by MMS alone yielded significantly divergent survival curves only for cutoffs of MMS ≥ 40, ≥ 50, ≥ 55 (log-rank statistic $P = .0061$, $P = .0002$, and $P < .0001$, respectively). Figure 1 (red) shows the difference in survival for MMS ≥ 55 vs MMS < 55, where the mean time to fall was 701 ± 88 days for those with a MMS ≥ 55 compared with 1,628 ± 65 days for MMS < 55.

When age cutoff alone (using 5-year age intervals) was used to construct fall survival curves, only breakpoints of age ≥ 60, ≥ 75, and ≥ 80 years yielded significantly divergent curves (log-rank statistic $P = .0215$, $P = .0264$, and $P = .011$, respectively). Figure 1 (green) shows the difference in survival for subjects aged < 60 years vs aged ≥ 60 years.

The hypothesized combined cutoff of subjects aged ≥ 65 years and MMS ≥ 55 yielded divergent survival curves (log-rank statistic of $P = .0011$). However, survival curves based on a cutoff of subjects aged ≥ 60 years and ≥ 55 MMS yielded the most statistically significant separation (log-rank statistic $P < .0001$) (Figure 2). Subjects aged < 60 years or with a MMS < 55 had a mean survival of 1,634 ± 65 days; whereas those aged ≥ 60 years and a MMS ≥ 55 had a mean survival of 668 ± 90 days.

A notable similarity of the survival curves for MMS ≥ 55 vs MMS < 55 compared with those based on a cutoff of subjects aged ≥ 60 years and ≥ 55 MMS is observed in comparing Figures 1 (red) and 2. The log-rank statistic chi-square values are 17.44 and 22.75, respectively, suggesting the separation of subjects by a combination of age and MMS yields a more robust divergence in outcomes than does separation by MMS alone.

DISCUSSION

This retrospective chart review evaluated the utility of a MMS combined with age in predicting the risk of patients with AF experiencing serious falls following hospital discharge. When used alone, the MMS separates those at relatively low and high risk of subsequent falls requiring acute medical care. When combined with the factor of patient age, this separation improves and is most predictive

for the group of AF patients aged ≥ 60 years with a MMS of ≥ 55. Half of this group had fallen 668 ± 90 days after discharge; whereas those aged < 60 years or with a MMS < 55 did not reach the point of 50% falling until 1,634 ± 65 days after discharge. Age alone allows a statistically significant differentiation of fall risk, but less so than does the MMS alone or the MMS combined with age.

Assessing fall risk can be as simple as asking whether a patient has fallen during the previous year or has a problem with balance or gait, or it can be as complex as an in-depth investigation of physical, cognitive, pharmacologic, environmental, and social factors.[12,13] Beyond the parameters of validity and discrimination power, a predictive tool must be easy to use. Within the VA hospital system, where the MFS is a part of every nursing intake assessment, a MMS can be obtained within seconds from the EMR. This, coupled with the patient's age, allows the provider to immediately identify those patients with AF who are at high risk for serious falls following hospital discharge.

Strengths and Limitations

A major strength of the present study is the fact that the data accuracy was ensured by individual review of each subject's EMR. Administrative coding was used only for the initial identification of potential subjects for inclusion. Although 28.5% of potential subjects were excluded from this analysis, > 50% of such exclusions were due to death as the reason for discharge and transient AF associated with an acute medical stressor. Other strengths include the length of follow-up (1,050 ± 869 days, excluding subject deaths) and the generalizability of the subject population. The major weakness of this study is the relatively small sample size and its retrospective methodology.

SUMMARY

The validity of the MFS modified for the postdischarge setting was demonstrated as a readily available tool for identifying patients with AF at high risk of falls following a hospital stay. Such a tool should allow physicians to appropriately prescribe anticoagulation therapy for those patients with AF who are at a lower risk of falls. ●

Author disclosures

The author reports no actual or potential conflicts of interest with regard to this article.

Disclaimer

The opinions expressed herein are those of the author and do not necessarily reflect those of Federal Practitioner, *Frontline Medical Communications Inc., the U.S. Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

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ISTODAX® (romidepsin) for injection is indicated for treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy.

This indication is based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.

ISTODAX FOR THE **2ND-LINE** TREATMENT OF PTCL

Important Safety Information

WARNINGS AND PRECAUTIONS

- **Myelosuppression:** ISTODAX® (romidepsin) can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; monitor blood counts regularly during treatment with ISTODAX; interrupt and/or modify the dose as necessary
- **Infections:** Fatal and serious infections, including pneumonia, sepsis, and viral reactivation, including Epstein Barr and hepatitis B viruses, have been reported during and within 30 days after treatment with ISTODAX in clinical trials. The risk of life threatening infections may be greater in patients with a history of prior treatment with monoclonal antibodies directed against lymphocyte antigens and in patients with disease involvement of the bone marrow. Reactivation of Epstein Barr viral infection led to liver failure. Consider monitoring for reactivation and antiviral prophylaxis in patients with evidence of prior hepatitis B infection. Ganciclovir prophylaxis failed to prevent Epstein Barr viral reactivation in one case
- **Electrocardiographic (ECG) changes:** ECG changes have been observed with ISTODAX. In patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation, consider cardiovascular monitoring of ECGs at baseline and periodically during treatment. Confirm that potassium and magnesium levels are within the normal range before administration of ISTODAX
- **Tumor lysis syndrome: TLS (Tumor lysis syndrome)** has been reported during treatment with ISTODAX. Patients with advanced stage disease and/or high tumor burden are at greater risk and should be closely monitored and managed as appropriate
- **Embryo-fetal toxicity:** ISTODAX may cause fetal harm when administered to a pregnant woman. Advise women of potential hazard to the fetus and to avoid pregnancy while receiving ISTODAX

ADVERSE REACTIONS

Peripheral T-Cell Lymphoma

The most common Grade 3/4 adverse reactions (>5%) regardless of causality in Study 3 (N=131) were thrombocytopenia (24%), neutropenia (20%), anemia (11%), asthenia/fatigue (8%), and leukopenia (6%), and in Study 4 (N=47) were neutropenia (47%), leukopenia (45%), thrombocytopenia (36%), anemia (28%), asthenia/fatigue (19%), pyrexia (17%), vomiting (9%), and nausea (6%).

Celgene

www.istodax.com

ISTODAX demonstrated efficacy in PTCL after at least one prior therapy[1]

Efficacy and safety evaluated in the largest prospective single-arm PTCL study (Study 3, N=131) in a pretreated, histologically diverse PTCL population. All patients received prior systemic therapy for PTCL. Patients could be treated until disease progression at their discretion and that of the investigator.

60% (12/20) of complete responses were known to exceed

11.6 Months

- Follow-up on the remaining 8 patients was discontinued prior to 8.5 months

26% ORR (34/130)
(CR + CRu + PR) [95% CI: 18.8, 34.6[a]]

15% CR/CRu (20/130) Primary End Point
(CR + CRu) [95% CI: 9.7, 22.8[a]]

56 days (1.8 months, n=34)
median time to objective disease response[2]

[a]95% confidence interval. Response rates above are rounded to the nearest whole number.
CR=complete response; CRu=complete response unconfirmed; ORR=overall disease response rate.

Infections were the most common type of serious adverse event reported in Study 3 (N=131) and Study 4 (N=47). In Study 3, 26 patients (20%) experienced a serious infection, including 6 patients (5%) with serious treatment-related infections. In Study 4, 11 patients (23%) experienced a serious infection, including 8 patients (17%) with serious treatment-related infections.

The most common adverse reactions regardless of causality in Study 3 (N=131) were nausea (59%), asthenia/fatigue (55%), thrombocytopenia (41%), vomiting (39%), diarrhea (36%), and pyrexia (35%), and in Study 4 (N=47) were asthenia/fatigue (77%), nausea (75%), thrombocytopenia (72%), neutropenia (66%), anemia (62%), leukopenia (55%), pyrexia (47%), anorexia (45%), vomiting (40%), constipation (40%), and diarrhea (36%).

DRUG INTERACTIONS

- Monitor more frequently prothrombin time and International Normalized Ratio in patients concurrently administered ISTODAX and warfarin or coumarin derivatives
- Romidepsin is metabolized by CYP3A4
  - —Monitor patients for toxicity related to increased romidepsin exposure and follow dose modifications for toxicity when ISTODAX is initially co-administered with strong CYP3A4 inhibitors
  - —Avoid co-administration of ISTODAX (romidepsin) with rifampin and other potent inducers of CYP3A4
- Exercise caution with concomitant use of ISTODAX and P-glycoprotein (P-gp, ABCB1) inhibitors

USE IN SPECIFIC POPULATIONS

- Pregnancy Category D: If this drug is used during pregnancy, or if the patient becomes pregnant while taking ISTODAX, the patient should be apprised of the potential hazard to the fetus
- Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ISTODAX, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother
- Patients with moderate and severe hepatic impairment and/or patients with end-stage renal disease should be treated with caution

Please see Brief Summary of Full Prescribing Information, including WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS, on the following pages.

References: 1. ISTODAX [package insert]. Summit, NJ: Celgene Corp; 2014.
2. Data on file, Celgene Corporation, Summit, NJ.

ISTODAX® (romidepsin) for injection
10-MG SINGLE-USE VIAL

ISTODAX® (romidepsin) for injection

For intravenous infusion only

The following is a Brief Summary only; see full Prescribing Information for complete product information.

1 INDICATIONS AND USAGE

ISTODAX is indicated for:

- Treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy.

These indications are based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of romidepsin is 14 mg/m^2 administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle. Cycles should be repeated every 28 days provided that the patient continues to benefit from and tolerates the drug.

2.2 Dose Modification

Nonhematologic toxicities except alopecia

- Grade 2 or 3 toxicity: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, then therapy may be restarted at 14 mg/m^2. If Grade 3 toxicity recurs, treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline and the dose should be permanently reduced to 10 mg/m^2.
- Grade 4 toxicity: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, then the dose should be permanently reduced to 10 mg/m^2.
- Romidepsin should be discontinued if Grade 3 or 4 toxicities recur after dose reduction.

Hematologic toxicities

- Grade 3 or 4 neutropenia or thrombocytopenia: Treatment with romidepsin should be delayed until the specific cytopenia returns to ANC ≥1.5×10^9/L and platelet count ≥75×10^9/L or baseline, then therapy may be restarted at 14 mg/m^2.
- Grade 4 febrile (≥38.5°C) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment with romidepsin should be delayed until the specific cytopenia returns to ≤ Grade 1 or baseline, and then the dose should be permanently reduced to 10 mg/m^2.

2.3 Instructions for Preparation and Intravenous Administration

ISTODAX is a cytotoxic drug. Use appropriate handling procedures.

ISTODAX must be reconstituted with the supplied diluent and further diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion.

- Each 10 mg single-use vial of ISTODAX (romidepsin) must be reconstituted with 2 mL of the supplied diluent. With a suitable syringe, aseptically withdraw 2 mL from the supplied diluent vial, and slowly inject it into the ISTODAX (romidepsin) for injection vial. Swirl the contents of the vial until there are no visible particles in the resulting solution. The reconstituted solution will contain ISTODAX 5 mg/mL. The reconstituted ISTODAX solution is chemically stable for up to 8 hours at room temperature.
- Extract the appropriate amount of ISTODAX from the vials to deliver the desired dose, using proper aseptic technique. Before intravenous infusion, further dilute ISTODAX in 500 mL 0.9% Sodium Chloride Injection, USP.
- Infuse over 4 hours.

The diluted solution is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene (PE) infusion bags as well as glass bottles, and is chemically stable for up to 24 hours when stored at room temperature. However, it should be administered as soon after dilution as possible.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with ISTODAX can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia. Monitor blood counts regularly during treatment with ISTODAX, and modify the dose as necessary *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

5.2 Infections

Fatal and serious infections, including pneumonia, sepsis, and viral reactivation, including Epstein Barr and hepatitis B viruses have been reported in clinical trials with ISTODAX. These can occur during treatment and within 30 days after treatment. The risk of life threatening infections may be greater in patients with a history of prior treatment with monoclonal antibodies directed against lymphocyte antigens and in patients with disease involvement of the bone marrow *[see Adverse Reactions (6)]*.

Reactivation of hepatitis B virus infection has occurred in 1% of PTCL patients in clinical trials in Western populations *[see Adverse Reactions (6)]*. In patients with evidence of prior hepatitis B infection, consider monitoring for reactivation, and consider antiviral prophylaxis.

Reactivation of Epstein Barr viral infection leading to liver failure has occurred in a trial of patients with relapsed or refractory extranodal NK/T-cell lymphoma. In one case, ganciclovir prophylaxis failed to prevent Epstein Barr viral reactivation.

5.3 Electrocardiographic Changes

Several treatment-emergent morphological changes in ECGs (including T-wave and ST-segment changes) have been reported in clinical studies. The clinical significance of these changes is unknown *[see Adverse Reactions (6)]*.

In patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation, consider cardiovascular monitoring of ECGs at baseline and periodically during treatment.

Confirm that potassium and magnesium levels are within normal range before administration of ISTODAX *[see Adverse Reactions (6)]*.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported to occur in 1% of patients with tumor stage CTCL and 2% of patients with Stage III/IV PTCL. Patients with advanced stage disease and/or high tumor burden may be at greater risk, should be closely monitored, and managed as appropriate.

5.5 Use in Pregnancy

There are no adequate and well-controlled studies of ISTODAX in pregnant women. However, based on its mechanism of action and findings in animals, ISTODAX may cause fetal harm when administered to a pregnant woman. In an animal reproductive study, romidepsin was embryocidal and resulted in adverse effects on the developing fetus at exposures below those in patients at the recommended dose of 14 mg/m^2/week. If this drug is used during pregnancy, or if the patient becomes pregnant while taking ISTODAX, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in other sections of the prescribing information.

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Infection *[see Warnings and Precautions (5.2)]*
- Electrocardiographic Changes *[see Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Peripheral T-Cell Lymphoma

The safety of ISTODAX was evaluated in 178 patients with PTCL in a sponsor-conducted pivotal study (Study 3) and a secondary NCI-sponsored study (Study 4) in which patients received a starting dose of 14 mg/m^2. The mean duration of treatment and number of cycles were 5.6 months and 6 cycles in Study 3 and 9.6 months and 8 cycles in Study 4.

Common Adverse Reactions

Table 2 summarizes the most frequent adverse reactions (≥ 10%) regardless of causality, using the NCI-CTCAE, Version 3.0. The AE data are presented separately for Study 3 and Study 4. Laboratory abnormalities commonly reported (≥ 10%) as adverse reactions are included in Table 2.

Table 2. Adverse Reactions Occurring in ≥10% of Patients with PTCL in Study 3 and Corresponding Incidence in Study 4 (N=178)

	Study 3 (N=131)		Study 4 (N=47)	
Adverse Reactions n (%)	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Any adverse reactions	*128 (97)*	*88 (67)*	*47 (100)*	*40 (85)*
Gastrointestinal disorders				
Nausea	77 (59)	3 (2)	35 (75)	3 (6)
Vomiting	51 (39)	6 (5)	19 (40)	4 (9)
Diarrhea	47 (36)	3 (2)	17 (36)	1 (2)
Constipation	39 (30)	1 (<1)	19 (40)	1 (2)
Abdominal pain	18 (14)	3 (2)	6 (13)	1 (2)
Stomatitis	14 (11)	0	3 (6)	0
General disorders and administration site conditions				
Asthenia/Fatigue	72 (55)	11 (8)	36 (77)	9 (19)
Pyrexia	46 (35)	8 (6)	22 (47)	8 (17)
Chills	14 (11)	1 (<1)	8 (17)	0
Edema peripheral	13 (10)	1 (<1)	3 (6)	0
Blood and lymphatic system disorders				
Thrombocytopenia	53 (41)	32 (24)	34 (72)	17 (36)
Neutropenia	39 (30)	26 (20)	31 (66)	22 (47)
Anemia	33 (25)	14 (11)	29 (62)	13 (28)
Leukopenia	16 (12)	8 (6)	26 (55)	21 (45)

(continued)

Table 2. Adverse Reactions Occurring in ≥10% of Patients with PTCL in Study 3 and Corresponding Incidence in Study 4 (N=178)

	Study 3 (N=131)		Study 4 (N=47)	
Adverse Reactions n (%)	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Metabolism and nutrition disorders				
Anorexia	37 (28)	2 (2)	21 (45)	1 (2)
Hypokalemia	14 (11)	3 (2)	8 (17)	1 (2)
Nervous system disorders				
Dysgeusia	27 (21)	0	13 (28)	0
Headache	19 (15)	0	16 (34)	1 (2)
Respiratory, thoracic and mediastinal disorders				
Cough	23 (18)	0	10 (21)	0
Dyspnea	17 (13)	3 (2)	10 (21)	2 (4)
Investigations				
Weight decreased	14 (11)	0	7 (15)	0
Cardiac disorders				
Tachycardia	13 (10)	0	0	0

Serious Adverse Reactions

Infections were the most common type of SAE reported. In Study 3, 26 patients (20%) experienced a serious infection, including 6 patients (5%) with serious treatment-related infections. In Study 4, 11 patients (23%) experienced a serious infection, including 8 patients (17%) with serious treatment-related infections. Serious adverse reactions reported in ≥ 2% of patients in Study 3 were pyrexia (8%), pneumonia, sepsis, vomiting (5%), cellulitis, deep vein thrombosis, (4%), febrile neutropenia, abdominal pain (3%), chest pain, neutropenia, pulmonary embolism, dyspnea, and dehydration (2%). In Study 4, serious adverse reactions in ≥ 2 patients were pyrexia (17%), aspartate aminotransferase increased, hypotension (13%), anemia, thrombocytopenia, alanine aminotransferase increased (11%), infection, dehydration, dyspnea (9%), lymphopenia, neutropenia, hyperbilirubinemia, hypocalcemia, hypoxia (6%), febrile neutropenia, leukopenia, ventricular arrhythmia, vomiting, hypersensitivity, catheter related infection, hyperuricemia, hypoalbuminemia, syncope, pneumonitis, packed red blood cell transfusion, and platelet transfusion (4%).

Reactivation of hepatitis B virus infection has occurred in 1% of patients with PTCL patients in clinical trials in Western population enrolled in Study 3 and Study 4 *[see Warnings and Precautions (5.2)]*.

Deaths due to all causes within 30 days of the last dose of ISTODAX occurred in 7% of patients in Study 3 and 17% of patients in Study 4. In Study 3, there were 5 deaths unrelated to disease progression that were due to infections, including multi-organ failure/sepsis, pneumonia, septic shock, candida sepsis, and sepsis/cardiogenic shock. In Study 4, there were 3 deaths unrelated to disease progression that were due to sepsis, aspartate aminotransferase elevation in the setting of Epstein Barr virus reactivation, and death of unknown cause.

Discontinuations

Discontinuation due to an adverse event occurred in 19% of patients in Study 3 and in 28% of patients in Study 4. In Study 3, thrombocytopenia and pneumonia were the only events leading to treatment discontinuation in at least 2% of patients. In Study 4, events leading to treatment discontinuation in ≥ 2 patients were thrombocytopenia (11%), anemia, infection, and alanine aminotransferase increased (4%).

6.2 Postmarketing Experience

No additional safety signals have been observed from postmarketing experience.

7 DRUG INTERACTIONS

7.1 Warfarin or Coumarin Derivatives

Prolongation of PT and elevation of INR were observed in a patient receiving ISTODAX concomitantly with warfarin. Although the interaction potential between ISTODAX and warfarin has not been formally studied, monitor PT and INR more frequently in patients concurrently receiving ISTODAX and warfarin.

7.2 Drugs That Inhibit Cytochrome P450 3A4 Enzymes

Romidepsin is metabolized by CYP3A4. Strong CYP3A4 inhibitors increase concentrations of romidepsin. In a pharmacokinetic drug interaction trial the strong CYP3A4 inhibitor ketoconazole increased romidepsin ($AUC_{0-\infty}$) by approximately 25%.

Monitor for toxicity related to increased romidepsin exposure and follow the dose modifications for toxicity [*see Dosage and Administration (2.2)*] when romidepsin is initially co-administered with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole).

7.3 Drugs That Induce Cytochrome P450 3A4 Enzymes

Avoid co-administration of ISTODAX with rifampin.

In a pharmacokinetic drug interaction trial with co-administered rifampin (a strong CYP3A4 inducer), romidepsin exposure was increased by approximately 80% and 60% for $AUC_{0-\infty}$ and C_{max}, respectively. Typically, co-administration of CYP3A4 inducers decrease concentrations of drugs metabolized by CYP3A4. The increase in exposure seen after co-administration with rifampin is likely due to rifampin's inhibition of an undetermined hepatic uptake process that is predominantly responsible for the disposition of ISTODAX.

It is unknown if other potent CYP3A4 inducers (e.g., dexamethasone, carbamazepine, phenytoin, rifabutin, rifapentine, phenobarbital, St. John's Wort) would alter the exposure of ISTODAX. Therefore, the use of other potent CYP3A4 inducers should be avoided when possible.

7.4 Drugs That Inhibit Drug Transport Systems

Romidepsin is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1). If ISTODAX is administered with drugs that inhibit P-gp, increased concentrations of romidepsin are likely, and caution should be exercised.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.5)].

There are no adequate and well-controlled studies of ISTODAX in pregnant women. However, based on its mechanism of action and findings in animals, ISTODAX may cause fetal harm when administered to a pregnant woman. In an animal reproductive study, romidepsin was embryocidal and resulted in adverse effects on the developing fetus at exposures below those in patients at the recommended dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking ISTODAX, the patient should be apprised of the potential hazard to the fetus.

Romidepsin was administered intravenously to rats during the period of organogenesis at doses of 0.1, 0.2, or 0.5 mg/kg/day. Substantial resorption or post-implantation loss was observed at the high-dose of 0.5 mg/kg/day, a maternally toxic dose. Adverse embryo-fetal effects were noted at romidepsin doses of ≥0.1 mg/kg/day, with systemic exposures (AUC) ≥0.2% of the human exposure at the recommended dose of 14 mg/m^2/week. Drug-related fetal effects consisted of folded retina, rotated limbs, and incomplete sternal ossification.

8.3 Nursing Mothers

It is not known whether romidepsin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ISTODAX, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of ISTODAX in pediatric patients has not been established.

8.5 Geriatric Use

Of the approximately 300 patients with CTCL or PTCL in trials, about 25% were >65 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects; however, greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No dedicated hepatic impairment study for ISTODAX has been conducted. Mild hepatic impairment does not alter pharmacokinetics of romidepsin based on a population pharmacokinetic analysis. Patients with moderate and severe hepatic impairment should be treated with caution.

8.7 Renal Impairment

No dedicated renal impairment study for ISTODAX has been conducted. Based upon the population pharmacokinetic analysis, renal impairment is not expected to significantly influence drug exposure. The effect of end-stage renal disease on romidepsin pharmacokinetics has not been studied. Thus, patients with end-stage renal disease should be treated with caution.

10 OVERDOSAGE

No specific information is available on the treatment of overdosage of ISTODAX.

Toxicities in a single-dose study in rats or dogs, at intravenous romidepsin doses up to 2.2 fold the recommended human dose based on the body surface area, included irregular respiration, irregular heartbeat, staggering gait, tremor, and tonic convulsions.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., clinical monitoring and supportive therapy, if required. There is no known antidote for ISTODAX and it is not known if ISTODAX is dialyzable.

Manufactured for: Celgene Corporation
Summit, NJ 07901

Manufactured by: Ben Venue Laboratories, Inc.
Bedford, OH 44146

or

Baxter Oncology GmbH
Halle/Westfalen, Germany

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IST_PTCL_BSv006 10/2014

Venous Thromboembolism Prophylaxis in Acutely Ill Veterans With Respiratory Disease

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This observational study assessed the rate and appropriateness of pharmacologic venous thromboembolism prophylaxis in veterans with pulmonary disease who were admitted to the hospital for a nonsurgical stay.

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism, is an important public health concern. Deep venous thrombosis is estimated to affect 10% to 20% of medical (nonsurgical) patients, 15% to 40% of stroke patients, and 10% to 80% of critical care patients who are not prophylaxed.[1] Venous thromboembolism is associated with significant resource utilization, long-term sequelae, recurrent events, and sudden death.[2]

The current guidelines of the American College of Chest Physicians recommend use of pharmacologic thromboprophylaxis as the preferred strategy for nonsurgical (or medical) patients (IB, formerly IA, recommendation) and for critically ill patients (2C recommendation) at low risk for bleeding.[1,3] Mechanical (or nonpharmacologic) thromboprophylaxis (eg, intermittent pneumatic compression) is an alternative for those at increased risk for bleeding (2C recommendation).[3] Pharmacologic thromboprophylaxis in high-risk patients, similar to those studied in randomized controlled clinical trials, reduces the occurrence of symptomatic DVT by 34 events per 1,000 patients treated.[3] However, data are conflicting regarding mortality benefit.[4,5]

The Joint Commission adopted any thromboprophylaxis (measure includes pharmacologic or nonpharmacologic strategies) as a core discretionary measure in the ORYX (National Quality Hospital Measures) program. The ORYX measurements are intended to support Joint Commission-accredited organizations in institutional quality improvement efforts. The thromboprophylaxis core measure became effective May 2009 and remains as an option for hospitals to meet the 4 core measure set accreditation requirement. A top-performing hospital should provide this measure to applicable patients ≥ 95% of the time, according to the Joint Commission.[6] The Joint Commission does not encourage use of any risk assessment model (RAM), such as the Padua Prediction Score to preferentially select high-risk medical patients.[3]

A disparity exists between thromboprophylaxis recommendations and practices in the nonsurgical patient, even when electronic prompts or alerts are available (eTables 1 and 2, available at www.fedprac.com). In the U.S., pharmacologic thromboprophylaxis is administered to 23.6% to 81.1% of medical patients and 37.9% to 79.4% of critical care patients.[7-21] In most cases, these rates are liberal estimates, because they include patients who are already on therapeutic anticoagulation or may have received only 1 prophylactic dose during hospitalization.[8-11,13-20] When studies exclude patients receiving therapeutic (or treatment doses) anticoagulation, pharmacologic thromboprophylaxis rates are substantially lower, typically 31% to 33% for medical patients and 37.9% for critical care patients.[7,12,21] Furthermore, when studies examine appropriateness of thromboprophylaxis (eg, within the first 2 days of hospitalization or at the correct dose,

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correct time, or predefined duration), calculations are often less robust.[10,11,13,14,22,23]

The VHA uses thromboprophylaxis of surgical patients as an external peer review (EPR) performance measure (PM). With the great attention to this national measure, Altom and colleagues reported 89.9% of surgeries adhered.[24] Before 2015, VTE thromboprophylaxis EPR PM did not exist. However, the VHA has initiated efforts to assure that providers are adherent to the new indications, which include VTE prophylaxis and treatment.

There is little published literature evaluating VHA performance. Quraishi and colleagues reported a pharmacologic prophylaxis rate of 63% in nonsurgical patients at a single VAMC, facilitated by the use of an admission VTE order set. Unfortunately, their estimate allowed inclusion of 5% of patients receiving treatment doses of anticoagulation and failed to provide any estimates on regimen appropriateness (eg, correct dose, correct time, or correct duration).[18] Lentine and colleagues documented a pharmacologic thromboprophylaxis rate of 48% for a subset of veteran critical care patients who were not already receiving indicated therapeutic anticoagulants.[21]

Veterans have poorer health status, more medical conditions, and higher medical resource use than do nonveterans; therefore, it is postulated that veterans can derive clinical benefit from improved attention to thromboprophylaxis benchmarking, performance improvement, and potentially, implementation of electronic alerts or reminder tools.[25] Nationally, VHA has no formal inpatient reminder tools to trigger use of thromboprophylaxis for high-risk medical patients, although individual health care systems may have created alerts or tools. Some studies demonstrated that order sets and electronic tools are helpful, whereas others demonstrated potential for harm.[17-20,26,27]

For any hospitalization at the VA Tennessee Valley Healthcare System (TVHS), the only electronic prompt to order VTE thromboprophylaxis occurs when the admission order set is completed. But the prompt can be readily bypassed if the quick admission orders are selected. Although no further electronic prompts in the Computerized Patient Record System (CPRS) are invoked following admission, the authors hypothesized that the rate of VTE thromboprophylaxis, specifically pharmacologic, in a subset of veterans with respiratory disease will be higher than the usual published rates.

PURPOSE AND RELEVANCE

This study's primary aim was to assess the rate of pharmacologic VTE prophylaxis in veterans with pulmonary disease who were admitted for a nonsurgical stay. The 2 secondary aims were to determine whether thromboprophylaxis was appropriate and to characterize whether differences exist for pharmacologic prophylaxis according to level of care (medical critical care unit [CCU] vs acute care medical ward).

This analysis emphasizes pharmacologic thromboprophylaxis instead of the combined endpoint of pharmacologic plus nonpharmacologic thromboprophylaxis traditionally used and will supplement the limited literature in 2 understudied cohorts: (1) nonsurgical veteran patients, specifically where advanced computerized thromboprophylaxis alerts are not in use; and (2) patients with the VTE risk factor of respiratory disease.[1,7-9,12,13,15,16,18,21]

Study Design

This observational study used retrospectively collected data. The data were extracted electronically from the VISN 9 data warehouse by a Decision Support Services analyst and manually validated by an investigator using the CPRS. Prior to initiation of research activities, the VHA Institutional Review Board and the Research and Development Committee at the facility level approved the study.

Sampling

Patients assigned to the treating specialties of medicine and medical critical care during fiscal years 2006 to 2008, admitted for ≥ 24 hours, and discharged with a diagnosis of chronic obstructive pulmonary disease (COPD), asthma, or acute, severe respiratory disease (eg, patients requiring mechanical ventilation) were eligible for inclusion. The authors also elected to include patients with asthma, because this diagnosis commonly overlaps with COPD and reflects real-world clinical practice and diagnostic challenges.[28] Pneumonia and other infectious pulmonary conditions were not a qualifying diagnosis for study inclusion.

Patients were excluded if aged > 79 years, because it is difficult to maintain de-identification in a small sample of inpatients in this age category. Unfortunately, octogenarians have the highest rate of VTE per 100,000 population and would gain substantial benefit from prophylaxis.[29] Similar to other VHA and non-VHA investigators, this study excluded patients who were prescribed therapeutic anticoagulation.[7,12,21,30] The authors believe continuation of therapeutic (or treatment) anticoagulation does not measure a clinical decision to use pharmacologic thromboprophylaxis, and any interruption of

Table 1. Study Demographics

	Median	IQR	No. (%)
Gender, male			123 (99.2)
Admission age, y	64.3	14.6	
41-50			7 (5.6)
51-60			36 (29)
61-70			46 (37.1)
71-79			35 (28.2)
Race			
American Indian/Alaska Native			1 (0.8)
African American			17 (13.7)
Unknown			7 (5.6)
White			99 (79.8)
Weight, kg	81.01	33.63	
Body mass index	26.31	8.89	
≥ 30			31 (25)
CrCl (Cockcroft Gault, mL/min (n = 119)	65.2	38.4	18 (14.5)
CrCl ≤ 30 mL/min			3 (2.4)
CrCl ≤ 10 mL/min			
Pulmonary acute or chronic diagnosis			
COPD			112 (90.3)
Asthma			3 (2.4)
Pulmonary fibrosis			2 (1.6)
Prior ARDS			1 (0.8)
Current ARDS			1 (0.8)
Nitric oxide synthase pulmonary			1 (0.8)
Acute respiratory distress			2 (2.4)
Restrictive lung disease			1 (0.8)
Admission directly related to COPD			21 (16.9)

	Median	IQR	No. (%)
LOS, h (n = 124)	91.5	112.3	
24-72			49 (39.5)
73-143			39 (31.5)
144-216			21 (16.9)
217-287			10 (8.1)
> 288			5 (4.0)
LOS < 3 d			47 (37.9)
LOS > 3 d			77 (62.1)
Subgroup administered VTE thromboprophylaxis (n = 78)	100	131.3	
Any pharmacologic thromboprophylaxis (n = 124)			78 (62.9)
Agent (n = 78):			
Heparin (5,000 units SC every 8-12 h)			49 (62.8)
Enoxaparin (30-40 units SC daily)			30 (38.5)
interchanged between agents			1 (1.3)
Renal function (n = 78)			
CrCl ≤ 10 mL/min and received thromboprophylaxis with heparin			3 (3.8)
Duration of hospitalization (n = 78):			50 (64.9)
LOS < 3 d			
Location of care (n = 78)			25 (80.6)
Medical critical care (n = 31)			53 (56.9)
Medical ward (n = 93)			
Mortality, overall			12 (9.7)
Medical critical care patient			10

Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; CrCl, creatine clearance; IQR, interquartile range; LOS, length of stay; VTE, venous thromboembolism.

therapeutic anticoagulation suggests that prophylactic anticoagulation is not warranted.

Additionally, patients were excluded if length of stay (LOS) exceeded 14 days, if known or potential contraindications to thromboprophylaxis existed, or if laboratory data that were needed to assess for contraindications were missing from the electronic data set. Known or potential contraindications included active hemorrhage, hemorrhage within the past 3 months, recent administration of packed red blood cells, bacterial endocarditis, known coagulopathy, recent or current heparin-induced thrombocytopenia, or a potential coagulopathy (International Normalized Ratio > 1.5, platelets < 50,000, or an activated partial thromboplastin time > 41 sec).

Contraindications were conservative in construct and were similar to the exclusion-based VTE checklist for the nonsurgical patient.[31] The authors did not examine the electronic data set for the contraindication of epidural or spinal anesthesia, because neither is commonly used in the medical ward or medical CCU. The authors also did not exclude patients with a creatinine clearance (CrCl) < 10 mL/min (a relative contraindication to VTE thromboprophylaxis), although these patients may be at an increased risk for bleeding complications.[32]

Endpoints and Measures

The primary endpoint of this study was the rate of any pharmacologic thromboprophylaxis (eg, ≥ 1 doses),

similar to the endpoint selected by other investigators.[7-9,12,13,15,16] Secondary endpoints included VTE protected time period on thromboprophylaxis, therapeutic appropriateness ratio for heparin and enoxaparin doses combined, and pharmacologic thromboprophylaxis rates according to level and location of care.

Sample Size

Although data have been forthcoming, at the time of study inception no studies documented the rate of pharmacologic thromboprophylaxis alone (defined as use of ≥ 1 dose of a pharmacologic agent) in patients with the VTE risk factor of respiratory disease.[15,23] However, an average combined pharmacologic and nonpharmacologic thromboprophylaxis rate of 48.8% was determined from available studies.[11,14] Although this percentage is an overestimate of pharmacologic thromboprophylaxis rates alone, this value was used to determine a sample size for the cohort.

About 122 subjects would be needed to provide 80% power and a significance level of < 0.05 to assess the hypothesis that pharmacologic prophylaxis rates at TVHS would exceed 60%. Additionally calculated was the sample size necessary to find a 20% expected difference in thromboprophylaxis rates according to location of care (eg, medical ward vs medical CCU), the secondary endpoint. This sample size was calculated to be 180 subjects, or 90 patients in each arm, to provide 80% power and a significance level (2-tailed alpha) of < 0.05. Subsequently, up to 130 patients from each location of care were randomly selected for study inclusion.

Data Analysis

A chi square test was used to compare groups on categorical variables. SPSS version 16.0 (SPSS Chicago, IL) was used for data analysis.

Endpoint Definitions

- Pharmacologic thromboprophylaxis accepted regimens:
  - Heparin SC 5,000 units every 8 hours (institutional guidelines and supported by a meta-analysis)[33]
  - Enoxaparin 40 mg SC daily for CrCl ≥ 30 mL/min
  - Enoxaparin 30 mg SC daily for CrCl < 30 mL/min
  - Fondaparinux 2.5 mg SC daily for CrCl ≥ 30 mL/min
- Appropriate (pharmacologic) thromboprophylaxis is measured using 2 different ratios: the VTE protected time period on thromboprophylaxis ratio and the therapeutic appropriateness ratio
- VTE protected time period on (pharmacologic) thromboprophylaxis ratio: This is the ratio of the duration of drug exposure (hours) to the patient's LOS (hours). The duration of drug exposure (numerator) is calculated by multiplying the number of doses and duration of drug effect (hours), because this reflects duration of treatment efficacy. The denominator is LOS (hours) limited to those patients prescribed thromboprophylaxis. As described later, the heparin coverage period was standardized as an 8-hour period of coverage regardless of how it was dosed[33]
- The VTE protected time period ratio approximates the Joint Commission ORYX measure of thromboprophylaxis, allowing receipt within 48 hours of admission to be counted as success but offers greater description.[6] For example, if a patient was admitted for 3 days and pharmacologic intervention was not initiated until almost 24 and 48 hours into the admission, the protected time period would be 48/72 or 66.66% and 24/72 or 33.33%, respectively. Additionally, this calculation allows inclusion of patients regardless of duration of hospitalization. Limitations on LOS could also have profound effects on sample size
- Therapeutic appropriateness ratio: This ratio is a proportion of patients who receive the correct dosing strategy (numerator) out of the entire sample. The correct dosing strategy is the number of subjects who receive the correct dose of pharmacologic thromboprophylaxis at the correct dosing interval. *Incorrect dosing* is defined as overdosing or underdosing for renal function for enoxaparin. At TVHS, heparin CPRS orders recommend dosing every 8 hours.[33] Appropriateness calculations in the study consider every 12-hour dosing as inappropriate, although accumulating evidence currently suggests that the 12-hour dosing strategy may be appropriate[3]

RESULTS

A sample of 3,762 hospitalizations for veterans with COPD, asthma, or acute, severe respiratory disease who received inpatient care in the medical ward or medical CCU were extracted from the data warehouse.

Electronic Data Set

An investigator reviewed the electronic data set, and exclusion criteria that could be ascertained electronically were applied. The primary reasons for exclusion were age (18.4%), potential coagulopathy (14.5%), recent transfusion (14.6%), use of therapeutic anticoagulation (11%), or an extended LOS (7%). Less common reasons for exclusion were coagulation disorders (1.4%), heparin-induced thrombocytopenia (1.2%), recent hemorrhage (1.1%), or missing baseline laboratory values (3.2%). Subsequently, the potential sample of subjects declined to 1,018 (27%) hospitalizations. Of the remaining hospitalizations, 46 and 972 were medical CCU and nonsurgical (medical) inpatients, respectively.

In line with the sampling plan, 130 (13.4%) medical ward hospitalizations were selected using a random number generator. As the ICU sample was smaller than anticipated,

Table 2. Venous Thromboembolism Protected Time Period on Pharmacologic Thromboprophylaxis (n = 78)

	Median, %	IQR, %	No. (%)
Therapeutic appropriateness ratio			(92.3)
VTE protected time period, h	82.8	48.5	
< 25			6 (7.7)
25 ≤ 50			14 (18)
50 ≤ 75			14 (18)
≥ 75			44 (56)
≥ 90			31 (40)

Abbreviations: IQR, interquartile range; VTE, venous thromboembolism.

the convenience sample of all 46 hospitalizations was used.

Manual Chart Abstraction

Manual chart abstraction (n = 176) clarified physician/provider decision making (eg, some patients were not appropriate for thromboprophylaxis due to upcoming invasive procedures), medical history that could not be extracted by ICD-9 coding (eg, recent non-VHA admissions for medical conditions that were contraindications to prophylaxis), and anticoagulation dosing. These exclusions led to an additional 52 (29.5%) excluded hospitalizations. Reasons for manual exclusion included recent bleeding or at high risk for bleeding (18, 34.6%), incorrect classification as nonsurgical or elective admission (5, 9.6%), no diagnosis of lung disease (21, 40.4%), invasive procedures planned (4, 7.7%), treatment anticoagulant doses selected (4, 7.7%), or patient transferred to a non-VA medical facility due to acuity level (1, 1.9%). One patient was excluded for multiple reasons.

Baseline Demographics

The sample was an elderly, male (98%), white (79.8%) cohort (Table 1). No patients were aged < 40 years. Racial information was missing for 5.6% of the patients. The chief pulmonary diagnosis was COPD, and few patients had new onset, acute, severe respiratory disease (3.2%) prompting admission, because pneumonia was not included as a qualifying diagnosis. Median body mass index (BMI) was 26.31. The median LOS was 3.8 days for the overall cohort and 4.1 days for those receiving pharmacologic thromboprophylaxis, although for the latter group a larger proportion of patients were hospitalized for < 3 days. Renal function, according to endpoint definitions, was for using enoxaparin as the appropriate strategy for thromboprophylaxis for the majority (97.5%) of hospitalizations.

Primary and Secondary Endpoints

Of those receiving pharmacologic thromboprophylaxis, heparin was prescribed most often (62.8%). One patient received both heparin and enoxaparin during a single hospitalization.

Pharmacologic thromboprophylaxis was more common in the medical CCU subgroup (80.6%) compared with the nonsurgical patient (56.9%). Pharmacologic thromboprophylaxis was used in 62.9% of patients (n = 124). However, the therapeutic appropriateness ratio was reduced to 58% of the entire sample (n = 124), because 6 patients of the cohort receiving thromboprophylaxis (n = 78) were prescribed suboptimal doses: Specifically, 1 patient was underdosed and 1 overdosed when prescribed enoxaparin (2, 2.6%). Four patients (5.1%) received underdoses of heparin, based on institutional guidance. For those prescribed pharmacologic thromboprophylaxis, the VTE protected time period ratio was 82.8% (Table 2). Overall inpatient mortality rate was low (12, 9.7%). Most deceased patients were managed in the medical CCU (10, 83.3%) and did receive pharmacologic thromboprophylaxis (10, 83.3%).

DISCUSSION

This study demonstrated moderate rates of VTE pharmacologic thromboprophylaxis, because 62.9% of nonsurgical patients with respiratory disease who were hospitalized for various reasons were prophylaxed with either SC heparin or enoxaparin. This rate represents active clinical decision making, because there was no indication to prescribe anticoagulation at therapeutic doses. As expected, pharmacologic thromboprophylaxis was more common in the critical care subgroup (80.6%) compared with the nonsurgical patients (56.9%). Although the study did not meet the intended sample size for this subgroup analysis, results were statistically significant for location of care ($P = .014$) and may be beneficial for future study design by other investigators.

As early studies of nonsurgical and critical care patients document ≤ 40% of patients receive pharmacologic thromboprophylaxis, this study's performance seems better.[7,12,21] Recently, VHA investigators Quraishi and colleagues seemed to document similar findings. Although 63% of medical patients at the Dayton VAMC in Ohio received

appropriate pharmacologic thromboprophylaxis, this value must be tempered by the proportion of subjects receiving therapeutic anticoagulation (5.4%).[18]

Similar to this study's results, recent studies of nonveterans document pharmacologic thromboprophylaxis rates of 41% to 51.8%, 41% to 65.9%, and 74.6% to 89.9% in patients with respiratory disease, nonsurgical patients, and critical care patients, respectively. Although findings seem similar to this study's results, adjustments in estimates again must be made, because these estimates included patients on therapeutic anticoagulation.[12,14-16] This study's results found that 58% of the patient cohort met the therapeutic appropriateness ratio, because they were administered pharmacologic thromboprophylaxis and received correct doses at indicated dosing intervals.

Because stringent exclusion criteria that minimized use of pharmacologic thromboprophylaxis in patients at risk for bleeding were applied, a higher rate of use was expected. This difference between expected and actual rates likely occurred because patient care is individualized and not all factors can be readily assessed in an observational study using retrospective data.

Additionally, for patients who remain ambulatory or have an invasive procedure, thromboprophylaxis may be appropriately delayed past the first 24-hour window of therapy or even temporarily interrupted. Subsequently, the measure of thromboprophylaxis initiation within the first 24 to 48 hours of admission was not elected. Instead, an alternative endpoint of VTE protected time period on thromboprophylaxis was selected. When thromboprophylaxis was used, the median period of protection was 83% of the time period hospitalized for this subgroup. Standardizing to a 7-day period, a VTE protected time period of 83% is coverage for 5.81 days. This would support the Joint Commission ORYX measure that allows for the receipt of thromboprophylaxis within 48 hours of admission to be counted as a success.[6]

Unfortunately, the authors did not assess whether mechanical thromboprophylaxis was provided to the remaining one-third of patients not receiving pharmacologic thromboprophylaxis. As a result, the complete data set is lacking, which would document whether the Joint Commission measure of ≥ 95% of the time was achieved. Therefore, the claim that TVHS is a top performing hospital for this ORYX measure cannot be made.

Although this study demonstrated a low mortality rate, this rate was not selected as a measure of interest, since one meta-analysis has demonstrated no mortality benefit from VTE thromboprophylaxis.[4] Although in-hospital mortality may be an appropriate measure for critical care patients, most of the study patients did not meet this criterion.[21] Last, mortality should be assessed no earlier than 30 days from admission.[17] Subsequently, statistical assessment and conclusions from this measure are not relevant.

LIMITATIONS

A number of limitations hindered the generalizability of the results. This was an observational study using retrospectively collected data. The sample was narrowed to those with chronic respiratory disease, which has been less studied and typically examined in concert with acute processes, such as pneumonia. The demographic was primarily white males. The BMI of subjects enrolled in this study (26 kg/m^2) was lower than the BMI of nonveteran subjects with COPD (28.6 kg/m^2), nonveteran subjects with COPD and VTE (29 kg/m^2), or veteran nonsurgical patients receiving thromboprophylaxis (29 kg/m^2).[18,34,35]

The exclusion criteria resulted in a 73% reduction in the cohort and severely limited the number of medical critical care patients included. However, the problem of a small cohort was anticipated.

Other researchers conducting a prospective VHA thromboprophylaxis study found only 7.6% of veterans screened were eligible for enrollment, although 25% of subjects were anticipated by chart review. Two of the 3 primary reasons for trial exclusion were indication for therapeutic anticoagulation and contraindications to heparin (other than thrombocytopenia), and these were also primary reasons for exclusion in this study.[30] Subsequently, the cohort appropriate for thromboprophylaxis in VHA seems relatively small.

Additionally, mobility is difficult to judge in a chart review. Day-to-day clinical assessments of mobility lead to individualization of care, including delayed initiation and timely termination of thromboprophylaxis. It is also possible that a significant portion of the patients had mechanical thromboprophylaxis, because they may have had an unrecognized risk factor for bleeding or patient preferences were considered. Last, some veterans may have classified as palliative care, and VTE prophylaxis may have been omitted for comfort care purposes.[32]

This study was not designed to evaluate the Padua Prediction Score, which categorizes risk and rationalizes use of thromboprophylaxis for nonsurgical patients.[3] This tool eliminates many of the established risk factors for VTE, including COPD, which was a qualifying

diagnosis for inclusion in this study.[1] It is not clear how the Padua Prediction Score would categorize the inpatient veteran population. Veterans clearly have poorer health status, more medical conditions, and higher medical resource use compared with the general patient population.[25]

Veterans with COPD have a higher comorbid illness burden than that of veterans without COPD.[36] Chronic obstructive pulmonary disease is associated with VTE development, and when VTE develops in patients with COPD, mortality is greater than that of patients without COPD.[37,38] VTE mortality may be related to an increased likelihood of fatal pulmonary embolism.[39] Therefore, the authors recommend that VHA conduct studies to examine the Padua Prediction Score and potentially other RAMs that include COPD subjects, to determine what tool should be used in VHA.[32]

The authors also recommend that VHA evaluate how to improve thromboprophylaxis care with time-based studies. Since manual extraction to determine study inclusion was a time-consuming process, this time frame likely was a barrier to physician implementation of pharmacologic thromboprophylaxis. Therefore an electronic tool that serves as a daily reminder for subjects calculated as high risk for VTE but low risk for bleeding may improve clinical outcomes.

CONCLUSIONS

Overall, about one-third of patients did not receive potentially indicated pharmacologic thromboprophylaxis on the medical wards. Use of pharmacologic thromboprophylaxis in medical CCU patients was robust (80%). Doses and dosing intervals were appropriate for > 90% of patients, and therapy clearly was started early and continued for much of the at-risk period, as the VTE protected time period exceeded 80%. Although computerized tools were limited, the authors feel their modest pharmacologic thromboprophylaxis rate is related to the facility's teaching hospital affiliation or the provider mix, because TVHS is one of the largest VA cardiology centers in the U.S.[7,8,13]

As it was challenging and time consuming to locate eligible subjects, it may also prove difficult for the admitting physician to have the same luxury of time to look for specific at-risk diagnoses in the medical record and evaluate for exclusions to therapy. If electronic alerts and reminder tools were included in clinical pharmacy inpatient templates, the authors believe the frequency of pharmacologic thromboprophylaxis would further improve in the facility. Also, the authors encourage VHA researchers to further evaluate VTE prophylaxis RAM, the role of daily electronic reminders, and tools to calculate VTE and bleeding risk. ●

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Program Profile

Redesign of a Screening Process for VA Homeless Housing

Dina Hooshyar, MD, MPH; Ledjona D. Bradshaw, MPH; Reed J. Robinson, PhD; Alina M. Surís, PhD, ABPP; James P. LePage, PhD; and Carol S. North, MD, MPE

Standardizing the screening processes for homeless housing among VA facilities can make programs more accessible to veterans experiencing homelessness and improve provider knowledge of existing and available services.

Homelessness is associated with disproportionate medical morbidity and mortality and use of nonpreventive health services.[1] In fiscal year 2010, veterans experiencing homelessness were 4 times more likely to use VA emergency departments and had a greater 10-year mortality risk than did veterans who were housed.[1] Veterans experiencing homelessness were more likely to be diagnosed with substance use disorder, schizophrenia, liver disease, and/or HIV/AIDS than were their housed counterparts.

Ending veteran homelessness is a federal priority, exemplified by the goal of President Obama to end veteran homelessness by 2015.[2] Since the goal's articulation, veteran homelessness has declined nationally by 33% (24,117 veterans) from 2009 to 2014 however, 49,933 veterans were identified as being homeless on a given night in January 2014.[3]

A crucial element needed to end veteran homelessness is veteran and health care provider knowledge of existing homeless services and mechanisms of access. In 2012, VHA launched a homelessness screening clinical reminder in the Computerized Patient Record System (CPRS), which prompts a discussion of housing status between the veteran and provider.[4] The staff of the VA North Texas Health Care System (VANTHCS) Comprehensive Homeless Center Programs (CHCP) realized that homeless housing programs at the facility could be more accessible if staff from each program could screen for all available programs and if a single phone number existed for scheduling appointments. Therefore, VANTHCS transformed its homeless housing screening process to a standardized process through which veterans are screened for all CHCP housing programs during a single screening assessment, Universal Homeless Housing Screening (UHHS).

This article describes the creation of the UHHS, the screening tool, 3-month postimplementation findings, and recommendations based on initial VANTHCS staff experiences with this process. During the redesign of screening process for homeless housing, VANTHCS staff found a paucity of guidance regarding best practices. This article attempts to fill this gap and provide guidance to institutions that are considering standardizing their screening process for homeless housing across multiple programs at different locations.

BACKGROUND

Established in 1990, VANTHCS CHCP is VA's first comprehensive homeless center. The CHCP provides both housing and vocational rehabilitation programs, including 13 housing programs in 6 different cities and long-standing partnerships between CHCP and 3 community agencies whose programs have specific housing for veterans.[5] Screenings performed in Dallas, Texas, for CHCP housing programs are completed at 4 separate locations.

Prior to the inception of the UHHS process, access to housing programs

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Table 1. Demographics of Veterans Who Completed the Universal Homeless Housing Screening Assessment (n = 356)[a]

Demographics	No. (%)
Age, y	
Mean	51
SD	11
Sex	
Male	330 (93)
Female	26 (7)
Ethnicity	
Not Hispanic or Latino	321 (90)
Unknown	18 (5)
Hispanic or Latino	17 (5)
Race	
African American	190 (53)
White	136 (38)
Unknown	24 (7)
American Indian or Alaska Native	3 (1)
Native Hawaiian or other Pacific Islander	3 (1)
Period of Service	
Post-Korean War	1 (< 1)
Vietnam War era	114 (32)
Post-Vietnam War era	121 (34)
Persian Gulf War	116 (33)
Unknown	4 (1)
Service Connection	
Yes	119 (33)
No	237 (67)
Combat Status	
Noncombat veteran	312 (88)
Combat veteran	23 (6)
Unknown	21 (6)
Accessed care in year prior to UHHS assessment	
Yes[b]	342 (96)
Any in-person outpatient visit	342 (96)
Substance use residential rehabilitation admission	94 (26)
Psychiatric admission	67 (19)
Medical, surgical, or observation admission	38 (11)
Medical rehabilitation admission	7 (2)
Homeless domiciliary admission	4 (1)
No	14 (4)
Owns a working phone	
Yes	260 (73)
No	96 (27)
Residence night prior to UHHS screening	
Shelter	96 (27)
Not meant for human habitation	82 (23)
Substance use treatment program	79 (22)
Living with friends/family	46 (13)
Housing program	29 (8)
Renting home	14 (4)
Hotel/motel	6 (2)
Halfway house	3 (1)
Domiciliary care for medical condition	1 (< 1)

Abbreviations: UHHS, Universal Homeless Housing Screening; VANTHCS, VA North Texas Health Care System.
[a]Time period is from August 26, 2013, to November 27, 2013.
[b]The same veteran could have accessed ≥ 1 type of service.

was limited by veteran awareness of the programs and transportation to various program locations. To participate in these programs, veterans needed to complete a form for the VA Northeast Program Evaluation Center (NEPEC), which staff at the Healthcare for Homeless Veterans (HCHV) CHCP program could administer. This process created an admission bottleneck, because HCHV staff needed to evaluate veterans even if they were being admitted to non-HCHV programs.

UHHS CREATION PROCESS

In 2011, NEPEC launched the electronic Homeless Operations Management and Evaluation System (HOMES) to replace paper-based reporting.[6] This tool allowed non-HCHV CHCP staff to complete NEPEC evaluation and allowed CHCP to meet its goal of designing a system where all CHCP housing programs could complete a screening assessment. This goal originated from the desire of then CHCP Director Teresa House-Hatfield to create a more efficient housing screening process and from similar feedback from veterans.

Furthermore, in 2009, then Secretary of Veterans Affairs Eric K. Shinseki described a "no wrong door" philosophy for ending veteran homelessness, which CHCP operationalized by screening veterans for any CHCP housing program regardless of initial point of contact within the CHCP system.[2] Subsequently, in 2010, the VA Office of Mental Health Services contracted with Mathematica Policy Research, Inc., to conduct a quality review of VA Mental Health Residential Rehabilitation Treatment Programs. Notable among their recommendations was to create a one-stop screening process for these programs.

In 2010, CHCP embarked on a process to transform the facility's screening procedure to a one-stop assessment with standardized

Table 2. Reasons That Veterans Did Not Complete the Universal Homeless Housing Screening Assessment

Reasons[a]	No. (%)
Ineligible for housing programs	20 (43)
Did not want care management	7 (15)
No psychosocial rehabilitation needs	6 (13)
Unable to perform activities of daily living	3 (6)
Income surpasses programs' maximum limit	3 (6)
Required hospitalization	1 (2)
Eligible but not interested in any programs	13 (28)
Already in housing program and not interested in others	10 (21)
Not homeless/at risk for homelessness and not interested in Compensated Work Therapy-Transitional Residence housing program	2 (4)
Not eligible for VA care	2 (4)

[a]Veteran could have had > 1 reason. Time period is from August 26, 2013, to November 27, 2013.

screening questions and create a systematic process to track outcomes across all CHCP housing programs. The new process allowed for a standardized appeal procedure when eligibility for a program was not met. It also improved the ease of communication by having 1 phone number for making appointments or informing about screening times. These changes were enacted without the addition of any new staff positions. Instead, in October 2011, Ms. House-Hatfield tasked Dina Hooshyar of the VANTHCS to champion and spearhead this transformation.

The challenge associated with the UHHS creation process was to balance individual program autonomy with standardized processes. This balance was achieved through weekly calls where Ms. House-Hatfield, Dr. Hooshyar, and CHCP program managers discussed how to design UHHS. The management of the CHCP also actively sought input from CHCP frontline staff. During the preimplementation phase, Dr. Hooshyar gave multiple UHHS trainings to CHCP staff who would become involved in UHHS process, another feedback mechanism.

Program managers retained their programs' autonomy by picking screeners and the number of employees in that position for their program, screening location and time, and screening type (appointment, walk-in, telephone, and/or combination). Managers and staff also assisted in the creation of the UHHS tool by providing their program's eligibility criteria and customary psychosocial assessment questions. The UHHS tool not only brought consistency to the screening process, but also removed any perceived biases by asking all veterans the same questions across all UHHS screening locations. Implemented on August 26, 2013, UHHS continues to be used.

UHHS Screening Tool

The UHHS tool is an assessment composed of 4 sections: (1) History; (2) Decision Tree; (3) Specific Program Eligibility Criteria; and (4) Plan. The sections exist as templates in the CPRS.

The History section asks about demographic information, diagnoses, alcohol and illicit drug use history, dependent status, outstanding legal issues, housing status, functional limitations, income and employment status, and potential benefit from and interest in psychosocial rehabilitation and care management. If the veteran would not benefit from and/or is not interested in participating in psychosocial rehabilitation and care management, the screener concludes the assessment, as these factors are eligibility requirements for all CHCP programs. Veterans can appeal their case to the screener's program manager.

The Decision Tree template consists of 6 core eligibility criteria across programs that can serve to narrow the list of eligible programs: (1) Is the veteran currently homeless; (2) Has the veteran been homeless continuously for ≥ 1 year, or has the veteran had ≥ 4 separate occasions of homelessness in the past 3 years; (3) Does the veteran have a mental health or substance use diagnosis; (4) Can the veteran pay a program fee (9 of 16 UHHS-associated programs have no fees); (5) Is the veteran capable of self-administering medications; and (6) Can the veteran perform activities of daily living and does not need acute hospitalization?

Veterans are then asked in which town(s) they want to reside. The questions for the Specific Program Eligibility Criteria section are asked only for those programs for which the veteran is found to be tentatively eligible by the Decision Tree and has interest in participating.

The Plan section gives veterans the opportunity to appeal a UHHS finding to the specific program's manager whose program they are not eligible to participate. Veterans also rank their preference for the programs for which they are interested and eligi-

ble. A shared folder contains all program census information. Through the screening tool, veterans devise a plan to contact the potential admitting program. Veterans are informed about the importance of keeping in contact with these programs, because programs will not hold openings for an indefinite time.

Completion of this screening assessment, which includes HOMES and the UHHS tool, generally takes 1.5 hours. After a veteran undergoes this assessment, a preadmission appointment is made with the first open program for which they are eligible and interested in participating. The main goal of this appointment varies by program, such as finalizing referral processes with associated community partners, performing a preliminary medical clearance, determining whether veterans have already used their program's maximum allotted time, coordinating a Therapeutic Supported Employment Services assessment, or obtaining the required documents from veterans. If at the preadmission appointment, either the veteran declines participation or the program declines admittance, the veteran can follow up with other programs for which they met eligibility criteria and were interested in participating during the initial UHHS assessment instead of undergoing another housing screening.

Notification of Screening Results

The CHCP staff member who performs the screening is responsible for documenting the veteran's name, phone number or means of contact, current residence, and housing outcome in a secure shared Microsoft Excel document called Housing Outcome. The Excel IF and VLOOKUP function link the original document to each program's acceptance and petition documents. This linkage auto populates information entered in the Housing Outcome document to each program's acceptance and petition documents if the veteran has a housing outcome associated with the program. CHCP staff members then look at their individual program's acceptance and/or petition documents to see the list of veterans who have a housing outcome involving their program instead of having to sort through the Housing Outcome document. As a backup to the Housing Outcome document, screeners add the point of contact for the programs that the veteran had an associated housing outcome as additional signers to their CPRS screening note.

When UHHS was first implemented, the screeners had a daily call to discuss the screened veterans' housing outcomes and screener experiences with the new system. Dr. Hooshyar also participated in this call as a means to answer screener questions and to get feedback. Within a month of UHHS implementation, these calls were cancelled, because the screeners felt comfortable with the UHHS process and the majority of housing programs were operating at full capacity.

UHHS Appointment Line

The UHHS appointment phone number uses an automatic call distributor, a call-center technology. Thus, 1 phone number can be answered by multiple people working in separate locations. The challenge was how to connect phones associated with offices located offsite from the VANTHCS campus. The solution was to use Internet phones in addition to existing staff phones.

RESULTS

During the review period from August 26, 2013, to November 27, 2013 (65 workdays), 392 unique veterans attended a UHHS assessment. Four veterans who were screened twice were included only once in the analysis; outcomes from only their initial screenings were evaluated. Three hundred fifty-six veterans completed a UHHS assessment; 36 had an assessment but did not complete it. Rates of veterans not presenting for their scheduled appointments increased over time, from 24% in August 2013 to 50% in November 2013. To address the no-show rate, program managers decreased the number of offered scheduled appointments and increased the number of walk-in visits. Overall, the schedule distribution consisted of about twice as much time allotted for walk-in appointments compared with scheduled appointments. The UHHS appointment line received 873 calls, where the number decreased over time.

The typical screened veteran who completed a UHHS assessment was a non-Hispanic, African American male aged 51 years with no service connection or history of combat who served either in the Vietnam War era, post-Vietnam War era, or Persian Gulf War. He had accessed VANTHCS care in the year prior to screening; owned a working phone; and was staying in a shelter, a place not meant for human habitation, or a substance use treatment program the night prior to screening (Table 1). Only 20 veterans (5%) were ineligible for participation in all programs, because they did not meet core eligibility criteria as defined by the UHHS Decision Tree, their income surpassed the program limit, or they were not eligible for VA care (Table 2).

To determine the housing outcome of the veterans screened during the reviewed period, a 3-month follow-up from the end of the review period was used. During this time, 269 veterans (76%) who completed

Table 3. Veteran Housing Status Postcompletion of the Universal Homeless Housing Screening Process (n = 356)[a]

Housing Status	No. (%)
Housed	269 (76)
Veteran admitted to UHHS-associated housing program	215 (60)
Veteran found non-UHHS housing	47 (13)
Veteran obtained community-based housing assistance	4 (1)
Veteran continued participation in current housing program	3 (1)
Did not complete screening process	45 (13)
Veteran did not completely engage with housing program staff to finalize admission	28 (8)
Staff unable to contact veteran to potentially finalize admission to housing program[b]	12 (3)
Veteran declined housing assistance	5 (2)
Veteran found to be ineligible for admission during preadmission appointment	18 (5)
Did not meet chronic homelessness criteria to participate in HUD-VASH and not interested in other housing programs	11 (3)
Did not meet chronic homelessness criteria and had no need for care management to participate in HUD-VASH	4 (1)
Had no need for care management	1 (< 1)
Unable to perform activities of daily living	1 (< 1)
Not eligible for VA care	1 (< 1)
Participated in Residential Rehabilitation Treatment Program	23 (6)
Substance Abuse Residential Rehabilitation Treatment Program	22 (6)
Post-Traumatic Stress Disorder Residential Rehabilitation Treatment Program	1 (< 1)
Died	1 (< 1)

Abbreviations: HUD-VASH, U.S. Department of Housing and Urban Development-VA Supportive Housing; UHHS, Universal Homeless Housing Screening.
[a]Evaluated time period included the reviewed time (August 26, 2013-November 27, 2013) plus 3 months. Chart abstraction stopped once the veteran had 1 of the listed outcomes.
[b]Staff documented their inability to contact the veteran in medical record given no contact information.

the UHHS process were housed, with 215 (60%) veterans housed in a UHHS-associated housing program (Table 3). Of the veterans who completed a UHHS assessment, 45 veterans (13%) did not complete the screening process; admitting program staff documented in CPRS unsuccessful attempts at reaching 12 veterans (3%), among whom 4 had no working phone at the time of their UHHS assessment. Time to admission depended on the program mission, openings, and the veteran's UHHS engagement. Admission date indicates the date that programs housed veterans except in the case of the U.S. Department of Housing and Urban Development-VA Supportive Housing (HUD-VASH), where admission date indicates the date the veteran gave all required documents to HUD-VASH staff.

DISCUSSION

Prior to the inception of UHHS, the staff of the CHCP housing program did not have a standardized process for communication across programs about veterans' housing status and outcomes. Veterans went to multiple locations for screening if they were interested in > 1 program or if they were not admitted to the first program they approached. The UHHS process improved communication across CHCP housing programs, resulting in increased veteran accessibility to these programs as suggested by 3 CHCP housing programs having fewer days with openings post-UHHS implementation. Furthermore, a new screener position did not need to be created, because existing CHCP social workers were all capable screeners due to process standardization.

Fifty-five percent of the screened veterans were interested in and eligible for participation in > 1 housing program. They were eligible for 3 programs on average and were usually admitted to the housing program with the earliest opening. The need for screenings across all the CHCP housing programs was potentially decreased by ≥ one-third. This increased available time for the screeners to accomplish their other clinical responsibilities.

Limitations

A limitation of the review period evaluation is little information on noncompleters. The available data are confined to information documented in CPRS regarding why 45 veterans (13% of those who completed UHHS assessment) did not complete the screening process. For 12, admitting staff of the housing program documented in CPRS that they had been unable to reach the veteran; 9 of these veterans attended subsequent non-UHHS VANTHCS visits. To further improve the homeless housing delivery service, the creation of a CPRS-related process that informs VA clinicians that a housing program is attempting to contact a veteran is needed.

Challenges and Recommendations

Because the Housing Outcome document is a shared document, only 1 person at a time can save information in it. Facility staff have been unable to create a simple macro that

closes the document automatically. Instead, screeners who need to save information when a document is already opened elsewhere must use a group e-mail list to alert others to close the document.

Streamlining the communication channel between the screeners and management evolved from the daily call, to e-mailing and program managers discussing topics with their staff, to Dr. Hooshyar facilitating a weekly call for screeners and program managers.

Optimizing the ratio of walk-in to scheduled appointments took time. Prior to the UHHS process, some CHCP housing programs offered scheduled appointments, whereas others had walk-in appointments. The decision to offer in-person scheduled appointments for veterans who preferred scheduled appointments or who commuted from a distance was made. Universal Homeless Housing Screening staff also offered scheduled telephone appointments for veterans who lacked transportation.

At times, admitting program staff was unable to reach veterans eligible for and interested in their program, despite screeners recommending to veterans that they should provide these programs with any changes in their contact information.

Recommendations for designing a screening process for homeless housing include:

1. Have periodic retreats instead of weekly conference calls to quicken the pre-implementation process.
2. Start with a pilot that includes some potential screeners to test the implementation process. The screeners involved in the pilot would train future screeners to expand the screener pool.
3. Invest time in electronic tracking tools despite upfront and maintenance time requirements.
4. Offer more walk-in than scheduled screening appointments.
5. Embrace the idea that the process is always under development.

CONCLUSION

To ameliorate anxiety associated with changing the system, UHHS-associated staff redesigned the housing screening process through openness to stakeholder feedback and building on consensus. The staff also nurtured a culture that could change newly revised processes, depending on quality assurance findings. Without this method, the unknown likely would have propagated continued status quo. Universal Homeless Housing Screening processes improved veteran access to CHCP housing programs through instituting a one-stop housing screening assessment that also reduced the potential number of screenings by ≥ one-third. ●

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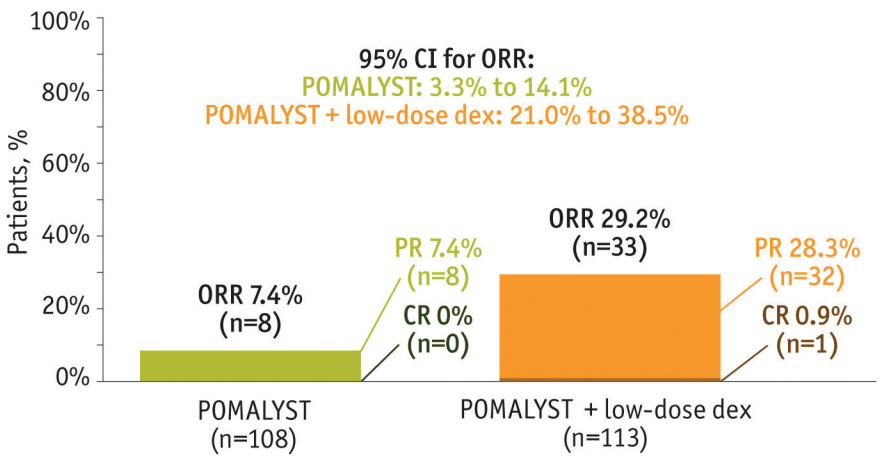

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(pomalidomide) capsules
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POMALYST® (pomalidomide) is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY and VENOUS THROMBOEMBOLISM

Embryo-Fetal Toxicity

- **POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment**
- **Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment**

POMALYST is only available through a restricted distribution program called POMALYST REMS™.

Venous Thromboembolism

- **Deep venous thrombosis (DVT) and pulmonary embolism (PE) occur in patients with multiple myeloma treated with POMALYST. Prophylactic anti-thrombotic measures were employed in the clinical trial. Consider prophylactic measures after assessing an individual patient's underlying risk factors**

CONTRAINDICATIONS: Pregnancy

- POMALYST can cause fetal harm and is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus
- Pomalidomide is a thalidomide analogue and is teratogenic in both rats and rabbits when administered during the period of organogenesis

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity

- Females of Reproductive Potential: Must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy. Must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALYST therapy. Must obtain 2 negative pregnancy tests prior to initiating therapy
- Males: Pomalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy. Males must not donate sperm
- Blood Donation: Patients must not donate blood during treatment with POMALYST and for 1 month following discontinuation of POMALYST therapy because the blood might be given to a pregnant female patient whose fetus must not be exposed to POMALYST

POMALYST REMS Program

Because of the embryo-fetal risk, POMALYST is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called "**POMALYST REMS**." Prescribers and pharmacies must be certified with the program; patients must sign an agreement form and comply with the requirements. Further information about the **POMALYST REMS** program is available at **www.CelgeneRiskManagement.com** or by telephone at 1-888-423-5436.

Venous Thromboembolism: Patients receiving POMALYST have developed venous thromboembolic events reported as serious adverse reactions. In the trial, all patients were required to receive prophylaxis or antithrombotic treatment. The rate of DVT or PE was 3%. Consider anticoagulation prophylaxis after an assessment of each patient's underlying risk factors.

Hematologic Toxicity: Neutropenia of any grade was reported in 50% of patients and was the most frequently reported Grade 3/4 adverse reaction, followed by anemia and thrombocytopenia. Monitor patients for hematologic toxicities, especially neutropenia, with complete blood counts weekly for the first 8 weeks and monthly thereafter. Treatment is continued or modified for Grade 3 or 4 hematologic toxicities based upon clinical and laboratory findings. Dosing interruptions and/or modifications are recommended to manage neutropenia and thrombocytopenia.

Hypersensitivity Reactions: Patients with a prior history of serious hypersensitivity associated with thalidomide or lenalidomide were excluded from studies and may be at higher risk of hypersensitivity.

Dizziness and Confusional State: 18% of patients experienced dizziness and 12% of patients experienced a confusional state; 1% of patients experienced Grade 3/4 dizziness, and 3% of patients experienced Grade 3/4 confusional state. Instruct patients to avoid situations where dizziness or confusional state may be a problem and not to take other medications that may cause dizziness or confusional state without adequate medical advice.

WARNINGS AND PRECAUTIONS (continued)

Neuropathy: 18% of patients experienced neuropathy (approximately 9% peripheral neuropathy). There were no cases of Grade 3 or higher neuropathy adverse reactions reported.

Risk of Second Primary Malignancies: Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

Tumor Lysis Syndrome: Tumor lysis syndrome (TLS) may occur in patients treated with pomalidomide. Patients at risk for TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

ADVERSE REACTIONS

In the clinical trial of 219 patients who received POMALYST alone (n=107) or POMALYST + low-dose dexamethasone (low-dose dex) (n=112), all patients had at least one treatment-emergent adverse reaction.

- In the POMALYST alone versus POMALYST + low-dose dex arms, the most common adverse reactions (≥30%), respectively, included fatigue and asthenia (55%, 63%), neutropenia (52%, 47%), anemia (38%, 39%), constipation (36%, 35%), nausea (36%, 22%), diarrhea (34%, 33%), dyspnea (34%, 45%), upper respiratory tract infection (32%, 25%), back pain (32%, 30%), and pyrexia (19%, 30%)
- 90% of patients treated with POMALYST alone and 88% of patients treated with POMALYST + low-dose dex had at least one treatment-emergent NCI CTC Grade 3 or 4 adverse reaction
- In the POMALYST alone versus POMALYST + low-dose dex arms, the most common Grade 3/4 adverse reactions (≥15%), respectively, included neutropenia (47%, 38%), anemia (22%, 21%), thrombocytopenia (22%, 19%), and pneumonia (16%, 23%). For other Grade 3 or 4 toxicities besides neutropenia and thrombocytopenia, hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician's discretion
- 67% of patients treated with POMALYST and 62% of patients treated with POMALYST + low-dose dex had at least one treatment-emergent serious adverse reaction
- In the POMALYST alone versus POMALYST + low-dose dex arms, the most common serious adverse reactions (≥5%), respectively, were pneumonia (14%, 19%), renal failure (8%, 6%), dyspnea (5%, 6%), sepsis (6%, 3%), pyrexia (3%, 5%), dehydration (5%, 3%), hypercalcemia (5%, 2%), urinary tract infection (0%, 5%), and febrile neutropenia (5%, 1%)

DRUG INTERACTIONS

Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp). Avoid the use of strong CYP1A2 inhibitors. If medically necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-gp, reduce POMALYST dose by 50%. Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

USE IN SPECIFIC POPULATIONS

Pregnancy: If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436.

Nursing Mothers: It is not known if pomalidomide is excreted in human milk. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from POMALYST, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of POMALYST in patients under the age of 18 have not been established.

Geriatric Use: No dosage adjustment is required for POMALYST based on age. Patients greater than or equal to 65 years of age were more likely than patients less than or equal to 65 years of age to experience pneumonia.

Renal and Hepatic Impairment: Pomalidomide is metabolized in the liver. Pomalidomide and its metabolites are primarily excreted by the kidneys. The influence of renal and hepatic impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Avoid POMALYST in patients with a serum creatinine >3.0 mg/dL. Avoid POMALYST in patients with serum bilirubin >2.0 mg/dL and AST/ALT >3.0 x ULN.

Please see brief summary of full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS on following pages.

This brief summary does not include all the information needed to use POMALYST® (pomalidomide) safely and effectively. See full Prescribing Information for POMALYST.

WARNING: EMBRYO-FETAL TOXICITY and VENOUS THROMBOEMBOLISM

Embryo-Fetal Toxicity

- **POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.**
- **Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment [see *Contraindications (4)*, *Warnings and Precautions (5.1)*, and *Use in Specific Populations (8.1, 8.6)*].**

POMALYST is only available through a restricted distribution program called POMALYST REMS™ [see *Warnings and Precautions (5.2)*].

Venous Thromboembolism

- **Deep venous thrombosis (DVT) and pulmonary embolism (PE) occur in patients with multiple myeloma treated with POMALYST. Prophylactic anti-thrombotic measures were employed in the clinical trial. Consider prophylactic measures after assessing an individual patient's underlying risk factors [see *Warnings and Precautions (5.3)*].**

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

POMALYST is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate [see *Clinical Studies (14.1)*]. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

2 DOSAGE AND ADMINISTRATION

2.1 Multiple Myeloma

Females of reproductive potential must have negative pregnancy testing and use contraception methods before initiating POMALYST [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.6)*].

The recommended starting dose of POMALYST is 4 mg once daily orally on Days 1-21 of repeated 28-day cycles until disease progression. POMALYST may be given in combination with dexamethasone [see *Clinical Studies (14.1)*].

POMALYST may be taken with water. Inform patients not to break, chew, or open the capsules. POMALYST should be taken without food (at least 2 hours before or 2 hours after a meal).

2.2 Dose Adjustments for Toxicities

Table 1: Dose Modification Instructions for POMALYST for Hematologic Toxicities

Toxicity	Dose Modification
Neutropenia	
• ANC <500 per mcL or febrile neutropenia (fever more than or equal to 38.5°C and ANC <1,000 per mcL)	Interrupt POMALYST treatment, follow CBC weekly
• ANC return to more than or equal to 500 per mcL	Resume POMALYST treatment at 3 mg daily
• For each subsequent drop <500 per mcL	Interrupt POMALYST treatment
• Return to more than or equal to 500 per mcL	Resume POMALYST treatment at 1 mg less than the previous dose
Thrombocytopenia	
• Platelets <25,000 per mcL	Interrupt POMALYST treatment, follow CBC weekly
• Platelets return to >50,000 per mcL	Resume POMALYST treatment at 3 mg daily
• For each subsequent drop <25,000 per mcL	Interrupt POMALYST treatment
• Return to more than or equal to 50,000 per mcL	Resume POMALYST treatment at 1 mg less than previous dose

ANC, absolute neutrophil count.

For other Grade 3 or 4 toxicities, hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician's discretion.

To initiate a new cycle of POMALYST, the neutrophil count must be at least 500 per mcL and the platelet count must be at least 50,000 per mcL. If toxicities occur after dose reductions to 1 mg, then discontinue POMALYST.

2.3 Dose Adjustment for Strong CYP1A2 Inhibitors in the Presence of Strong CYP3A4 and P-gp Inhibitors

Avoid co-administration of strong inhibitors of CYP1A2. If necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-gp, reduce POMALYST dose by 50%. No clinical efficacy or safety data exist [*see Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

4 CONTRAINDICATIONS

Pregnancy

POMALYST can cause fetal harm when administered to a pregnant female [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)*]. POMALYST is contraindicated in females who are pregnant. Pomalidomide is a thalidomide analogue and is teratogenic in both rats and rabbits when administered during the period of organogenesis. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

POMALYST is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death [see *Use in Specific Populations (8.1)*]. POMALYST is only available through the POMALYST REMS program [see *Warnings and Precautions (5.2)*].

Females of Reproductive Potential

Females of reproductive potential must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy.

Females must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALYST therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing POMALYST therapy, and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles, or every 2 weeks in women with irregular menstrual cycles [see *Use in Specific Populations (8.6)*].

Males

Pomalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy. Male patients taking POMALYST must not donate sperm [see *Use in Specific Populations (8.6)*].

Blood Donation

Patients must not donate blood during treatment with POMALYST and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to POMALYST.

5.2 POMALYST REMS™ Program

Because of the embryo-fetal risk [see *Warnings and Precautions (5.1)*], POMALYST is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called "**POMALYST REMS**."

Required components of the **POMALYST REMS** program include the following:

- Prescribers must be certified with the **POMALYST REMS** program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Prescriber agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (8.6)*] and males must comply with contraception requirements [see *Use in Specific Populations (8.6)*].
- Pharmacies must be certified with the **POMALYST REMS** program, must only dispense to patients who are authorized to receive POMALYST, and comply with REMS requirements.

Further information about the **POMALYST REMS** program is available www.CelgeneRiskManagement.com or by telephone at 1-888-423-5436.

5.3 Venous Thromboembolism

Patients receiving POMALYST have developed venous thromboembolic events (VTEs) (venous thromboembolism) reported as serious adverse reactions. In the trial, all patients were required to receive prophylaxis or anti-thrombotic treatment; 81% used aspirin, 16% warfarin, 21% heparin, and 3% clopidogrel. The rate of deep vein thrombosis or pulmonary embolism was 3%. Consider anti-coagulation prophylaxis after an assessment of each patient's underlying risk factors.

5.4 Hematologic Toxicity
Neutropenia was the most frequently reported Grade 3/4 adverse reaction, followed by anemia and thrombocytopenia. Neutropenia of any grade was reported in 50% of patients in the trial. The rate of Grade 3/4 neutropenia was 43%. The rate of febrile neutropenia was 3%.

Monitor patients for hematologic toxicities, especially neutropenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification [see *Dosage and Administration (2.2)*].

5.5 Hypersensitivity Reactions
Patients with a prior history of serious hypersensitivity associated with thalidomide or lenalidomide were excluded from studies and may be at higher risk of hypersensitivity.

5.6 Dizziness and Confusional State
In the trial, 18% of patients experienced dizziness and 12% of patients experienced a confusional state; 1% of patients experienced Grade 3/4 dizziness, and 3% of patients experienced Grade 3/4 confusional state. Instruct patients to avoid situations where dizziness or confusional state may be a problem and to not take other medications that may cause dizziness or confusional state without adequate medical advice.

5.7 Neuropathy
In the trial, 18% of patients experienced neuropathy, with approximately 9% of the patients experiencing peripheral neuropathy. There were no cases of Grade 3 or higher neuropathy adverse reactions reported.

5.8 Risk of Second Primary Malignancies
Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

5.9 Tumor Lysis Syndrome
Tumor lysis syndrome (TLS) may occur in patients treated with pomalidomide. Patients at risk for TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

6 ADVERSE REACTIONS
The following adverse reactions are described in detail in other labeling sections:

- Fetal Risk [see *Boxed Warnings, Warnings and Precautions (5.1, 5.2)*]
- Venous Thromboembolism [see *Boxed Warnings, Warnings and Precautions (5.3)*]
- Hematologic Toxicity [see *Warnings and Precautions (5.4)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.5)*]
- Dizziness and Confusional State [see *Warnings and Precautions (5.6)*]
- Neuropathy [see *Warnings and Precautions (5.7)*]
- Risk of Second Primary Malignancies [see *Warnings and Precautions (5.8)*]
- Tumor Lysis Syndrome [see *Warnings and Precautions (5.9)*]

6.1 Clinical Trials Experience in Multiple Myeloma
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In Clinical Trial 1, data were evaluated from 219 patients (safety population) who received treatment with POMALYST + Low-dose Dexamethasone (Low-dose Dex) (112 patients) or POMALYST alone (107 patients). Median number of treatment cycles was 5. Sixty-three percent of patients in the study had a dose interruption of either drug due to adverse reactions. Thirty-seven percent of patients in the study had a dose reduction of either drug due to adverse reactions. The discontinuation rate due to treatment-related adverse reaction was 3%.

Tables 2, 3, and 4 summarize all treatment-emergent adverse reactions reported for the POMALYST + Low-dose Dex and POMALYST alone groups regardless of attribution of relatedness to pomalidomide. In the absence of a randomized comparator arm, it is often not possible to distinguish adverse events that are drug related and those that reflect the patient's underlying disease.

In the clinical trial of 219 patients who received POMALYST alone[a] (n=107) or POMALYST + Low-dose Dex (n=112), all patients had at least one treatment-emergent adverse reaction.

Adverse reactions ≥10% in either arm, respectively, included: **General disorders and administration site conditions:** Fatigue and asthenia (55%, 63%), Pyrexia (19%, 30%), Edema peripheral (23%, 16%), Chills (9%, 11%), Pain (6%, 5%); **Blood and lymphatic system disorders:** Neutropenia (52%, 47%), Anemia (38%, 39%), Thrombocytopenia (25%, 23%), Leukopenia (11%, 18%), Lymphopenia (4%, 15%); **Gastrointestinal disorders:** Constipation (36%, 35%), Diarrhea (34%, 33%), Nausea (36%, 22%), Vomiting (14%, 13%); **Infections and infestations:** Pneumonia (23%, 29%), Upper respiratory tract infection (32%, 25%), Urinary tract infection (8%, 16%); **Musculoskeletal and connective tissue disorders:** Back pain (32%, 30%), Musculoskeletal chest pain (22%, 20%), Muscle spasms (19%, 19%), Arthralgia (16%, 15%), Musculoskeletal pain (11%, 15%), Pain in extremity (5%, 14%), Muscular weakness (12%, 12%), Bone pain (12%, 5%); **Respiratory, thoracic and mediastinal disorders:** Dyspnea (34%, 45%), Cough (14%, 21%), Epistaxis (15%, 11%); **Metabolism and nutritional disorders:** Decreased appetite (22%, 18%), Hyperglycemia (12%, 15%), Hyponatremia (10%, 13%), Hypercalcemia (21%, 12%), Hypocalcemia (6%, 12%), Hypokalemia (10%, 11%); **Skin and subcutaneous tissue disorders:** Hyperhidrosis (6%, 16%), Rash (22%, 16%), Night sweats (5%, 13%), Dry skin (9%, 11%), Pruritus (15%, 11%); **Nervous system disorders:** Dizziness (20%, 17%), Tremor (9%, 13%), Headache (13%, 8%), Neuropathy peripheral (10%, 7%); **Investigations:** Blood creatinine increased (15%, 11%), Weight increased (1%, 11%), Weight decreased (14%, 8%); **Psychiatric disorders:** Insomnia (7%, 14%), Confusional state (10%, 13%), Anxiety (11%, 7%); **Renal and urinary disorders:** Renal failure (15%, 10%).

Grade 3/4 adverse reactions reported in 90% of patients treated with POMALYST[a] alone (96/107) and 88% with POMALYST + Low-dose Dex (99/112).

Grade 3/4 Adverse Reactions ≥ 5% in either arm, respectively, included: **Blood and lymphatic system disorders:** Neutropenia (47%, 38%), Anemia (22%, 21%), Thrombocytopenia (22%, 19%), Leukopenia (6%, 10%), Lymphopenia (2%, 7%); **Infections and infestations:** Pneumonia (16%, 23%), Urinary tract infection (2%, 8%), Sepsis (6%, 3%); **Metabolism and nutritional disorders**: Hypercalcemia (9%, 1%); **General disorders and administration site conditions**: Fatigue and asthenia (11%, 13%); **Investigations**: Blood creatinine increased (6%, 3%); **Respiratory, thoracic and mediastinal disorders**: Dyspnea (7%, 13%); **Musculoskeletal and connective tissue disorders:** Back pain (12%, 9%), Muscular weakness (6%, 4%); **Renal and urinary disorders:** Renal failure (9%, 6%).

Serious adverse events were reported in 67% of patients treated with POMALYST[a] (72/107) and 62% with POMALYST + Low-dose Dex (69/112).

Serious Adverse Reactions in ≥2 patients in either arm, respectively, included: **Infections and infestations**: Pneumonia (14%, 19%), Urinary tract infection (0%, 5%), Sepsis (6%, 3%); **Respiratory, thoracic and mediastinal disorders**: Dyspnea (5%, 6%); **General disorders and administration site conditions**: Pyrexia (3%, 5%); General physical health deterioration (0%, 2%); **Cardiac disorders:** Atrial fibrillation (2%, 3%), Cardiac failure congestive (0%, 3%); **Renal and urinary disorders**: Renal failure (8%, 6%), **Gastrointestinal disorders:** Constipation (1%, 3%); **Blood and lymphatic system disorders:** Febrile neutropenia (5%, 1%); **Metabolism and nutrition disorders**: Dehydration (5%, 3%), Hypercalcemia (5%, 2%); **Musculoskeletal and connective tissue disorders:** Back pain (4%, 2%)

[a]POMALYST alone arm includes all patients randomized to the POMALYST alone arm who took study drug; 61 of the 107 patients had dexamethasone added during the treatment period.

Other Adverse Reactions
Other adverse reactions of POMALYST in patients with multiple myeloma, not described above, and considered important:

Ear and labyrinth disorders: Vertigo
Hepatobiliary disorders: Hyperbilirubinemia
Infections and infestations: Pneumocystis jiroveci pneumonia, Respiratory syncytial virus infection, Neutropenic sepsis
Investigations: Alanine aminotransferase increased
Metabolism and nutritional disorders: Hyperkalemia
Renal and urinary disorders: Urinary retention
Reproductive system and breast disorders: Pelvic pain
Respiratory, thoracic, and mediastinal disorders: Interstitial lung disease

6.2 Postmarketing Experience
The following adverse drug reactions have been identified from the worldwide post-marketing experience with POMALYST: Pancytopenia, tumor lysis syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS
Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp).

7.1 Drugs That May Increase Pomalidomide Plasma Concentrations
CYP1A2 inhibitors: Pomalidomide exposure is increased when POMALYST is co-administered with a strong CYP1A2 inhibitor (fluvoxamine) in the presence of a strong CYP3A4/5 and P-gp inhibitor (ketoconazole). Ketoconazole in the absence of a CYP1A2 inhibitor does not increase pomalidomide exposure. Avoid co-administration of strong CYP1A2 inhibitors (eg, ciprofloxacin and fluvoxamine) [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*]. If it is medically necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-gp, POMALYST dose should be reduced by 50%.

The effect of a CYP1A2 inhibitor in the absence of a co-administered CYP3A4 and P-gp inhibitor has not been studied. Monitor for toxicities if CYP1A2 inhibitors are to be co-administered in the absence of a co-administered CYP3A4 and P-gp inhibitor, and reduce dose if needed.

7.2 Drugs That May Decrease Pomalidomide Plasma Concentrations
Smoking: Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

CYP1A2 inducers: Co-administration of POMALYST with drugs that are CYP1A2 inducers has not been studied and may reduce pomalidomide exposure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X **[see *Boxed Warnings* and *Contraindications (4)*]**

Risk Summary

POMALYST can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy. POMALYST is a thalidomide analogue.

Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented, and mortality at or shortly after birth has been reported in about 40% of infants.

Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

Animal Data

Pomalidomide was teratogenic in both rats and rabbits in the embryo-fetal developmental studies when administered during the period of organogenesis.

In rats, pomalidomide was administered orally to pregnant animals at doses of 25 to 1000 mg/kg/day. Malformations or absence of urinary bladder, absence of thyroid gland, and fusion and misalignment of lumbar and thoracic vertebral elements (vertebral, central, and/or neural arches) were observed at all dose levels. There was no maternal toxicity observed in this study. The lowest dose in rats resulted in an exposure (AUC) approximately 85-fold of the human exposure at the recommended dose of 4 mg/day. Other embryo-fetal toxicities included increased resorptions leading to decreased number of viable fetuses.

In rabbits, pomalidomide was administered orally to pregnant animals at doses of 10 to 250 mg/kg/day. Increased cardiac malformations such as interventricular septal defect were seen at all doses with significant increases at 250 mg/kg/day. Additional malformations observed at 250 mg/kg/day included anomalies in limbs (flexed and/or rotated fore- and/or hindlimbs, unattached or absent digit) and associated skeletal malformations (not ossified metacarpal, misaligned phalanx and metacarpal, absent digit, not ossified phalanx, and short not ossified or bent tibia), moderate dilation of the lateral ventricle in the brain, abnormal placement of the right subclavian artery, absent intermediate lobe in the lungs, low-set kidney, altered liver morphology, incompletely or not ossified pelvis, an increased average for supernumerary thoracic ribs, and a reduced average for ossified tarsals. No maternal toxicity was observed at the low dose (10 mg/kg/day) that resulted in cardiac anomalies in fetuses; this dose resulted in an exposure (AUC) approximately equal to that reported in humans at the recommended dose of 4 mg/day. Additional embryo-fetal toxicity included increased resorption.

8.3 Nursing Mothers

It is not known if pomalidomide is excreted in human milk. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from POMALYST, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of POMALYST in patients below the age of 18 years have not been established.

8.5 Geriatric Use

No dosage adjustment is required for POMALYST based on age.

Of the total number of patients in clinical studies of POMALYST, 41% were aged 65 years and older, while 12% were aged 75 years and older. No overall differences in effectiveness were observed between these patients and younger patients. In this study, patients aged greater than or equal to 65 years were more likely to experience pneumonia than patients aged less than or equal to 65 years.

8.6 Females of Reproductive Potential and Males

POMALYST can cause fetal harm when administered during pregnancy [see *Use in Specific Populations (8.1)*]. Females of reproductive potential must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy.

Females

Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously: one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner's vasectomy, and 1 additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALYST therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

Females of reproductive potential must have 2 negative pregnancy tests before initiating POMALYST. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing POMALYST. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. POMALYST treatment must be discontinued during this evaluation.

Males

Pomalidomide is present in the semen of males who take POMALYST. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy. Male patients taking POMALYST must not donate sperm.

8.7 Renal Impairment

Pomalidomide and its metabolites are primarily excreted by the kidneys [see *Clinical Pharmacology (12.3)*]. The influence of renal impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Patients with serum creatinine greater than 3.0 mg/dL were excluded in clinical studies. Avoid POMALYST in patients with a serum creatinine greater than 3.0 mg/dL.

8.8 Hepatic Impairment

Pomalidomide is metabolized in the liver [see *Clinical Pharmacology (12.3)*]. The influence of hepatic impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0 x upper limit normal (ULN) were excluded in clinical studies. Avoid POMALYST in patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0 x ULN.

10 OVERDOSAGE

No specific information is available on the treatment of overdose with pomalidomide, and it is unknown whether pomalidomide or its metabolites are dialyzable.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies examining the carcinogenic potential of pomalidomide have not been conducted. One of 12 monkeys dosed with 1 mg/kg of pomalidomide (an exposure approximately 15-fold of the exposure in patients at the recommended dose of 4 mg/day) developed acute myeloid leukemia in a 9-month repeat-dose toxicology study.

Pomalidomide was not mutagenic or clastogenic in a battery of tests, including the bacteria reverse mutation assay (Ames test), the in vitro assay using human peripheral blood lymphocytes, and the micronucleus test in orally treated rats administered doses up to 2000 mg/kg/day.

In a fertility and early embryonic development study in rats, drug-treated males were mated with untreated or treated females. Pomalidomide was administered to males and females at doses of 25 to 1000 mg/kg/day. When treated males were mated with treated females, there was an increase in post-implantation loss and a decrease in mean number of viable embryos at all dose levels. There were no other effects on reproductive functions or the number of pregnancies. The lowest dose tested in animals resulted in an exposure (AUC) approximately 100-fold of the exposure in patients at the recommended dose of 4 mg/day. When treated males in this study were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (*Medication Guide)*

Embryo-Fetal Toxicity

Advise patients that POMALYST is contraindicated in pregnancy [see *Contraindications (4)*]. POMALYST is a thalidomide analogue and may cause serious birth defects or death to a developing baby [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)*].

- Advise females of reproductive potential that they must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy.
- Initiate POMALYST treatment in females of reproductive potential only following a negative pregnancy test.
- Advise females of reproductive potential of the importance of monthly pregnancy tests and the need to use 2 different forms of contraception, including at least 1 highly effective form, simultaneously during POMALYST therapy, during therapy interruption, and for 4 weeks after she has completely finished taking POMALYST. Highly effective forms of contraception other than tubal ligation include IUD and hormonal (birth control pills, injections, patch, or implants) and a partner's vasectomy. Additional effective contraceptive methods include latex or synthetic condom, diaphragm, and cervical cap.
- Instruct patient to immediately stop taking POMALYST and contact her doctor if she becomes pregnant while taking this drug, if she misses her menstrual period or experiences unusual menstrual bleeding, if she stops taking birth control, or if she thinks FOR ANY REASON that she may be pregnant.
- Advise patient that if her doctor is not available, she can call 1-888-668-2528 for information on emergency contraception [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.6)*].
- Advise males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy.
- Advise male patients taking POMALYST that they must not donate sperm [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.6)*].
- All patients must be instructed to not donate blood while taking POMALYST and for 1 month following discontinuation of POMALYST [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.6)*].

POMALYST REMS Program

Because of the risk of embryo-fetal toxicity, POMALYST is only available through a restricted program called POMALYST REMS [see *Warnings and Precautions (5.2)*].

- Patients must sign a Patient-Prescriber agreement form and comply with the requirements to receive POMALYST. In particular, females of reproductive potential must comply with the pregnancy testing, contraception requirements, and participate in monthly telephone surveys. Males must comply with the contraception requirements [see *Use in Specific Populations (8.6)*].
- POMALYST is available only from pharmacies that are certified in POMALYST REMS. Provide patients with the telephone number and Web site for information on how to obtain the product.

Venous Thromboembolism

Inform patients of the potential risk of developing venous thromboembolic events and discuss the need for appropriate prophylactic treatment [see *Venous Thromboembolism (5.3)*].

Hematologic Toxicities

Inform patients on the risks of developing neutropenia, thrombocytopenia, and anemia and the need to report signs and symptoms associated with these events to their healthcare provider for further evaluation [see *Hematologic Toxicities (5.4)*].

Hypersensitivity

Inform patients of the potential for a severe hypersensitivity reaction to POMALYST if they have had such a reaction in the past to either THALOMID® or REVLIMID® [see *Hypersensitivity Reaction (5.5)*].

Dizziness and Confusional State

Inform patients of the potential risk of dizziness and confusional state with the drug, to avoid situations where dizziness or confusional state may be a problem, and not to take other medications that may cause dizziness or confusional state without adequate medical advice [see *Dizziness and Confusional State (5.6)*].

Neuropathy

Inform patients of the risk of neuropathy and to report the signs and symptoms associated with these events to their healthcare provider for further evaluation [see *Neuropathy (5.7)*].

Second Primary Malignancies

Inform the patient that the potential risk of developing acute myelogenous leukemia during treatment with POMALYST is unknown [see *Risk of Second Primary Malignancies (5.8)*].

Tumor Lysis Syndrome

Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see *Warning and Precautions (5.9)]*.

Dosing Instructions

Inform patients on how to take POMALYST [see *Dosage and Administration (2.1)*]

- POMALYST should be taken once daily at about the same time each day.
- POMALYST should be taken without food (at least 2 hours before or 2 hours after a meal).
- The capsules should not be opened, broken, or chewed. POMALYST should be swallowed whole with water.
- Instruct patients that if they miss a dose of POMALYST, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take POMALYST at the usual time. Warn patients not to take 2 doses to make up for the one that they missed.

Other Information

Advise patients who smoke to stop because smoking may reduce the efficacy of pomalidomide [see *Drug Interactions (7.2)*].

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