COUNTY OF LOS ANGELES **DEPARTMENT OF HEALTH SERVICES**

HARBOR-UCLA MEDICAL CENTER

SUBJECT: BLACK BOX WARNING MEDICATION GUIDELINES **POLICY NO. 327**

PURPOSE:
To provide guidance on handling medications with FDA Black Box Warnings (BBW).

DEFINITION:
Boxed Warnings, also called **"Black Box"** warnings, are prominently displayed summaries of serious adverse reactions and potential safety hazards for a drug product in its prescribing information as required by the Food and Drug Administration (FDA). These boxed warnings are the most serious of warnings for a drug. A boxed warning is warranted when a drug presents a unique risk to benefit concern compared with other drugs in the same class, when a potential adverse reaction is extremely significant above the drug's benefit, and when such adverse reactions can be prevented or reduced by restricted use or observance of defined cautions. Often boxed warnings are based on observed adverse reactions, but they can also be based on animal toxicity or expected adverse reactions. These boxed warnings are described in the U.S. Food and Drug Administration, Center for Devices and Radiological Health, Code of Federal Regulations [21CFR 201.57(e)].

POLICY:
At Harbor-UCLA Medical Center, all healthcare providers shall refer to the guidelines specified in this policy when handling medications with identified Black Box Warnings. DHS Medication Safety Committee and DHS Pharmacy & Therapeutics Committee will maintain and update the guidelines as necessary.

PROCEDURE:
Refer to Appendix A: DHS High Priority Black Box Warning Medications

Revised and Approved by:
Medical Executive Committee on 11/2020

Janine R. E. Vintch, M.D.
Professional Staff Association, President

EFFECTIVE DATE: 8/08 **SUPERSEDES:**
REVISED: 3/14, 8/17, 11/20
REVIEWED: 5/14, 8/17, 11/20
REVIEWED COMMITTEE: Pharmacy and Therapeutics Committee

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Appendix A: DHS High Priority Black Box Warning Medications

Drug Name/Class	Formulary Restriction	Summary of Selected Black Box Warning	Physician: Recommended Baseline and Ongoing Treatment Considerations	RN Advisory	Pharmacist Advisory
Acetaminophen (Tylenol)	IV requires Prior Authorization Form	Hepatotoxicity	• Ensure total daily dose does not exceed maximum recommendations (4 grams/24 hours for adult patients; 75mg/kg/24hrs for pediatric patients) • Check LFT of patients on chronic acetaminophen therapy • When feasible use pain management PowerPlans		• Review patient's profile for multiple acetaminophen containing products to ensure total acetaminophen does not exceed max recommendations: For adults NTE: 4grams/24hrs (Consider avoiding use or adjusting doses in patients with severe liver disease or increased alcohol consumption; recommend limit to ≤2g/day). For pediatrics NTE 75mg/kg/24hrs. • Counsel outpatients not to exceed the max daily recommendations
Amiodarone (Cordarone)	No Restriction	• Can cause potentially fatal toxicities including pulmonary toxicity, hepatic toxicity and worsened arrhythmias.	Obtain baseline ECG, CXR, thyroid function tests, liver function tests, and pulmonary function tests. • Check LFT every 3-6 months if patients receiving high maintenance therapy. • Repeat thyroid function tests, liver function tests yearly • Repeat history, physical exam and CXR every 3-6 months • Discontinue or reduce dose if the increase exceeds three times normal or doubles in a patient with an elevated baseline. • The BBW pertains to the tablet but may also apply to IV admin.	Monitor for arrhythmias	• Review patient's profile for potential cyp3A4 drug-drug interactions • Review LFT and recommend discontinuation or dose reduction if increase exceeds 3x normal or doubles in patient with elevated baseline

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Andexanet alfa (Andexxa)	Prior Authorization Form required	Thromboembolic Risks, Ischemic Risks, Cardiac Arrest, and Sudden Deaths	• Re-evaluate Anti-FXa activity upon completion of administration. • Monitor for thromboembolic events • Initiate anticoagulation when clinically appropriate. • Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.	Monitor signs/symptoms of venous thromboembolic events, ischemic events, or cardiac arrest and notify provider immediately.	• Review patient's medication history of apixaban or rivaroxaban. (Ensure appropriately used for acute, life- threatening reversal of oral factor Xa inhibitors (i.e., Rivaroxaban, apixaban, exodaban, betrixaban) • Verify prior authorization form has been submitted and patient meets the approval criteria and the correct dose is ordered based on the criteria
Antiarrhythmics (Class 1C) • **Propafenone (Rythmol SR)** • **Flecainide (Tambocor)**	Cardiology	• Significant risk in patients with structural heart disease • Flecainide is not recommended in patients with chronic atrial fibrillation/flutter due to ventricular proarrhythmic effects. • Reserved for patients with life-threatening ventricular arrhythmias.		Monitor heart rate signs/symptoms of cardiac failure	• Verify baseline ECG is completed or ordered for newly initiated therapy
Carbamazepine (Tegretol)	No Restriction	• Aplastic Anemia • Agranulocytosis • Severe & fatal dermatologic reactions, including: - toxic epidermal necrolysis (TENS) - Stevens-Johnson syndrome (SJS) • The risk is increased in patients with the variant HLA-B*1502 allele, found almost exclusively in patients of Asian ancestry. Patients who test positive for HLA- B*1502 should not be treated with carbamazepine unless the expected benefit clearly outweighs the increased risk of SJS/TEN. • Over 90% of carbamazepine treated patients who will experience SJS/TEN	• Order CBC at baseline and every 3-6 months. • If a patient, in the course of treatment exhibits low or decreased white blood cell or platelet counts, monitor closely and discontinue medication if significant bone marrow depression develops • Prior to therapy, patients with ancestry in at-risk populations should be screened for the HLA-B*1502 allele. • Discontinue in patients who have a serious dermatological reaction.	• Monitor for baseline CBC; and notify physician for any decrease in WBC or platelets • Monitor for skin reactions (rash, hives, sores in the mouth, or blistering/peeling of the skin) during the therapy and notify physicians immediately.	• Verify CBC is ordered at baseline

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		have this reaction within the first few months of treatment. • Patients of any ethnicity or genotype (including HLA-B*1502 positive) who have been taking carbamazepine for more than a few months are at low risk of SJS/TEN from carbamazepine.			
Erythropoiesis-Stimulating Agents: • **Darbepoetin alfa (Aranesp)** **Epoetin Alfa (Procrit)**	• Restricted to initiation of therapy only when hemoglobin (Hgb) levels <10g/dL. Monitor Hgb levels: maximum Hgb of 10g/dL for chronic kidney disease (CKD) without dialysis and 11g/dL for CKD with dialysis Non-formulary: Epoetin Alfa (Procrit)	• Increase the risk of: (Risk is increased when administered to target Hb levels >11g/dL) - death - myocardial infarction & stroke - venous thromboembolism - thrombosis of vascular access - tumor progression or recurrence in patients with cancer. • In patients with cancer, ESAs shortened overall survival. • Patient with chronic kidney disease have increased risk of death, serious cardiovascular events (thromboembolic events), and strokes when hemoglobin >11g/dL. For Epoetin alfa in perisurgery use, prophylaxis for deep venous thrombosis is recommended	• For chronic kidney disease (CKD) patients that require dialysis, reduce or withhold dose if hemoglobin exceeds 11 g/dL • For non-dialysis chronic kidney disease (CKD) patients, reduce or hold dose if hemoglobin exceeds 10 g/dL • For CKD and cancer patients, reduce dose if hemoglobin increases more than 1g/dl in any 2 week period. • Do not prescribe for patients receiving myelosuppressive therapy when the anticipated outcome is cure • For patients with incurable malignancies on palliative or supportive therapy – use the lowest dose needed to avoid red blood cell transfusions.	Withhold drug as ordered.	• For chronic kidney disease (CKD) patients that require dialysis, do not dispense dose and notify prescriber if hemoglobin exceeds 11 g/dL • For non-dialysis chronic kidney disease (CKD) patients, do not dispense dose and notify prescriber if hemoglobin exceeds 10 g/dL • For non-CKD patients, do not dispense dose and notify prescriber if hemoglobin exceeds • 12 g/dL or rises by 1g/dL in any 2 week period
Direct Oral Anticoagulants (DOACs) • **Rivaroxaban (Xarelto)** • **Apixaban (Eliquis)** • **Dabigatran (Pradaxa)** • **Edoxaban (Savaysa)**	• Restrictions per Rivaroxaban (Xarelto) Prior Authorization Form • VTE prophylaxis after hip/knee surgery • Non-valvular atrial	• Spinal/Epidural Hematomas have occurred in patients who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. optimal timing between the administration of rivaroxaban and neuraxial procedures is not known.	• Prior to scheduling patients for spinal procedures consider risk of developing epidural or spinal hematoma which can result in long- term or permanent paralysis. • Prior to scheduling a spinal procedure evaluate patient for age, renal and hepatic impairment and	• Follow withholding parameters ordered for patients on or with a pending epidural • Monitor for signs/symptoms of bleeding (e.g., neurological impairment, GI bleeding)	• Verify patient's CrCl and adjust dose accordingly • Before initiating/switching anticoagulants therapy, ensure appropriate time has elapsed between doses • Review patient's profile to assess

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	fibrillation Stroke Prevention ▯ DVT/PE treatment ▯ Non-formulary: - Apixaban (Eliquis) - Dabigatran (Praxada) - Edoxaban (Savaysa)	• Premature discontinuation increases the risk of thrombotic events • Edoxaban should not be used in patients with nonvalvular arterial fibrillation who have a CrCl greater than 95 mL/ min due to an increased risk of ischemic stroke	make necessary adjustments to regimen. • Wait at least 18 hours after last dose before removing epidural catheter. • Wait at least 6 hours after catheter removal prior to administering next dose. • If traumatic puncture occurs, administration is to be delayed for 24 hours if renal function is normal • Monitor for signs/symptoms of neurological impairment. • If neurologic compromise is noted, urgent treatment is necessary. • Initiate and maintain anticoagulant therapy based on evidence-based practice guideline and patient-specific risk factors. • Use evidence-based practice guidelines to manage oral anticoagulants in perioperative setting. • None of the DOCs have been approved for use in the setting of a prosthetic heart valve • Apixaban, edoxaban, and rivaroxaban are not recommended for use in patients with severe hepatic impairment • If edoxaban or dabigatran are to be used for therapeutic indication, the patients require treatment for 5 to 10 days with a parenteral agent prior to starting these two oral agents.		a need for dosage adjustment based on risk factors and drug. (indication) • Avoid DOAC therapy while indwelling catheter is in place • Prior to resuming DOAC therapy, ensure appropriate amount of time has elapsed since procedure • Avoid in patients with history of traumatic or repeated epidural or spinal punctures and history of spinal deformity or spinal surgery • Avoid concomitant use of other drugs that affect hemostasis, such as non- steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
Divalproex Sodium and	No Restriction	• Hepatic failure resulting in fatalities • Greater risk of developing fatal	• Check LFTs 3-6 months with initial therapy or dosing change	• Verify pregnancy status prior to administration.	• Verify LFTs are ordered with initial therapy (Verify CBC and LFTs at

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Derivatives		hepatotoxicity in: >> in children under the age of two years >> in patients with hereditary mitochondrial disease. • Increased risk of pancreatitis • Teratogenicity	• Exercise increased caution when prescribing valproate to: - patients with a prior history of hepatic disease - children under two years old - patients with hereditary mitochondrial disease • Check amylase and triglyceride if symptoms of possible pancreatitis • Order pregnancy test for women of childbearing age. • Do not use for migraine if pregnant • When treating a pregnant woman or a woman of childbearing potential, carefully consider both the potential risks and benefits of treatment and provide appropriate counseling.	• If patient is pregnant, notify prescriber prior to administration. • Report to the physician if elevated LFTs.	baseline annually) • Verify pregnancy status prior to order verification/dispensing • Dark urine or pale stools, loss of appetite, stomach pain, yellow skin or eyes; sudden and severe stomach pain, n/v
Dopamine	No Restriction	Vesicant. Antidote for peripheral ischemia provided as boxed warning.	• Recommended extravasation treatment: As soon as possible after extravasation is noted – infiltrate the area with 10 to 15 mL of 0.9% Sodium	• Ensure proper needle or catheter placement prior to and during infusion. • Watch I.V. site closely.	
Fentanyl Transdermal (Duragesic)	• Management of pain in opioid-tolerant patients (dose 60mg/day of ORAL morphine or equivalent for 7 days). Do not use for acute, intermittent, or mild pain • Prior Authorization required for outpatient use.	• Addiction, abuse, and misuse • Life-threatening respiratory depression • Should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. • Accidental ingestion/exposure may occur. • Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in	• Assess patients for their clinical risks for opioid abuse or addiction prior to prescribing and routinely monitor all patients for signs of misuse, abuse and addiction during treatment. • Do not use in opioid-naive patients • Do not use for break through pain • Do not use for acute post-op pain. • Use facility fentanyl patch order form for all fentanyl patch prescriptions. • Order only if all dosing criteria are met.	• Apply patch to intact, non-irritated, and non-irradiated skin on a flat surface such as chest, back, flank, or upper arm. • Do not apply heat to patch area. Notify prescriber if patient develops fever while wearing the transdermal system. • Monitor respiratory status while on medication • Ensure prescriber has completed fentanyl patch order form for prescriptions.	• Inpatient: Verify prescriber has completed Fentanyl Patch Order Form and the dosing criteria is met before order verification and dispensing. • Outpatient: Pharmacist to confirm provider on authorized prescriber list. Counsel patients on recommended handling and disposal instructions.

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		profound sedation, respiratory depression, coma and death • Neonatal Opioid Withdrawal Syndrome • Cytochrome P450 3A4 Interaction • Risk of Increased Fentanyl Absorption with Application of External Heat • Contraindicated for use in conditions in which the risk of life- threatening respiratory depression is significantly increased, including use as an as-needed analgesic, use in non-opioid tolerant patients, acute pain, and postoperative pain.	• Review patient's profile for drug-drug interactions and consider implications. • Counsel patients and/or their caregivers on safe use, serious risks, storage, and disposal of these products. • Strict adherence to the recommended handling and disposal instructions may prevent accidental exposure.	• Remove old patch and always assess patient to ensure not patch is on patient before applying new patch. • Document application site on MAR	
Haloperidol (Haldol)	Haloperidol IV administration to be monitored by continuous and/or 12-lead ECG. If not possible in combative patients, initiate ECG as soon as possible	• Sudden death, QT prolongation and Torsade's de Pointes (TdP) with haloperidol, especially when given intravenously, or at doses higher than recommended. FDA approved for IM. • Considerable evidence that the IV use of haloperidol is a relatively common off-label clinical practice. • Increased mortality in elderly patients with dementia-related psychosis	• Order ECG monitoring prior and during IV administration • If not possible in combative patient, initiate ECG as soon as possible. • Haloperidol injection is not approved for the treatment of patients with dementia-related psychosis.	• ECG monitoring prior and during IV administration. If not possible in combative patient, monitor ECG as soon as possible and monitor for prolonged QT and TdP • Monitor heart rate, signs/symptoms of cardiac failure.	• Review profile for concomitant medications known to produce Torsade's de Pointes/ QTc elongation.
Hydromorphone Injection (Dilaudid-HP)	No Restriction	• Risk of respiratory depression with abuse, addiction, and misuse • Life-threatening respiratory depression • Sedative effect is potentiated with concomitant use of alcohol, benzodiazepines and other CNS depressants • Neonatal Opioid Withdrawal Syndrome • Accidental ingestion • Risk of Medication Errors >> Do not confuse hydromorphone hydrochloride high potency injection (10mg/mL)	• Oral and Intravenous hydromorphone doses are not interchangeable. Hydromorphone Intravenous is 3-5 times more potent than the oral formulation. • Morphine and hydromorphone doses are not interchangeable. Hydromorphone is 5-6 times more potent that parenteral morphine. • Providers are encouraged to complete REMS-compliant education program prior to prescribing.	• Monitor respiratory status while on medication. • HYDROmorphone hydrochloride injection (high potency formulation) is a more concentrated solution of HYDROmorphone than HYDROmorphone hydrochloride injection and is for use in opioid- tolerant patients only. Do not confuse HYDROmorphone hydrochloride injection (high potency formulation) with	• Review appropriateness of narcotic order change, especially dosing change from morphine to hydromorphone. • Verify opioid-tolerance for HYDROmorphone hydrochloride HP injection orders. (Opioid tolerant patient is defined as using at least 60mg morphine PO, 8mg hydromorphone PO, or other equianalgesic opioid daily for a week or longer.) • Oral Solution dosing errors due to confusion between mg and mL

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		with standard parenteral formulations (1, 2, or 4mg/mL) of hydromorphone hydrochloride or other opioids.		standard parenteral formulations of HYDROmorphone hydrochloride or other opioids, as overdose and death could result.	
Immune Globulins (human, equine, rabbit)	• Hematology/Oncology • Neurology • Rheumatology • Infectious Disease • Allergy/Immunology • Pediatrics • Renal Transplant	• Renal dysfunction, acute renal failure, osmotic nephrosis, and death • Risk of thrombosis with or without risk factors.	• Check renal function (BUN, Scr, I/O's) and review profile for other concurrent nephrotoxic agents. • Carefully consider the following risk factors: advanced age, prolonged immobilization, recent surgery, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, presence of IVG filter, hyperviscosity and cardiovascular risk factors. • For patients at risk of thrombosis, administer at the minimum concentration available and at the minimum rate of infusion practicable • Ensure adequate hydration in patients before administration.	• Follow infusion as ordered. • Monitor patients carefully for signs and symptoms of thrombosis both at the time of infusion and after infusion and encourage patients to report any signs or symptoms and educate about return precautions	• Review concentration and infusion rate and follow manufacturer's recommended infusion rate. • Review profile for other concurrent nephrotoxic agents. • Call providers if NS is not ordered with appropriate hydration instructions with IVIG.

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Ketorolac (Toradol)	Restricted to a maximum of 5 days of therapy	• Oral ketorolac is only indicated as continuation of IV/IM ketorolac, if necessary. • Maximum total daily dose of oral ketorolac (40mg) • Maximum total daily dose for injectable (120mg) • Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock, have occurred. • Dosage should be adjusted for: - patients 65 years or older - patients under 50 kg (110 lbs) of body weight - patients with moderately elevated serum creatinine. • Increased risk of bleeding; Inhibits platelet function. • Reports of acute renal failure, nephritis, and nephrotic syndrome. • Increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which may be fatal. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. • Increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach and intestines, which may be fatal. • CONTRAINDICATION: - patients with advanced renal impairment - patients at risk for renal failure due to volume depletion - patients currently receiving ASA or NSAIDs because of the cumulative	• Check renal function (BUN, Scr, I/O's) • Do not order for more than 5 days • Adjust dose to renal function, age, and weight. Do not exceed 60 mg (total dose per day) of ketorolac injection in patients 65 years or older, under 50 kg (110 lbs.) of body weight, and/or for patients with moderately elevated serum creatinine. • Do not use in patients with renal impairment and in patients at risk for renal impairment due to volume depletion. • Do not administer ketorolac via epidural or intrathecal route. • Do not use in patients who have previously demonstrated hypersensitivity to ketorolac or allergic manifestations to aspirin or other (NSAIDs). Appropriate counteractive measures must be available when administering first dose. • Do not use in labor and delivery and in nursing mothers. • Do not use in patients with active peptic ulcer disease, recent GI bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding. Exercise increased caution for elderly patients, as they are at increased risk, • Do not use for the treatment of peri- operative pain in the setting of coronary artery bypass graft (CABG) surgery	• Notify prescriber if ketorolac treatment is expected to exceed 5 days. • Do not exceed total daily dose, oral (40mg), injectable (120mg) • Contact prescriber if order written for intrathecal or epidural route. • Notify prescriber of any decline in renal function prior to administering next dose. • Alert prescriber of bleeding. • Monitor signs and symptoms for thrombosis and promptly notify the prescriber. • Notify prescriber if patient is breastfeeding	• Treatment not to exceed 5 days, including total duration of IV/IM and PO use. • Check Age (>65), Weight (<50kg) and renal function and recommend appropriate dose. • Injection is contraindicated for epidural or intrathecal admin due to alcohol content

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		risk of inducing serious NSAID- related side effects. - in the setting of coronary artery bypass graft (CABG) surgery - as prophylactic analgesic before any major surgery - bleeding pts and those at high risk of bleeding - for intrathecal and epidural administration due to its alcohol content. - during labor and delivery since it may inhibit uterine contractions and adversely affect fetal circulation. - To nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates.	• Do not use in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding • Do not use as a prophylactic analgesic before any major surgery, or intra-operatively when hemostasis is critical.		
Lithium	No Restriction	• Lithium toxicity is closely related to serum lithium levels and can occur at doses close to therapeutic levels. • Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy.	• Monitor CrCl routinely • Exercise caution with concurrent administration of NSAIDs, diuretics, ACE inhibitors and ARBs, which can increase serum Li levels. Utilize lowest dose and monitor serum Li after initiation of the above medications. Determine serum concentrations twice per week during the acute phase of treatment and until serum level and clinical condition of the patient have stabilized. Renal function should be monitored every 2-3 months during the first 6 months of treatment then once a year in stables patients by the provider • Serum concentrations in uncomplicated cases receiving	Monitor for signs and symptoms of lithium toxicity: (diarrhea, vomiting, tremor, mild ataxia, drowsiness, muscular weakness, lack of coordination) and notify provider	• Verify patient's renal function and notify provider if: - Adults: avoid use if CrCl < 30 mL/min - Pediatrics: dose reduction required for CrCl < 89 mL/min • Serum lithium concentrations should be available before initiating therapy

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			maintenance therapy during remission are to be monitored at least once every 2 months. • Exercise increased caution when dosing geriatric patients.		
Long Acting Beta Agonists (Salmeterol, Formoterol/Mometasone)	Formoterol/Mometasone (Dulera): Restricted to moderate to severe asthma and COPD in patients >12 years of age.	• Increased risk of asthma-related death as monotherapy without inhaled corticosteroids (ICS) thus contraindicated. When treating patients with asthma, long acting beta agonists (LABAs) should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications which should include ICS) In pediatric and adolescent patients may increase the risk of asthma-related hospitalization when used as monotherapy, should be used in combination with ICS	• Do not initiate in patients with acutely deteriorating asthma • Do not use a LABA alone without the use of a long-term asthma control medication, such as an inhaled corticosteroid • For pediatric and adolescent patients, if adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended and must be considered. • Counsel patients to notify physician with signs/symptoms of deteriorating asthma control and seek medical attention promptly if warranted. • As LABAs do not relieve sudden-onset asthma symptoms. A rescue inhaler, such as an albuterol inhaler, should be prescribed to treat sudden asthma symptoms.	• Counsel discharged patients to notify physician with sign/symptoms of deteriorating asthma control and seek medical attention promptly if warranted Monitor respiratory status while on medication.	• Counsel patients to notify physician with signs/symptoms of deteriorating asthma control and seek medical attention promptly if warranted. • Review patient's medication profile and notify provider if LABA is being used as monotherapy for asthma and contact prescriber
Lamotrigine (Lamictal)	No restriction	• May cause severe and potentially life-threatening skin rashes requiring hospitalization (including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Angioedema). • Incidence of serious rash is higher in pediatric patients than adults. • Risk may be increased by co-administration with valproic acid, higher than recommended starting	• Monitor for signs/symptoms of rash or skin disorder. • Discontinue at first sign of rash, unless the rash is not drug related • Exercise increased caution when dosing pediatrics. • Do not exceed recommended initial dose and dose escalation • Carefully dose lamotrigine if co-	• Monitor for signs/symptoms of rash or skin disorder. Withhold dose and notify physician at first sign of rash.	• Counsel outpatients to notify physician and discontinue at first sign of rash and seek urgent medication attention

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		doses, and exceeding recommended dose titration.	administering valproic acid.		
LMWH (Enoxaparin) Fondaparinux (Arixtra)	• Enoxaparin- No restriction • Fondaparinux- Restricted to Orthopedics or patients requiring anticoagulation that have suspected acute Heparin-Induced-Thrombocytopenia (HIT) or a confirmed history of HIT. Prior Authorization required for Outpatient Use.	Risk of spinal/epidural hematoma with neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture, which can result in long-term or permanent paralysis.	• If neurologic compromise is noted, urgent treatment is necessary. • For enoxaparin, placement or removal of a spinal catheter should be delayed for at least 12 hours after administration of prophylactic doses and 24 hours for patients receiving therapeutic doses. • For fondaparinux, delay needle placement of a spinal catheter for a minimum of 72 hours and removal for at least 48 hours after previous dose. • Do not give post-procedure doses of either enoxaparin or fondaparinux for at least 4 hours after catheter removal. • A benefit-risk assessment should consider both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors.	• Follow ordered holding parameters for patients on or with a pending epidural • Monitor for signs/symptoms of neurological impairment. DO NOT administer if <4 hours after spinal catheter has been removed.	• Verify patient's renal function and adjust dose based on CrCl. • Fondaparinux is contraindicated if CrCl < 30mL/min or weight < 50kg • Avoid LMWH while indwelling catheter is in place • Prior to resuming LMWH, ensure appropriate amount of time has elapsed since procedure
Metformin containing products	No Restriction	• Lactic acidosis is a rare, but serious, metabolic complication that may occur due to metformin accumulation during treatment. When it occurs, it is fatal in approximately 50% of cases. • Death, hypothermia, hypotension, and resistant brady-arrhythmias have been reported due to metformin-associated lactic acidosis	• Check eGFR - do not initiate (or discontinue) if eGFR<30 ml/min/1.73m^2 • Initiating metformin when eGFR is between 30-45 ml/min/1.73m^2 is not recommended. Reassess risk and benefit if eGFR drops to 30-45 ml/min/1.73m^2 during therapy • Hold medication for 48 hours after IV contrast administration; reassess eGFR before restarting • Discontinue Metformin immediately if acidosis is	• Ensure metformin is held for 48 hours after IV contrast administration. • Monitor for nonspecific symptoms of lactic acidosis such as malaise, myalgia, somnolence, respiratory and abdominal distress.	

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			suspected. • Obtain an eGFR at least annually.		
Methadone (Dolophine)	• Injectable for inpatient use • Management of pain for opioid-tolerant patients (dosed with an opiate for 7 days or longer). Continuation of therapy for inpatients being treated • Palliative Care patients initiated in the inpatient setting who have a long-term need for methadone. • Do not use for acute, intermittent, or mild pain • PA required for outpatient use	• Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioids • Life-threatening Respiratory depression is the chief hazard associated with methadone hydrochloride • Life-threatening QT elongation and serious arrhythmias have been reported. • Abuse, addiction, misuse potential. • Accidental ingestion • Neonatal opioid withdrawal syndrome • Interactions with drugs affecting cytochrome p450 isoenzymes • Sedative effects are potentiated with concomitant use of alcohol, benzodiazepines and other CNS depressants	• Avoid use in opioid-naïve patients. • Do not use for acute, intermittent pain, or "PRN" use • Titrate dose slowly. Adverse effects may have delayed manifestation due to accumulation and long half-life • Monitor ECG for patient on long term (≥6 months) use or when concomitantly used with pro-arrhythmic medications (e.g. propafenone, flecainide, procainamide). • Use caution when prescribing concomitantly with medications known to cause respiratory depression • Evaluate patient for any history of structural heart disease, arrhythmia, syncope, and for existence of potential drug interactions. • Closely monitor patients for changes in cardiac rhythm during initiation and titration. • Assess patients for their clinical risks for opioid abuse or addiction prior to prescribing and routinely monitor all patients for signs of misuse, abuse and addiction during treatment. • When treating a pregnant woman for prolonged period, advised the risk of neonatal opioid withdrawal syndrome, and ensure treatment is available.	For hospitalized patients monitor cardiac and respiratory functions and alert prescriber for excessive sedation, lethargy and/or changes in cardiac rhythm.	• Review patient's medication profile for potential interaction with pro-arrhythmic medications and/or medications associated with QT changes. • Review appropriateness of methadone dose, frequency and indication. • Do not dispense for as needed (PRN) use • Counsel outpatients to strictly adhere to the recommended handling and disposal instructions to prevent accidental exposure to themselves or others. • Do not dispense for mild, intermittent or acute pain. • Outpatient: Do not dispense for opioid use disorder (OUD) • Inpatient: Refer to SHOUT guidelines for initiation/maintenance dosing for OUD

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Methotrexate	• Hematology/Oncology • Rheumatology • Dermatology* • OB/GYN • Ophthalmology • Gastroenterology	• Intended use for life- threatening neoplastic disease or severe rheumatoid arthritis and psoriasis unresponsive to other therapies • Bone marrow suppression • Aplastic anemia • Gastrointestinal toxicity • High dose of MTX and concurrent NSAIDs use may increase risk of severe bone marrow suppression, aplastic anemia, and GI toxicity. • Hepatotoxicity • Pulmonary toxicity/pneumonitis • Teratogenicity • Renal toxicity • Tumor lysis syndrome	• Check CBC, CMP, chest X-ray at baseline and every 3-6 months, consider more frequent monitoring with high doses, especially in oncology patients. • Avoid use of NSAIDs that increase risk of ulcerative stomatitis, aplastic anemia and bone marrow suppression. • Monitor for pulmonary toxicity symptoms and if is suspected, refer for pulmonary function testing. • Monitor gastrointestinal toxicity symptoms. • Monitor for renal toxicity and tumor lysis syndrome • Evaluate/educate patient for teratogenicity risk and order pregnancy test if indicated	• Monitor for diarrhea, ulcerative stomatitis, decreased urine output, infections, couch, shortness of breath, skin rash, enlarged lymph nodes, fever, night sweats, pruritus and notify physician if patient exhibits these symptoms Monitor for hypersensitivity reactions and notify physician if exhibited.	• Verify dose is appropriate for indication. Confirm oncological indication if dose ordered daily. • Check CBC, CMP with new orders and all oncology orders. • Review if the patient is at childbearing age and notify physician if pregnancy test should be performed. • OP to provide all patients with a copy of the free ISMP high-alert medication consumer leaflet on oral methotrexate (found at: www.ismp.org/AHRQ/default.asp).
Metoclopramide (Reglan)	No restriction	• Chronic treatment can cause tardive dyskinesia, a serious movement disorder that is often irreversible Risk is increased with duration of treatment and total cumulative dose Prolonged treatment with metoclopramide (greater than 12 weeks) should be avoided in all but rare cases where therapeutic benefit outweighs the risk	• Discontinue metoclopramide therapy in patients who develop signs or symptoms of tardive dyskinesia • Avoid prolonged treatment (> 12 weeks).	Monitor signs of tardive dyskinesia (jerky muscle movements, tongue thrusting, facial grimacing/ticks, and random movements of extremities) extrapyramidal side effects, parkinsonian-like symptoms and notify the prescriber.	• Review medication profile for concomitant use of other drugs that are likely to cause EPS • Avoid prolonged treatment of >12 weeks
Midazolam (Versed)	• Anesthesiology • Emergency Medicine Specialties/ area approved per facility moderate sedation policies	• May cause severe respiratory depression, respiratory arrest, or apnea. Use with extreme caution, particularly in noncritical care settings. For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout	• Ensure immediate availability of flumazenil before administration • Utilize lower doses for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system	• Closely monitor respiratory and cardiovascular status. • Verify IV rate prior to administration in neonates.	• Verify dose is appropriate based on patient population and concurrent medication list

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		the procedure. • Initial doses in older (over 60 years) or debilitated patients should be conservative; start at the lower end of dosing range. • Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Lower dose of midazolam should be initiated if necessary. • Do not administer by rapid I.V. injection in neonates; severe hypotension and seizures have been reported; particularly with concomitant fentanyl use.	depressants. • Initial doses and subsequent doses are to be titrated slowly. • Pediatric doses are to be calculated on an mg/kg basis.		
Midodrine	No Restriction	• Can cause supine hypertension. Systolic elevations of this degree were most likely to be observed in patients with relatively elevated pre- treatment systolic blood pressures (mean 170 mmHg). Not recommended in patients with initial supine systolic pressure above 180 mmHg. It is essential to monitor supine and sitting blood pressures in patients while on midodrine.	Carefully consider the risks and benefits of midodrine use in inpatients Prescribe only for patients whose lives are considerably impaired despite standard clinical care for symptomatic orthostatic hypotension (OH). • Assess potential for supine and sitting hypertension, renal function and hepatic function prior to prescribing. • Although doses may be given in 3 hour intervals, if required, to control symptoms, do not prescribe more frequently • Closely monitor hepatic function, renal function and blood pressure.	• Check blood pressure every shift. For ambulatory patients, check standing blood pressure with every shift. Withhold dose and notify prescriber if signs or symptoms of supine hypertension.	•

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Morphine Extended-release (e.g. Kadian, MS Contin)	**Inpatient:** • Kadian-Restricted to G-tube or J-tube patients who are unable to swallow pills • Kadian 100mg strength restricted to opioid tolerant patients (dosed at 60mg/day of ORAL morphine or equivalent for 7 days) • MS Contin- No restriction. **Outpatient** • Kadian has quantity limit of 2 capsules daily, prior authorization required when limits exceeded. • MS Contin has quantity limit 90 tablets per dispense, maximum 3 dispenses per 75-day period • No prior authorization required when patient has cancer related pain and/or end-stage medical condition.	• Abuse, addiction, and misuse potential • Fatal respiratory depression may occur, with highest risk at initiation and with dose increases. • Indicated for opioid tolerant patients for management of moderate to severe pain when continuous around the clock opioid is needed. Not to be used for "as needed" (PRN) analgesic • Opioid-naïve patients are NOT to receive ≥ 100 mg single dose • Capsule beads that are chewed, crushed, or dissolved may increase the risk of rapid release and absorption resulting in a fatal dose • Accidental ingestion can result in a fatal overdose of morphine, especially in children. • Neonatal Opioid Withdrawal Syndrome; • Sedative effects are potentiated with concomitant use of benzodiazepines, alcohol or other CNS depressants	• Do not prescribe partial doses - Only full capsule dosages are to be used • Kadian extended-release capsules are indicated for once daily administration for moderate to severe pain requiring continuous, around the clock therapy for a period of time • Do not use as a PRN analgesic • Review patient's history with opioid tolerance • Oral solution 100mg/5mL is for opioid- tolerant patient Assess patients for their clinical risks for opioid abuse or addiction prior to prescribing and routinely monitor all patients for signs of misuse, abuse and addiction during treatment. • When treating a pregnant woman for prolonged period, advised the risk of neonatal opioid withdrawal syndrome, and ensure treatment is available. • Providers are encouraged to complete REMS-compliant education program prior to prescribing.	• Capsules must be swallowed whole or the contents of the capsules sprinkled on applesauce. • Should not be administered as PRN analgesic. Notify prescriber if written as PRN. Oral solution 100mg/5mL is for opioid-tolerant patient	• If written as PRN, notify prescriber that medication is to be used on a scheduled basis only
Mycophenolate (CellCept)	• Transplant Patients • Nephrology • Dermatology • Rheumatology	• Increased susceptibility to serious infection and possible development of lymphoma. • Increased risk of pregnancy loss and congenital malformations	• Complete Mycophenolate REMS training prior to prescribing. • Verify pregnancy status prior to administration. Perform repeat pregnancy tests during routine follow- up visits. • Order initial and periodic WBC panel • Check initial and periodic renal function	Verify pregnancy status and notify physician if patient informs of pregnancy or suspected pregnancy	• CellCept and Myfortic dosage forms should not be used interchangeable due to difference in absorption

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Neuromuscular Blocking Agents (NMBA) **Pancuronium Bromide** **Vecuronium Bromide**	▯ OR ▯ ER ▯ ICU	This drug should be administered by adequately trained individuals familiar with its actions, characteristics, and hazards	• Should not be utilized prior to adequate sedation and analgesia. • Verify that reversal agent is readily available.	Prior to administration, ensure that patient will have immediate secured airway.	• Prior to order verification, ensure patient is intubated (or pending intubation) and has adequate sedation ordered • Affix an auxiliary label stating "Warning: Paralyzing Agent" upon receipt of an NMBA
Oxycodone Controlled Release (OxyContin)	• Pain Service • Hematology/Oncology • Prior Authorization required for outpatient use.	• Abuse potential • Fatal respiratory depression may occur, with highest risk at initiation and with dose increases. • Indicated for opioid tolerant patients for management of moderate to severe pain when continuous around the clock opioid is needed. Not to be used for "as needed" (PRN) analgesic • Opioid-naïve patients are NOT to receive > 40 mg single dose or total daily dose > 80 mg • Tablets should not be crushed, cut, broken, dissolved, or chewed as this may lead to rapid release of oxycodone • Accidental exposure may result in fatal overdose of oxycodone, especially in children. • Cytochrome P450 3A4 Interaction • Accidental Ingestion • Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants Neonatal Opioid Withdrawal Syndrome	• Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy. • Not intended for PRN use. Do not prescribe for PRN use. • Prescribe full dosage forms (no partial dosages) • Prescribe an alternate agent if patient requires oral dosages to be crushed or chewed (e.g. NG tube) • Review patients' history with opioid tolerance • Do NOT order > 40 mg single dose or total daily dose > 80 mg for Opioid- naïve patients • Assess patients for their clinical risks for opioid abuse or addiction prior to prescribing and routinely monitor all patients for signs of misuse, abuse and addiction during treatment. • When treating a pregnant woman for prolonged period, advised the risk of neonatal opioid withdrawal syndrome, and ensure treatment is available. • Providers are encouraged to complete REMS-compliant education program prior to prescribing.	• Do not crush, chew, or break • Controlled release oxycodone (Oxycontin) 10mg is not interchangeable with oxycodone 10mg Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy.	• Do not dispense for PRN use and notify prescriber that medication is not intended for PRN use • Review patients' history with opioid tolerance • Do NOT dispense > 40 mg single dose or total daily dose > 80 mg to Opioid-naïve patients and notify prescriber. • Counsel patients to swallow tablets intact. The tablets are not to be crushed, dissolved, or chewed to prevent a potentially fatal overdose, especially in opioid-naïve individuals. • Counsel outpatients to take precautionary measures to prevent accidental exposure to themselves or others

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Phytonadione	No restriction	Fatal Hypersensitivity Reactions with IV and IM use	• Avoid the IV and IM, unless SQ administrations is not feasible and the serious risk is justified.	• Monitor signs/symptoms of dermatologic reactions and contact provider immediately upon reaction. • Verify the parenteral route before administration. Avoid the IV and IM, unless SQ administrations is not feasible and the serious risk is justified.	
Pioglitazone (Actos)	Restricted to documented failure/intolerance to metformin OR sulfonylurea.	• Pioglitazone hydrochloride may cause or exacerbate congestive heart failure in some patients • After initiation and dose increases, monitor patients carefully for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of must be considered. • ACTOS is not recommended in patients with symptomatic heart failure. • Initiation of ACTOS in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated.	• Prescribe with caution in patients with history of CHF or previous MI • Counsel discharged patient to contact physician immediately for signs of edema, dyspnea and rapid weight gain.	• Check daily weights Counsel discharged patient to contact physician immediately for signs of edema, dyspnea and rapid weight gain.	• Counsel discharged patient or outpatient to contact physician immediately for signs of edema, dyspnea, and rapid weight gain.
Procainamide (Pronestyl)	No Restriction	• Agranulocytosis • Bone marrow depression • Neutropenia • Hypoplastic anemia • Thrombocytopenia. • Prolonged administration may lead to a positive anti-nuclear antibody (ANA) test.	• Order CBC, basic metabolic panel, and anti-nuclear antibody test promptly if the patient develops any signs of infection, bruising, or bleeding • Perform CBC, including white cell, differential and platelet counts at weekly intervals for the first three months of therapy, and periodically	• Monitor for signs/symptoms of bleeding, bruising, or fever while on medication • Counsel discharged patient to contact physician immediately with signs/symptoms of bruising, bleeding, or anemia.	• Counsel discharged patient to contact physician immediately with signs/symptoms of bruising, bleeding, or anemia.

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			• thereafter. • If any of these hematologic disorders are identified, discontinue procainamide therapy.		
Rituximab (Rituxan)	• Hematology/Oncology. • Rheumatology patients who have failed traditional DMARDs and at least 1 TNF inhibitor. ▯ Nephrology for patients who have failed traditional immunosuppressant therapy. ▯ Dermatology for patients with Pemphigus Vulgaris that have failed 2 systemic standard immunosuppressant agents. ▯ Neurology	Fatal Infusion Reactions within 24 hours of infusion • Severe Mucocutaneous Reactions, some with fatal outcomes • Hepatitis B Virus Reactivation in some cases resulting in fulminant hepatitis, hepatic failure, and death. • FDA recommends discontinuing all chemotherapy until HBV infection is controlled or resolved. Progressive Multifocal Leukoencephalopathy resulting in death	• Pre-medicate patients with acetaminophen and an antihistamine (if patient has RA, use recommended dose of methylprednisolone or equivalent. • Discontinue in patients experiencing severe mucocutaneous skin reactions • Screen for HBV using HBsAG and anti-HBc prior to initiating treatment. • For patients at risk of HBV reactivation, consult with local facility experts regarding monitoring and use of HBV anti-viral therapy. • During therapy and for several months thereafter, monitor patients with history of HBV infection for clinical and laboratory signs of HBV reactivation. • If reactivation occurs, immediately discontinue rituximab and initiate HBV anti-viral therapy.	Closely monitor for reactions during infusion. Notify prescriber if patient presents with severe Mucocutaneous skin reaction	• Verify appropriate indication, dosage, and infusion rate. • Ensure premedication is ordered. • Ensure HBV screening has been ordered.
Succinylcholine Chloride	• OR • ER • ICU	• Increases risk of cardiac arrest from hyperkalemic rhabdomyolysis. • Increased risk in children.	• Monitor signs/symptoms of hyperkalemic rhabdomyolysis. Provide immediate treatment for hyperkalemia once present. • Reserved for emergency situations such as rapid sequence induction/intubation or known or suspected difficult airways.	▯ Monitor vital signs, consider EKG & Chem 7. Notify provider immediately once hyperkalemia is present. Prior to administration, ensure that patient will have immediate secured airway.	• Review most recent chemistries and notify provider if patient has pre-existing hyperkalemia • Prior to order verification, ensure patient is intubated (or pending intubation)

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Tumor Necrosis Factor (TNF) Blockers	• Rheumatology* • Dermatology* • GI Service for treatment of inflammatory bowel disease. • Formulary: Adalimumab	• Increased risk for developing serious infections involving multiple organ systems and sites that may lead to hospitalization or death due to bacterial, mycobacterial, fungal, viral, parasitic, and other opportunistic pathogens, including Legionella and Listeria. • Cases of active TB have developed in patients receiving adalimumab whose screening for latent TB infection was negative. • Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients. Hepatosplenic T-cell lymphoma has been reported in patients with Crohn's disease or ulcerative colitis treated with infliximab and concurrent or prior azathioprine or mercaptopurine use, usually reported in adolescent and young adult males.	Consider the risks and benefits prior to initiating therapy in patients with chronic or recurrent infection, patients with underlying conditions that may predispose them to infection, patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy. Prior to initiating treatment, test for latent TB. If positive, start treatment for TB prior to starting TNF Blocker. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. During treatment, monitor for signs and symptoms of serious infections. Consider empiric antifungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness. • Discontinue if a patient develops a serious infection or sepsis.	• Ensure TB skin test or CXR has been ordered and reviewed by prescriber Notify prescriber if patient presents with signs or symptoms of serious infection.	• Ensure HBV screening has been ordered
Warfarin (Coumadin)	No Restriction	Risk of major or fatal bleeding	• Check Hb/Hct and PT/INR at initiation of therapy and at regular intervals thereafter, per facility protocol • Ensure that dietician reviews patient diet • Instruct patient to report bleeding.	• Monitor for signs and symptoms of bleeding or excessive bruising • Ensure that dietician reviews patient diet Instruct patient to report bleeding.	• Review profile for severe drug-drug interaction. • Check PT/INR

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