Cleveland Clinic Pharmacotherapy Update
From the Department of Pharmacy

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**Drug Information Service**
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Comprehensive information about medications, biologics, nutrients, and drug therapy

Formulary Information

Medication Inservices

# Intravenous Immune Globulin (IVIG): A Review of Formulary Restrictions

***Introduction:*** There is a nationwide shortage of IVIG due to a consolidation of manufacturers and less plasma donations. When there is a critical supply of IVIG, the Cleveland Clinic Pharmacy and Therapeutics (P&T) Committee has approved Formulary restrictions. These Formulary restrictions will help ensure an adequate supply of IVIG.

***Indications:*** During shortages of IVIG, it is restricted to FDA-approved indications and selected non-FDA-approved indications (See Table 1).

**Table 1: Formulary-Approved Indications of IVIG**

| |
|---|
| Bone marrow transplant (BMT) |
| Idiopathic thrombocytopenic purpura (ITP) |
| Primary immunodeficiency disorder (PID or hypogammoglobulinemia) |
| Pediatric HIV infection |
| Kawasaki disease |
| Chronic lymphocytic leukemia (CLL) |
| Chronic inflammatory demyelinating polyneuropathy (CIDP) |
| Guillain-Barre syndrome |
| Multi-focal motor neuropathy |
| Treatment of antibody-mediated rejection with allograft dysfunction or treatment of highly HLA-sensitized patients prior to transplantation |
| *If the indication for IVIG does not meet the formulary-approved indications, then the IVIG medication order must be approved by the Drug Information Center.* |

***Dose:*** There are three key points when dosing IVIG based on the Formulary restrictions. First, the dose of IVIG is calculated based on ideal body weight (IBW), not actual body weight (ABW). If the person is 30-40% above IBW, then an adjusted BW will be used. Therefore, it is important to have the current weight of the patient. Second, the total dose of IVIG should be no more than 2 grams/kg (e.g., 0.4 gram/kg/day for 3 to 5 days or 1 gram/kg/day for 2 days). All doses greater than 1 gram/kg must be approved by the Drug Information Center. Third, IVIG should not be dosed any more frequently than every 4 to 6 weeks.

***Brand of IVIG:*** The Cleveland Clinic stocks and dispenses only Gammagard® (lyophilized; Baxter Healthcare). Due to the shortage, the Cleveland Clinic Pharmacy is unable to obtain other IVIG products.

***Rate of Administration:*** For Gammagard® (5% solution), the usual rate of administration is 0.5 ml/kg/hr up to a maximum of 4 ml/kg/hr. For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing at a rate less than 4 ml/kg/hr. A 15-micron filter set is sent by pharmacy and should be utilized during administration.

Questions regarding the shortage and Formulary restrictions of IVIG should be directed to the Drug Information Center (216-444-6456, option #1).

# Ask the Drug Information Center a Question

**Question:** Is the Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine (Twinrix®) dosed the same as the individual hepatitis vaccines?

**Answer:** No, the Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine (Twinrix®) is NOT dosed the same as the individual hepatitis vaccines.

**Explanation:** Hepatitis A vaccine is indicated for induction of active immunity against infection caused by hepatitis A virus in both adults and children over the age of 1 year. There are two brand name hepatitis A vaccines: Vaqta® (Merck) and Havrix® (GlaxoSmithKline). Hepatitis B vaccine is indicated for induction of active immunity against hepatitis B virus in both adults and children. There are two brand name hepatitis B vaccines: Recombivax HB® (Merck) and Engerix-B® (GlaxoSmithKline). See Tables 1 and 2 for dosing information.

**Table 1: Hepatitis A**

| **Havrix®** | | | |
|---|---|---|---|
| **Age Groups** | **# of doses** | **Schedule** | **Dose** |
| Children age 2-18 years | 2 | 0 and 6-12 months | 720 ELISA units (0.5 ml) |
| Adults 18 years and older | 2 | 0 and 6-12 months | 1,440 ELISA units (1 ml) |
| **Vaqta®** | | | |
| **Age Groups** | **# of doses** | **Schedule** | **Dose** |
| Children age 2-17 years | 2 | 0 and 6-18 months | 25 units (0.5 ml) |
| Adults 17 years and older | 2 | 0 and 6-18 months | 50 units (1 ml) |

**Table 2: Hepatitis B**

| **Age Groups** | **# of doses** | **Schedule** | **Dose of Recombivax HB®** | **Dose of Engerix-B®** |
|---|---|---|---|---|
| Infants, children, and adolescents (birth – 19 years) | 3 | 0, 1 month, and 6 months | 5 mcg (0.5 ml) | 10 mcg (0.5 ml) |
| Adolescents 11-15 years* | 2 | 1 and 4-6 months | 10 mcg (1 ml) | |
| Adults > 19 years | 3 | 0, 1 month, and 6 months | | 20 mcg (1 ml) |
| Adults ≥ 20 years | 3 | 0, 1 month, and 6 months | 10 mcg (1 ml) | |

*Adolescents can receive either the 2 dose regimen of 10 mcg or the 3 dose regimen of 5 mcg.

Twinrix® (GlaxoSmithKline) is indicated for induction of active immunity against infections caused by hepatitis A and hepatitis B virus in patients 18 years of age and older. It is a combination of 720 ELU (ELISA units) of Havrix® hepatitis A vaccine and 20 mcg of Engerix-B® hepatitis B vaccine. It is administered as a three dose schedule (unlike the two dose adult schedule with the 1,440 ELU Havrix®) given on day 1 and then 1 month and 6 months later.

All of the above products should be shaken well prior to withdrawal from the vial for IM administration into the deltoid muscle. It is important to remember that there is alternate dosing for dialysis patients as well as an accelerated dosing regimen for transplant patients. Finally, the Twinrix® vaccine is the only product that does not have an indication / dosing schedule for pediatric patients (under the age of 18 years).

# Formulary Update

The Cleveland Clinic Pharmacy and Therapeutics Committee met on Wednesday, January 30, 2008, and the following decisions were made:

**Formulary Additions**

**1. Adefovir Dipivoxil (Hepsera™)**: Adefovir dipivoxil is a nucleotide analogue indicated for the treatment of chronic hepatitis B in patients ≥12 years of age who have evidence of active viral replication and either evidence of persistent elevation in serum aminotransferases (ALT or AST) or histologically active disease. The recommended dose is 10 mg orally once daily. Adefovir dipivoxil use is ***restricted*** to the Departments of Hepatology and Liver Transplantation. However, if a patient is admitted to the hospital and is receiving adefovir dipivoxil as an outpatient, the patient may remain on therapy as an inpatient and does not require a Hepatology consult.

**2. AquADEKs™ Liquid Pediatric Multivitamins**: AquADEKs fat soluble vitamins will be used in place of ADEKs drops that were discontinued by the manufacturer.

**3. Entecavir (Baraclude®)**: Entecavir, a guanosine nucleoside analogue, is indicated for the treatment of chronic hepatitis B infection in adults and adolescents ≥16 years of age who have evidence of active viral replication and either evidence of persistent elevation in serum aminotransferases (ALT or AST) or histologically active disease. The recommended dose in nucleoside-naïve patients is 0.5 mg orally once daily; the recommended dose in patients with a history of hepatitis B viremia while receiving lamivudine or known lamivudine resistance mutations is 1 mg orally once daily. Entecavir use is ***restricted*** to the Departments of Hepatology and Liver Transplantation. However, if a patient is admitted to the hospital and is receiving entecavir as an outpatient, the patient may remain on therapy as an inpatient and does not require a Hepatology consult.

**4. Ibuprofen Lysine Injection (NeoProfen®)**: NeoProfen® is indicated for closing a clinically significant patent ductus arteriosus (PDA) in premature infants weighing between 500- and 1500-grams, who are no more than 32 weeks gestational age when usual medical management (e.g., fluid restriction, diuretics, respiratory support, etc.) is ineffective. An initial dose of 10 mg/kg IV should be followed by two IV doses of 5 mg/kg each, after 24 and 48 hours. All doses should be based on birth weight. Second or third doses should be held if patients become anuric or have marked oliguria (urinary output <0.6 mL/kg/hr). If the ductus arteriosus fails to close or reopens following the first course, then a second course of NeoProfen®, alternative pharmacological therapy, or surgery may be necessary. NeoProfen® use is ***restricted*** to the Neonatal and Pediatric Intensive Care Units.

**5. Ixabepilone (Ixempra™)**: Ixabepilone is a semisynthetic epothilone B analog FDA-approved as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine. It can also be used as combination therapy. The recommended dosage of ixabepilone is 40 mg/m$^2$ administered as an IV infusion over 3 hours once every 3 weeks. Its use is ***restricted*** to the Department of Hematology and Medical Oncology for outpatient use only.

**6. Polyethylene Glycol Electrolyte, Sodium Sulfate, Sodium Chloride, Potassium Chloride, Sodium Ascorbate, and Ascorbic Acid for Oral Solution (MoviPrep®)**: MoviPrep® is FDA-approved for colon cleansing as a preparation for colonoscopy in adults ≥18 years of age. Unlike standard 4 liter bowel preparations, the dose is 2 liters of MoviPrep® solution with 1 additional liter of clear fluids taken orally prior to the colonoscopy.

**7. Poractant Alfa Intratracheal Suspension (Curosurf®)**: Curosurf® is a lung surfactant indicated for the treatment of Respiratory Distress Syndrome in premature infants. It is more concentrated than other lung surfactants (i.e., calfactant [Infasurf®] and beractant [Survanta®]); therefore, less volume of Curosurf® is required for initial and repeat dosing. In addition, repeat doses are only 50% of the initial dose. The initial intratracheal dose of Curosurf® is 2.5 mL/kg of birth weight. Up to two subsequent doses of 1.25 mL/kg of birth weight can be administered at 12-hour intervals if needed. It is available as 80 mg/mL 1.5-mL and 3-mL vials. With the addition of Curosurf® to the Formulary, both Infasurf® and Survanta® will be removed from the Formulary.

**8. Raltegravir (Isentress™)**: Raltegravir is a highly selective HIV-1 integrase strand transfer inhibitor FDA-approved for the treatment of HIV-1 infection in adult patients with evidence of viral replication and viral strains resistant to multiple antiretroviral agents. The recommended dose is 400 mg orally twice daily.

**9. Sevelamer HCl (Renagel®)**: Sevelamer HCl is a non-calcium, non-aluminum containing phosphate binder indicated for controlling serum phosphorus levels in patients with chronic kidney disease on dialysis. The 800 mg tablets have been added to the Formulary. Initial dosing and dosage titrations should be based on serum phosphorus levels. **Please note:** lanthanum carbonate (Fosrenol®) will no longer be stocked in the Pharmacy. When lanthanum carbonate is ordered and the patient cannot supply their own medication, the prescriber will be contacted by a pharmacist with the following dose conversion: lanthanum carbonate 500 mg is approximately equivalent to sevelamer HCl 1600 mg.

**Formulary Restriction Changes**

**1. Intravenous Immune Globulin (IVIG)**: The restriction for IVIG use has been altered to include use by Transplant Staff Physicians for the treatment of antibody-mediated rejection with allograft dysfunction or treatment of highly HLA-sensitized patients prior to transplantation. When used as a part of protocols with plasmapheresis, doses of IVIG should be administered after plasmapheresis treatment.

**2. Levetiracetam Injection (Keppra® Injection) Pediatric Restrictions**: Levetiracetam injection is restricted for treating patients having acute seizures, suspected or confirmed status epilepticus, patients with migraine headaches as third-line therapy, or in those patients who are unable to receive oral medications as follows:

a. Acute seizures or suspected or confirmed status epilepticus: Levetiracetam injection may be prescribed by Pediatric Neurology and Epilepsy Staff Physicians and Fellows, and PICU Physicians.

b. Status Migrainosis: Levetiracetam injection may be prescribed by Pediatric Neurology Fellows and Residents after receiving approval from their Staff Physician.

c. Patients already receiving oral levetiracetam that need to be switched to the injectable formulation because they are NPO do not require a Pediatric Neurology consult.

**3. Natalizumab (Tysabri®)**: In January 2008, natalizumab received FDA-approval for the treatment of moderate-to-severe Crohn's disease in patients with evidence of inflammation that have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies. Therefore, the restriction for natalizumab has been expanded to include the Department of Gastroenterology for the treatment of Crohn's disease patients failing to respond to other agents.

**4. Rituximab (Rituxan®)**: The restriction for rituximab has been changed to include use by Transplant Staff Physicians for the treatment of antibody-mediated rejection with allograft dysfunction. For treatment of post-transplant lymphoproliferative disease (PTLD), a Hematology/Medical Oncology consult is required. The recommended dose is 375 mg/$m^2$ IV (up to 4 doses may be administered on a weekly schedule).

**Therapeutic Interchanges**

**IV Phenytoin to IV Fosphenytoin**: On April 15, 2008, all new medication orders for injectable phenytoin will automatically be converted to injectable fosphenytoin by a pharmacist. All IV phenytoin in Pyxis machines will be switched to IV fosphenytoin. The dose, concentration in solutions, and infusion rates for fosphenytoin are expressed as phenytoin equivalents (PE); fosphenytoin should always be prescribed and dispensed in phenytoin equivalents (PE):

**For example, phenytoin 100 mg IV BID = fosphenytoin 100 mg PE IV BID**

The rationale for the interchange program is that injectable phenytoin has been associated with adverse reactions and outcomes such as venous irritation and pain, thrombophlebitis, and local cutaneous reactions and purple glove syndrome (from extravasation). Fosphenytoin has not been associated with these adverse outcomes. Additionally, fosphenytoin is now available generically and the price of the medication has dramatically decreased. In summary, fosphenytoin has the same efficacy as phenytoin, but has a better safety profile and is available as a generic. IV phenytoin will be removed from Formulary; oral phenytoin products will remain on Formulary.

**Additional Information**

Product labeling for haloperidol injection has been revised to include a new Cardiovascular subsection regarding cases of sudden death, QT prolongation and Torsade de Pointes in patients treated with haloperidol, especially when given intravenously, or at doses higher than recommended. The Pharmacy and Therapeutics Committee and its Specialty Panels have evaluated these data and are in the process of devising recommendations for IV haloperidol use and appropriate monitoring parameters. These recommendations will be communicated in the near future.

For more detailed information on the above medications, please consult the Formulary on the Intranet (under Clinical Resources/Drug Information), specifically under Lexi-Drugs Online. Furthermore, please call the Drug Information Center at 4-6456, option #1 if you have any questions.


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# Department of Pharmacy/Hb-03
# Drug Information Center