Pharmacy and Therapeutics Committee Approvals, April 2012

P&T Date: April 3, 2012

<table>
<tr><th>AGENDA ITEM</th><th>P&T COMMITTEE DECISION</th><th>COMMENTS</th></tr>
<tr><td>Belatacept (Nulojix®)</td><td>Do not add to formulary</td><td>
Indication: Prophylaxis of acute rejection in renal transplant patients

Mechanism of Action: Belatacept is a human fusion protein that antagonizes surface ligands CD80 and CD86 on antigen presenting cells. T-cell activation, which is responsible for allograft rejection, is thereby inhibited as CD80 and CD86 are required in the costimulation of the transmembrane immunoglobulin CD28 of naïve T-cells.

Adverse effects (most common): Common side effects include (>20%) urinary tract infection, GI effects (diarrhea, constipation, nausea, vomiting, abdominal pain), peripheral edema, pyrexia, anemia, leukopenia, hypertension, cough, headache, graft dysfunction, and hypo/hyperkalemia.

Precautions:
• Black Box Warning: Due to increased risk for developing post-transplant lymphoproliferative disorder (PTLD), the FDA requires that the manufacturer have a Risk Evaluation and Mitigation Strategy (REMS) in place. PTLD associated with belatacept generally involves the central nervous system, and therefore, belatacept should only be used in Epstein-Barr virus (EBV) seropositive patients. Belatacept has been shown to increase risk of graft loss and death in a clinical trial of liver transplant patients, and therefore, it is not recommended for use in liver transplant patients.
• REMS: Requirements of the REMS include
1. Medication Guide to be dispensed with each infusion
2. Pre-infusion Checklist to be completed prior to each infusion and filed in patient's medical record
• Serious infections, including those listed below
o Cytomegalovirus (CMV) is a risk factor for PTLD, and CMV prophylaxis is recommended for at least 3 months post-transplant.
o As immunosuppressants may increase risk of opportunistic infections, prophylaxis for Pneumocystis jiroveci is also recommended after transplantation.
o Since tuberculosis has been observed in patients administered belatacept, patients should be assessed for tuberculosis before initiating therapy.
o Polyoma virus-associated nephropathy (PVAN), predominantly attributed to BK virus infection, has been reported with use of belatacept.

Dosing:
<table>
<tr><th>Initial Phase</th><th>Dose</th></tr>
<tr><td>- Day 1 (day of transplantation, administered prior to transplant)
- Day 5</td><td>10 mg/kg</td></tr>
<tr><td>- End of week 2
- End of week 4</td><td>10 mg/kg</td></tr>
<tr><td>- End of week 8
- End of week 12</td><td>10 mg/kg</td></tr>
<tr><th>Maintenance Phase</th><th>Dose</th></tr>
<tr><td>- End of week 16
- Every 4 weeks thereafter</td><td>5 mg/kg</td></tr>
</table>
*Note: Dose based on actual body weight and should be calculated to nearest multiple of 12.5 mg
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ADDITIONS TO FORMULARY	• **Micafungin (Mycamine®)** o Added to the formulary with the following restrictions: ▪ Febrile neutropenia **<u>and</u>** receiving broad spectrum agents **<u>or</u>** hemodynamically unstable in ICU

<table>
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Empiric, non-neutropenic on broad spectrum agents <u>and</u> hemodynamically unstable in the ICU
Empiric, non-neutropenic on broad spectrum agents <u>and</u> history of fluconazole resistant yeast
Documented azole-resistant Candida infection
Esophageal candidiasis
Empiric – C. glabrata or C. krusei infection pending susceptibility

Automatic substitution from caspofungin (all indications except esophageal candidiasis) to micafungin 100 mg IV daily with the same restrictions

Oseltamivir (Tamiflu®) – Added to formulary for suspected or documented influenza infection

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<tr><td>REMOVALS FROM FORMULARY</td><td>

Caffeine 100 mg/ergotamine 2mg (Cafergot®) suppository – No longer available

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<tr><td>AUTOMATIC SUBSTITUTION</td><td>
<table>
<tr><th>Medication Ordered</th><th>Automatic Substitution</th></tr>
<tr><td>Atorvastatin (Lipitor®) 80mg in HIV patients on a protease inhibitor or patients receiving cyclosporine or tacrolimus</td><td>Rosuvastatin (Crestor®) 10mg</td></tr>
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<tr><td>ANTIBIOTIC USE REVIEW COMMITTEE</td><td>

Vancomycin Per Pharmacy Protocol Revisions (Attachment 1)

Updated with serum vancomycin level to be drawn and dose adjusted in patients with SCr increase or decrease of ≥0.3mg/dL from baseline or urine output < 0.5ml/kg/hr x 6 hours

Tdap vaccination in OB – Patient education (Attachment 2)

Pharmacists will provide patient education regarding Tdap vaccination to post-partum patients who are unable to have it administered during hospitalization when receiving anticoagulation.

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<tr><td>DRUG SHORTAGES</td><td>

Drug Shortages Update (Attachment 3)

The following shortage implementation plans were approved:

Metoclopramide (Reglan®) inj

If patient is tolerating orals for at least 24 hours, “including NPO except for meds”, autosub Metoclopramide inj with Metoclopramide PO at the same dose and frequency
Pharmacists to notify Prescriber via phone when the switch occurs.
For patients with gastric motility issues, pharmacist to contact prescriber to consider using alternative pro-motility agents (i.e. erythromycin).

Antiemetic Shortages (Attachment 4)

Injectable Benzodiazepines and Sodium Bicarbonate Inj Shortages (Attachment 5)

Ranitidine inj (Zantac®) Shortage

If patient is tolerating orals for at least 24 hours including ‘NPO except for medications,’ autosub

Ranitidine 50 mg IV Q8 hours to Ranitidine 150 mg oral or enteral BID
Ranitidine 50 mg IV Q18-24 hours to Ranitidine 150 mg oral or enteral daily

If patient requires intravenous H2 blocker (during ranitidine inj shortage only), autosub

Ranitidine 50 mg IV Q8 hours to famotidine 20 mg IV push q 12 hours
Ranitidine 50 mg IV Q18- 24 hours to famotidine 20 mg IV push q 24 hours

Replace Ranitidine inj floor stock with Famotidine inj (Pepcid) during Ranitidine inj shortage

Doxorubicin Liposome Inj (Doxil®) Shortage

Due to a national shortage of Doxil®, FDA has allowed the temporary importation of a similar product (Lipodox™) from India. The use of Lipodox™ as a substitute for Doxil® will be permitted during the shortage period.

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<tr><td>OTHER TOPICS</td><td>

Dabigatran (Pradaxa®) Safety Updates

Safety Updates (Attachment 6)
Reversal Guidelines – Updates (Attachment 7)

2012 Priority Black Box Warnings (Attachment 8)

A complete list of the 2012 Priority Black Box warnings can also be found at http://web.csmc.edu/clinical/clinical-departments/pharmacy/clinical-library/documents/reference---black-box-warning-bbw-priority-list-2012.pdf

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</table>

- **PRN Anti-Hypertensive Clarification Orders in the Neuro ICU When >1 PRN Anti-hypertensive Medication is Ordered**: In order to meet regulatory requirements and to ensure nurses have clear instructions as to which agent(s) to administer to patients, the following automatic clarification orders were approved:
  - Allow the pharmacist to enter the following in the administration instructions of each anti-hypertensive without a clarification order:
    - Labetalol inj: try labetalol inj first. Hold for HR < 50.
    - Hydralazine inj: try Hydralazine inj if inadequate response to Labetalol inj. Hold if HR >100
    - Nicardipine inj: try nicardipine inj if inadequate response to both Labetalol inj and Hydralazine inj
  - Allow the pharmacist to enter the following in the administration instructions of each anti-hypertensive without a clarification order during labetalol inj shortage:
    - Hydralazine inj: try Hydralazine inj first
    - Labetalol inj: try labetalol inj if inadequate response to Hydralazine inj. Hold for HR <50. If HR > 100, Use Labetalol first
    - Nicardipine inj: try nicardipine if inadequate response to both Labetalol inj and Hydralazine inj

- **CS Link Order Sets -** The following changes were approved for CS-Link Order Sets
  - Neurosurgery Aneurysmal Subarachnoid Order Set (1534)
    - Change Rosuvastatin (Crestor®) to Pravastatin (Pravachol®) 40mg
  - VAS Post-op Order Set (1501)
    - Add Aspirin 81mg PO daily
    - Add Rosuvastatin (Crestor®) ___mg PO daily
  - Heartburn Panel
    Change from Ranitidine (Zantac®) 150mg PO Q8H or Ranitidine (Zantac®) 50mg Q8H to:
    - Ranitidine (Zantac®) 150mg PO BID prn
    - Ranitidine (Zantac®) 50mg IV q8H prn, if not tolerating PO

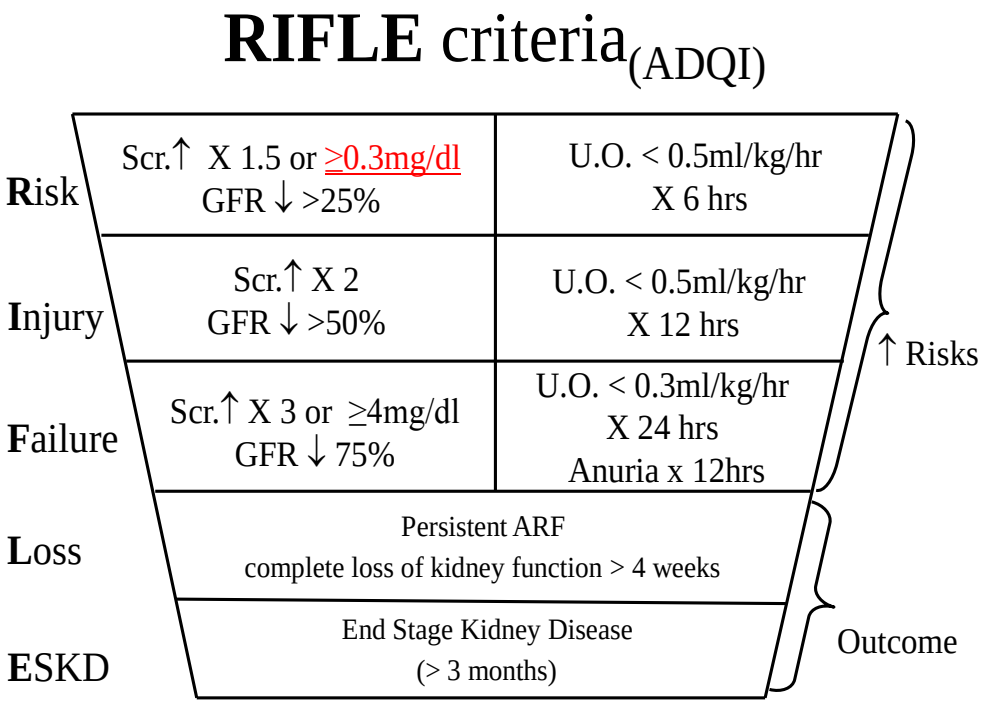
Requests for full monographs or questions regarding this listing may be addressed to the Drug Information Center at **(310) 423-3784**

Rachel Ngo, PharmD — *Pharmacy Program Coordinator*
Hai Tran, PharmD — *Manager, Department of Pharmacy*
Rita Shane, PharmD, FASHP — *Director, Department of Pharmacy*

ATTACHMENT 1

DEPARTMENT OF PHARMACY
VANCOMYCIN PROTOCOL
(Protocol Changes 3/12)

a. **Serum levels should be (re)ordered and dosage adjustment made for:**
   - **i.** Patients with Scr. ↑ or ↓ ≥0.3mg/dl. from baseline or UO<0.5ml/kg/hr x 6hrs (appendix1)
   - **ii.** Patients dosed to trough of >15-20mcg/ml must have a trough level drawn every 3 days..
   - **iii.** All patients receiving concomitant nephrotoxins (IV contrast dye, loop diuretics, NSAIDs, or COX2s, aminoglycosides, cyclosporine, amphotericin, tacrolimus, cisplatin, carboplatin, ifosfamide, methotrexate, foscarnet, etc. **must have a serum vancomycin trough level ordered every 3 days.** (for IV contrast dye, 2-3 sets of levels are needed as the effect of contrast induced nephropathy may last up to 5 days or longer)
   - **iv.** More frequent serum level monitoring **up to daily** in ICU patients who are hemodynamically unstable by consulting with ICU team. Monitoring parameters include but not limit to:
     1. Blood pressure, fluid status, **increasing** doses of vasopressors, **decreasing** UOP (anuric), **increasing** Bun/Scr or on concomitant nephrotoxic agents, IV contrast, and receiving blood transfusion.
   - **v.** Patients dosed to a trough level of 10-15mcg/ml should have a trough level drawn every 3 days if there are risk factors present for renal insufficiency (e.g., concomitant nephrotoxins, disease states, sepsis, volume depletion, etc.)
   - **vi.** ALL patients should have a level drawn at least weekly following the required initial serum level.
   - **vii.** Patient not responding to therapy ie: (↑ WBC, Bandemia, febrile etc.) consider an additional level to verify the patient's serum level is within the therapeutic goal range
   - **viii.** Changing renal function: Non-steady state conditions require several serum levels to determine when to re-dose the patient. Remember that the above calculations in section 4 do not apply when renal function is changing.
b. Document specific clinical reason/justification for any deviation from the protocol



Critical Care 2004 (8), R204-R212

ATTACHMENT 2

CEDARS-SINAI MEDICAL CENTER

TDAP VACCINE: WHAT YOU NEED TO KNOW

1. Whooping cough (pertussis):
    - Respiratory tract infection that is easy to spread
    - Spread by coughing or sneezing while in close contact with others
    - Infants may be infected by parents or caregivers
    - May seem like an ordinary cold but may turn more serious (especially in infants).
    - Can be spread even before coughing starts.
    - Can be prevented through immunizations

2. Tdap Vaccine:
    - Protects against whooping cough (pertussis), tetanus, and diphtheria
    - An epidemic of whooping cough has led to an increase in infant Death
    - All adolescents and adults need to be revaccinated as the Childhood vaccine does not protect you for a lifetime
    - Given as an injection deep into the muscle

3. **Tdap Vaccine and blood thinners:**
    - Injections can cause significant bleeding/bruising at the injection site for patients taking blood thinners
    - For patients NOT on blood thinners, Tdap should be given immediately postpartum, before leaving the hospital (if not previously vaccinated)
    - **For patients ON blood thinners**, Tdap may be delayed and given at the doctor's office after the blood thinner is stopped or if the doctor says it is appropriate

****All people in close contact with an infant should get a dose of Tdap** (if not previously received Tdap). It is **very important** for you to follow up with your doctor to prevent spreading the disease to your infant.

ATTACHMENT 3

Overview of Current Drug Shortage Management Processes

Identification of drug shortages

- Currently **243** medications and dose forms on shortage
- Anticipated length of shortage often unknown
- Ongoing monitoring of governmental & professional shortage sites/lists.
- Shortages may be identified when orders placed and medication is not available

Drug shortage decision-making process

- Development of recommendations in collaboration with MD experts representing populations impacted including clinical chairs/ directors, P&T members
  - Identification of alternative medications for the same indication
  - Development of criteria restricting use of remaining product
    - May require discontinuing existing order when pt is on an alternative agent
- Approval Process
  - For acute shortage, interim approval by P&T Committee Chair followed by Committee approvals including P&T and CIC

Implementation & Communication

- Communication to medical staff leadership at Department/ Division level and nursing leadership
- Order Management
  - Notification via EMAR and other CS-Link methodology to be determined
- Presentation of key shortages to PICs
- Pharmacy and nursing staff email/flyer notifications
- CSMC drug shortage webpage updated

Medication Safety Webpage (web→ Clinical Resources → Medication Safety) http://web/clinical/clinical-resources/medication-safety/

ATTACHMENT 3

Commonly-Utilized Medications in Limited Supply Due to National Shortages

Parenteral Benzodiazepines	• Diazepam (Valium®) • Lorazepam (Ativan®) • Midazolam (Versed®)
Parenteral Anti-emetics	• Metoclopramide (Reglan®) • Droperidol • Promethazine (Phenergan®) • Prochlorperazine (Compazine®) • Ondansetron (Zofran®) • Fosaprepitant (Emend®) • Granisetron (Kytril®) • Dolasetron (Anzemet®)
Anesthetics	• Bupivacaine (Marcaine®) • Chloroprocaine (Nesacaine®) • Lidocaine (Xylocaine®) • Ropivacaine (Naropin®)
Parenteral Non-steroidal Anti-inflammatory Drugs	• Ketorolac (Toradol®)

In the event of continuing interruptions in the supply chain, additional strategies to conserve the remaining supplies of these medications may be necessary

ATTACHMENT 3

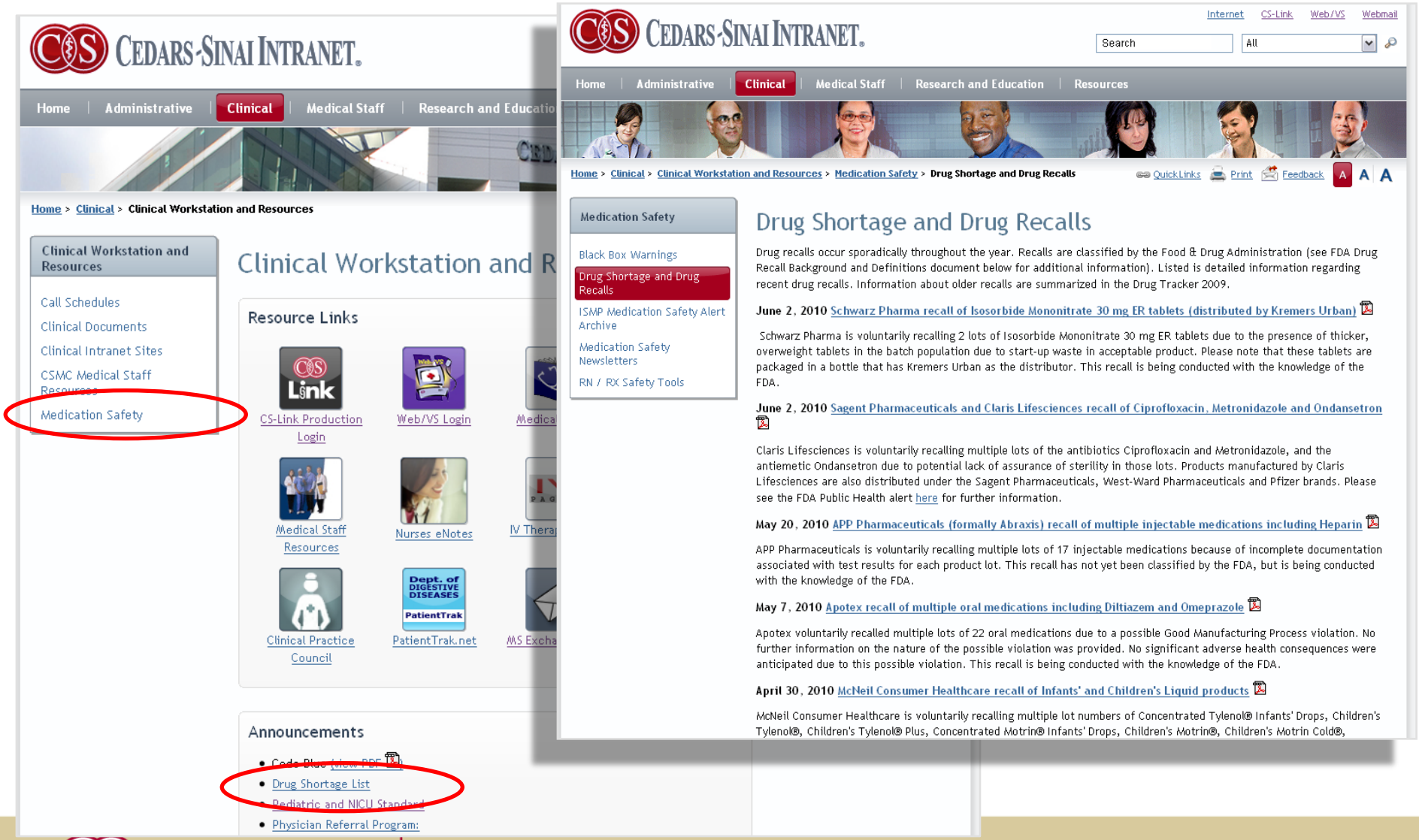
Recent New Drug Critical Supply /Shortage

- Sodium bicarbonate 8.4% vials and syringes
  - Restrictions for pediatric patients, code situation, management of acid-base disorders, TCA overdose, and urine alkalization in oncology patients
- Midazolam inj, Lorazepam inj
  - Consider propofol first for sedation
  - Benzodiazepines may be used in the following situations
    - Severe hypotension/ hemodynamic compromise
    - Use of continuous paralytics (if the level of sedation cannot be continuously monitored)
    - Status epilepticus
    - High triglycerides
  - If benzodiazepines infusion is needed, lorazepam should be used when possible
- Atracurium – consider Cisatracurium, Rocuronium, Succinylcholine, Vecuronium
- Esomeprazole injection - Automatic substitution to famotidine injection
- Methotrexate injection

The Pharmacy Department continues to track 235 medications/dose forms due to critical supply/shortage

ATTACHMENT 3

Drug Shortage – *Electronic Notification on the Web*



ATTACHMENT 4

CEDARS-SINAI MEDICAL CENTER

Anti-emetics Injectable Nationwide Shortages

Situation: Multiple anti-emetics are in short supply nationwide including: Ondansetron inj & ODT (Zofran®), Granisetron (Kytril®) inj, Promethazine (Phenergan®), Metoclopramide (Reglan®) inj, Prochlorperazine (Compazine®)

Background:
We have been experiencing an acute shortage of multiple anti-emetics since late 2011. The Pharmacy Department has been working closely with the manufacturers and wholesaler to secure additional supply. Although the earliest estimated release date is Mid-March, it is not reliable.

Currently, Prochlorperazine inj supply has been depleted. It is estimated that we will run out of Metoclopramide inj by early next week.

Drug	Estimated Product Release Date	Current Supply
Metoclopramide inj (Reglan®)	Late March	7 days
Ondansetron inj (Zofran®)	Mid-March	3 months
Prochlorperazine inj (Compazine®)	Unknown	None

Assessment:
Alternatives to Ondansetron inj for patients who can't tolerate PO and failed Ondansetron are limited. A very limited supply of Ondansetron ODT, Prochlorperazine suppository, Promethazine suppository, Fosaprepitant inj-oncology only, Promethazine inj, Droperidol inj were secured. Promethazine and Droperidol carry Black Box Warnings (BBW) and therefore, were previously removed from CSMC formulary.

Recommendations:
In light of nationwide anti-emetic shortages, add droperidol and promethazine to formulary for NPO patients who failed ondansetron, and for whom prochlorperazine/promethazine suppository is not an option. Additional criteria for use are as follow

1. Droperidol inj
   - MD will have to answer the following questions at the time of order entry
     " Droperidol has a Black Box Warning. Click here for more information
     Does the patient have known or suspected QT prolongation? If yes, order a 12-lead EKG"
   - Maximum 0.625mg/dose every 6 hours; 2.5mg/24hr
   - Initial Assessment
     - Pharmacist to review orders to ensure compliance with orders as 2nd line and order for 12-lead EKG if indicated
     - If EKG demonstrates QT interval prolongation (QTc > 440 msec for males or 450 msec for females), pharmacist to contact MD regarding need for continuous EKG monitoring
   - Monitoring
     - If 2nd medication with known risk of torsades de pointes* is ordered, pharmacist to order 12-lead EKG and contact physician to recommend continuous ECG monitoring

       * * Medications with known risk based on Arizona CERT (www.azcert.org) will result in a drug interaction alert classified as contraindicated/severe in CS-Link. (Arizona Cert is an independent research and education center and one of 14 national CERTs funded by the U.S. Agency for Healthcare Research and Quality (AHRQ).)

   - In patients with prolonged QT interval or when a 2nd medication with known risk of torsades de pointes* is ordered, if MD does not want to place the patient to on continuous EKG monitoring, pharmacist will document in the patient record
   - A concurrent evaluation of patients receiving droperidol will be conducted to determine any cardiac related ADRs for 30 days after implementation. This information will be used to evaluate continued restricted formulary status.

2. Promethazine inj
   - Promethazine inj may be give via IM or central line as IVPB over 30 minutes only

3. Reserve the remaining supply of Metoclopramide inj and Fosaprepitant inj for oncology patients

ATTACHMENT 4

CEDARS-SINAI MEDICAL CENTER

Black Box Warning Information

Promethazine BBW: *"Promethazine hydrochloride injection should not be used in pediatric patients less than 2 yr of age because of the potential for fatal respiratory depression. Respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years of age in postmarketing experience. Exercise caution when administering promethazine hydrochloride injection to pediatric patients 2 years of age and older. Regardless of the administration route, promethazine hydrochloride injection can cause severe chemical irritation and damage to the tissue. Adverse reactions include burning, pain, thrombophlebitis, tissue necrosis, and gangrene, requiring surgical intervention, skin graft and/or amputation in some cases. Due to the risks of IV administration, the preferred route of administration is deep IM injection. SubQ injection is contraindicated"*

Droperidol BBW: *"Cases of QT prolongation and/or torsade de pointes, some fatal, have been reported in patients receiving droperidol at doses at or below recommended doses. All patients should undergo a 12-lead ECG prior to administration of droperidol to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. Do not administer droperidol if there is a prolonged QT interval. Droperidol is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome. Administer droperidol with extreme caution to patients who may be at risk for development of prolonged QT syndrome, are over 65 years old, abuse alcohol, or when used concomitantly with benzodiazepines, volatile anesthetics, and IV opiates. ECG monitoring should be performed prior to treatment and continued for 2 to 3 hours after completing treatment to monitor for arrhythmias"*

ATTACHMENT 5

CEDARS-SINAI MEDICAL CENTER

Injectable Benzodiazepines and Sodium Bicarbonate Shortage

Situation: Multiple injectable benzodiazepines are in short supply nationwide including Diazepam (Valium®) inj, Lorazepam (Ativan®) inj, and Midazolam (Versed®) inj. In addition, there is also a national shortage of Sodium Bicarbonate inj.

Background:
We have been experiencing an acute shortage of multiple injectable benzodiazepines since late 2011 and injectable sodium bicarbonate since early 2012. The Pharmacy Department has been working closely with the manufacturers and wholesaler to secure additional supply.

Drug	Estimated Product Release Date	Current Supply
Diazepam (Valium®) inj	April	~2 months
Lorazepam (Ativan®) inj	Late March to late April	~2 months
Midazolam (Versed®) inj	Mid April	~ 2 weeks
Sodium Bicarbonate inj	Mid April, May	~ 2 weeks

Assessment:
Criteria for use should be developed in order to ensure there is adequate supply for patients who are not candidate for alternative therapies.

Recommendations:
In light of the nationwide injectable benzodiazepine and sodium bicarbonate shortages, the following criteria for use were developed in conjunction with Divisions of Critical Care and Nephrology and Departments of Emergency Medicine and Pharmacy:

1. IV Infusion Benzodiazepine
   - Consider propofol first for sedation
   - Benzodiazepines may be used in the following situations:
     - Severe hypotension/hemodynamic compromise
     - Use of continuous paralytics (if the level of sedation cannot be continuously monitored)
     - Status epilepticus
     - High triglycerides
   - If benzodiazepine infusion is needed, use lorazepam if possible (midazolam drip may be used for status epilepticus patients when appropriate as long as supply remains)
2. IV Sodium Bicarbonate Restricted to:
     - Pediatric patients
     - Management of Acidosis
     - Code situation
     - TCA overdose
     - Urinary alkalization in oncology setting
   - Allow nursing to use lidocaine 1% inj as a local anesthetic prior to catheter insertion under scope of practice, as specified in the *'Intravenous Therapy-Initiation and Management of Peripheral Intravenous Lines policy*, during sodium bicarbonate inj shortage period
   - Replace buffered lidocaine 1% inj with lidocaine 1% inj in the following order sets
     - 1227 OB IP Labor and Delivery Admission
     - 1263 CAR IP Diagnostic/ Interventional Pre-Procedure
     - 1268 OB IP Hyperemesis
     - 1332 OB IP Maternal Fetal Care Unit Admission
     - 1438 ANE IP Pre-procedural/ pre-op for PACU only

ATTACHMENT 5

CEDARS-SINAI MEDICAL CENTER

- 1235 OB IP Preterm labor/ PROM Admission
- 1270 OB IP Pregnancy Induced Hypertension
- 1550 GEN IP Lumbar puncture/ CSF Orders
- 1335 GI IP Pre-Procedure
- 1612 ED Fast Track
- 1203 ED Animal Bite
- 1306 ED Laceration
- 1286 ED Cellulitis/ Abscess
- 1192 ED Joint Pain

ATTACHMENT 6

Dabigatran (Pradaxa®) 2012 Safety Update

1. **March 2012 Recent New Zealand Data** *(Harper P. Bleeding Risk with Dabigatran in Frail Elderly NEJM March 2012)*
    a) 7000 patients in 1st 2 months of availability
        i. 78 episodes of bleeding; 44 cases reviewed with 12 major bleeds identified
            - 4 Risk Factors Identified
                - Prescriber error (25%)
                - Age >80 years (66%)
                - Moderate-Severe renal impairment (58%
                - Weight <60kg (50%)

2. **February 2012 – Periprocedural Dabigatran in Atrial Fibrillation (AF) Ablation**
    a) Multicenter observational study of 145 patients receiving uninterrupted warfarin compared with 145 patients receiving dabigatran 150mg BID when undergoing ablation
        i. Dabigatran was held morning of procedure and resumed 3 hours post-hemostasis
        ii. 57% with paroxysmal AF, average age 60 years
    b) Dabigatran use & age >75 years were predictors of composite of **bleeding and thromboembolic** complications
    c) All thromboembolic complications were in nonparoxysmal AF (5% in dabigatran group – high, but NS vs warfarin)
    d) Unfractionated heparin was administered as standard of care during ablation in all patients (ACT goal 300-400sec)
    e) Considerations based on Winkle et al study *(J Cardiovasc Electrophysiol March 2012)*
        i. Stop dabigatran 36-60 hours pre-procedure
        ii. Target lower ACT (225 sec vs 300-400 sec)

3. **January 2012 – Institute of Safe Medication Practices (ISMP) Report**
   a) 932 serious adverse events reported to the FDA
      i. 543 cases requiring hospitalization
         - 505 involved hemorrhage, more than any other monitored drug **including warfarin**
            - 120 deaths, 25 cases of permanent disabili
      ii. Median age of 80; 25% ≥ 84

4. **January 2012 - Dabigatran Association with Higher Risk of Acute Coronary Events** *(Arch Intern Med-online 01/09/12)*
   a. Meta-analysis of 7 non-inferiority worldwide randomized controlled trials *(30,514 patients)*
      i. All studies sponsored by Boehringer Ingelheim
      ii. 2 a.fib, 1 ACS, 1 VTE treatment, 3 short term VTE prophylaxis – vs warfarin, enoxaparin or placebo
   b. Conclusions:
      i. No relationship between baseline risk of acute coronary events and risk with use of dabigatran
      ii. Warfarin +/- ASA reduced risk of MI
         - Dabigatran may not directly ↑ risk of MI, but may lack preventive effects of warfarin/ASA
      iii. Cardiac risk should be further evaluated particularly in high cardiac event risk patient

ATTACHMENT 7

Dabigatran (Pradaxa®) Reversal Guidelines

March 2012 Update

CEDARS-SINAI

LEADING THE QUEST

cedars-sinai.edu

Proposed Plan for Reversal Guidelines

- March 22, 2012 Meeting
  - Members from Departments of Laboratory Medicine, Neurology, Emergency Medicine and Pharmacy Services

- Proposed Interim Plan
  - Reconvene at regular intervals to assess any newly published literature/recommendations
  - Interim Plan - Reformat/rename current guideline as **'Physician Considerations for Managing Bleeding Related to Dabigatran Therapy'** based on the following:
    1) Lack of studies/case reports/recommendations for the use of PCC
       – Various products with differing amounts of factors, heparin, ATIII, protein C & S
       – Potential inactivation in presence of dabigatran
    2) Lack of studies/case reports/recommendations for the use of Factor VII
       – Thrombotic risks related to Factor VII, specifically in dabigatran-related ICH patients
    3) Minimal impact on factor levels following multiple units of FFP
       – Dilutional effect of FFP
       – Theoretical neutralization of FFP in the presence of supratherapeutic dabigatran levels (inhibition of thrombin)
    4) Risks related to rapid shift from from HYPO- to HYPERcoagulable
    5) Lack of established data regarding monitoring (TAT, ECT, TEG)
    6) Specific needs of different populations - traumatic bleeding vs 'closed space' bleeding
    7) Consider evaluating TEG monitoring in dabigatran patients with approval from IRB

ATTACHMENT 8

2012 Priority Black Box Warnings

CEDARS-SINAI

LEADING THE QUEST

cedars-sinai.edu

ATTACHMENT 8

Black Box Warnings (BBWs)– Added to Priority List

Drug Name *BBWs*	MD Actions	Rx Actions	Rn Actions
Cidofovir (Vistide®) • *Nephrotoxicity* • *Neutropenia*	• Order IV prehydration & probenecid • Monitor renal function & neutrophil counts	• Restrict to ID Physicians only • Contact MD if prehydration & probenecid are not ordered • Monitor renal function & CBC. • Order BUN/SCR & CBC with diff every other day	Monitor renal function & neutrophil counts
Terbutaline (Brethine®) *Risk of serious ADR including death*	Do not use beyond 72 hours	Maximum allowed duration = 3 days per hospitalization	None

ATTACHMENT 8

Black Box Warnings (BBWs)– Added to Priority List

Drug Name *BBWs*	MD Actions	Rx Actions	Rn Actions
Pioglitazone containing products *Cause or exacerbate CHF*	Ordering question "Does the pt have symptomatic HF or NYHA Class III & IV HF? Yes or No"	Contact prescriber in pts with symptomatic HF or with NYHA Class III & IV HF	Monitor pt for signs & symptoms of HF
Rosiglitazone containing products • *Cause or exacerbate CHF* • *Risk of myocardial infarction*	Ordering questions • Was the pt on rosiglitazone PTA? Yes or No • Is the pt enrolled in the Rosiglitazone Medicines Access Program? Yes or No • Does the pt have symptomatic HF or NYHA Class III & IV HF? Yes or No	• No new starts in hospital • If pt was on rosiglitazone PTA, confirm pt's enrollment in the Avandia-Rosiglitazone Medicines Access Program • Contact MD in pts with symptomatic HF or with NYHA Class III & IV HF	• Dispense Medication Guide • Monitor pt for signs & symptoms of HF.

ATTACHMENT 8

Black Box Warnings (BBWs)– Removed from Priority List

- Anti-Thymocyte Immune Globulin Rabbit (Thymoglobulin)
- Methadone
- Propylthiouracil (PTU)