Follow-on Biologic: Long-acting Analogue Glargine

U.S. Food and Drug Administration

Approved by the U.S. Food and Drug Administration (FDA) on June 11, 2020, Semglee (insulin glargine injection) is a follow-on insulin that is automatically labeled as a biologic under section 351(a) of the Public Health Service Act of the Biologics Price Competition and Innovation Act despite having undergone approval through the generic 505(b)(2) New Drug Application pathway under the Food, Drug and Cosmetic Act. A long-acting insulin analogue co-developed by Mylan and Biocon Biologics, Semglee has an amino acid sequence identical to and shares the same FDA-approved indications as the reference product, Sanofi’s Lantus (insulin glargine). Of note, Semglee is not technically considered a biosimilar product.

Investigators of the 52-week type 1 diabetes (n=558) and the 24-week type 2 diabetes (when taken with oral antidiabetic medications for diabetes type 2, including insulin-naïve patients) (n=560) INSTRIDE studies reported Semglee to be noninferior to Lantus based on similar differences in the mean change of glycated hemoglobin (HbA1c) (0.03 [95% confidence interval (CI), -0.06 to 0.12] and 0.05 [95% CI, -0.11 to 0.21], respectively). Overall, there were no differences in the pharmacokinetics or pharmacodynamics, efficacy, safety and immunogenicity between Semglee and Lantus.

The long-acting insulin analogue will be available in similar strength and package sizes as the reference product (i.e., 10 mL vials and 3 mL single-use prefilled pens containing 100 mg/mL insulin glargine). At this time, Semglee is not deemed an ‘interchangeable product’ to Lantus but the manufacturers intend to pursue this approval status in the U.S., as they already have in Australia. The interchangeable status will likely require comparative analytical assessment based on state-of-the-art technology that supports a demonstration that Semglee and Lantus are “highly similar” and that there would be little or no residual uncertainty regarding immunogenicity between the two products.
The KIDs List: Inappropriate Medications in Pediatrics
Journal of Pediatric Pharmacological Therapeutics

There have been several published systematic reviews that mention a higher incidence and prevalence of adverse drug reactions in pediatric as compared to the adult population; this risk is increased when medications are used off-label in the pediatric population. In order to further improve medication safety for pediatric patients, there is a need for a clinical resource that identifies medications that have a greater likelihood of causing an adverse drug reaction due to altered medication-related pharmacokinetics and/or pharmacodynamics unique to this population.

Based on a comprehensive review of published literature and clinical resources commonly used to retrieve pediatric drug information, a panel of seven pharmacists specialized in pediatric care, commissioned by the Pediatric Pharmacy Association, developed the KIDs List, which represents the acronym for Key Potentially Inappropriate Drugs in pediatrics. Prior to finalizing this critically-evaluated, evidence-based KIDs list, the included medications and associated adverse drug reaction risks were peer-reviewed and open to a 30-day public comment period.

The KIDs list defines a potentially inappropriate medication as “medications or medication classes that should generally be avoided in persons younger than 18 years because they pose unnecessary high risk for children and a safer alternative is available.” The final KIDs list consists of 67 prescription or over-the-counter medications and/or medication classes alongside 10 excipients which should be ‘avoided’ (based on a strong recommendation strength or a life-threatening/altering adverse drug reaction) or ‘used with caution’ (based on low quality of evidence, weak recommendation strength, or clear therapeutic medication need despite high risk) in all or a subset of the pediatric population. For the purposes of the KIDs list, the pediatric populations are subcategorized as neonates, infants, young children, older children, and adolescents.

The KIDs list includes recommendations for avoiding use of 33 medications/classes and using 19 products with caution; there were six and four pharmaceutical vehicles classified as ‘avoid’ and ‘use with caution,’ respectively. The panel considered sufficient supporting evidence and availability of accepted therapeutic alternatives in the United States in determining inclusion of products on the KIDs list. Selected medications from the KIDs list associated with a strong strength of recommendation and high quality of evidence are presented in Table 1; this list is not all-inclusive.

Table 1. Sample Medications from the KIDs List

<table>
<thead>
<tr>
<th>Medication</th>
<th>Risk or Rationale</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzocaine</td>
<td>Methemoglobinemia</td>
<td>Avoid in infants for teething or pharyngitis</td>
</tr>
<tr>
<td>Codeine</td>
<td>Respiratory depression, death</td>
<td>Avoid in children unless used with pharmacogenetic test</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Serious skin rash</td>
<td>Caution in children; titration needed</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Hypertrophic pyloric stenosis</td>
<td>Avoid in neonates, unless for certain infections</td>
</tr>
<tr>
<td>Tricyclic anti-depressants</td>
<td>Sudden cardiac death</td>
<td>Avoid in children (desipramine)</td>
</tr>
</tbody>
</table>

The medications most commonly appearing in the KIDs list were anti-infectives, antipsychotics, dopamine antagonists and gastrointestinal agents. Despite a label Boxed warning regarding suicidality and suicidal ideation for antidepressants, the panel included only specific antidepressants that posed a greater risk in pediatrics based on sufficient available evidence.

Clinicians should use the KIDs list as a reference tool when selecting medications for a pediatric patient and apply sound clinical judgment in determining the appropriate therapy in light of patient-specific factors. If avoidance of a KIDs-listed medication is not clinically possible, close monitoring throughout administration and regular re-evaluation of therapy appropriateness are highly recommended.

Highlights: Development and application of the KIDs list

- The list of Key Potentially Inappropriate Drugs in pediatrics, known as the KIDs list, is a reference tool to alert clinicians to medications, medication classes or excipients that are associated with a higher risk of adverse drug reactions in pediatrics.
- The KIDs list contains 67 medications and/or medication classes and 10 excipients; the list includes 39 products to avoid and 23 products to use with caution.
- Clinical judgment should be applied regardless of the recommendations offered by the KIDs list.
The Evidence Behind Clinically Significant Psychotropic Drug-Drug Interactions

From Pharmacotherapy

As the practice of prescribing multiple psychotropics becomes increasingly prevalent, there is a need to evaluate the clinical relevance of reported psychotropic drug-drug interactions in light of apparent inconsistent inclusion and/or severity classification by reputable drug references.

Investigators reviewed primary literature consisting of 124 controlled and uncontrolled studies (n=2,716 patients) supporting each of the 58 drug-drug interactions deemed as either "major" or "contraindicated" in three clinical databases; Clinical Pharmacology, Micromedex, and Lexicomp. For the purpose of this review, psychotropics included anticonvulsants, antidepressants, an antimanic agent (i.e., lithium), antipsychotics, anxiolytic-sedative-hypnotic agents, and central nervous system stimulants. The most commonly reported adverse effects induced by psychotropic drug-drug interactions included central nervous system depression, decreased effectiveness, neurotoxicity, QT-interval prolongation, and serotonin syndrome.

Table 1. Psychotropic Drug-Drug Interactions Supported by a Clinical Trial (n=50 patients) and Statistical Evaluation

<table>
<thead>
<tr>
<th>Interaction pair</th>
<th>Adverse/pharmacokinetic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine, carbamazepine</td>
<td>Increased triglyceride, weight gain</td>
</tr>
<tr>
<td>Tranylcypromine, amitriptyline</td>
<td>High PR-interval, weight gain</td>
</tr>
<tr>
<td>Fluoxetine/paroxetine/venlafaxine, trazodone</td>
<td>Self-harm</td>
</tr>
<tr>
<td>Citalopram, risperidone</td>
<td>Increased risperidone concentration</td>
</tr>
<tr>
<td>Fluoxetine, haloperidol</td>
<td>Increased haloperidol concentrations</td>
</tr>
<tr>
<td>Fluoxetine, risperidone</td>
<td>Increased risperidone concentration</td>
</tr>
<tr>
<td>Lamotrigine, carbamazepine</td>
<td>Increased lamotrigine clearance</td>
</tr>
<tr>
<td>Olanzapine, carbamazepine</td>
<td>Decreased olanzapine concentration</td>
</tr>
<tr>
<td>Duloxetine, fluvoxamine</td>
<td>Increased duloxetine levels</td>
</tr>
<tr>
<td>Nefazodone, triazolam</td>
<td>Increased triazolam levels</td>
</tr>
</tbody>
</table>

Results showed that 18 (31%) and 51 (88%) of the 58 drug interaction pairs were not supported by primary literature in humans and included a combined study population of 100 or less, respectively. Of the 58 psychotropic drug interactions identified, 35 (60.3%) and 17 (29.3%) drug interaction pairs had evidence supporting adverse events and effects on drug plasma concentration, respectively. Of the 48 controlled studies (e.g., randomized controlled trials, clinical trials, observational studies) included in the review, 32 (66.7%) and 21 (43.8%) studies reported on pharmacokinetic and clinical adverse event data, respectively. Table 1 identifies ten psychotropic drug interactions pairs for which the reported adverse event or pharmacokinetic effect was supported by controlled stud(ies) consisting of at least 50 patients and included a formal statistical evaluation.

In interpreting the study results, it is important to note that any recently identified psychotropic drug-drug interaction would be omitted from this systematic review since the study included interaction pairs identified up to the year 2018. The investigators also excluded studies reporting adverse events of other psychotropic drug-drug interactions involving medications belonging to the same therapeutic drug classes as those targeted for this review.

The results of this systematic review reveal the lack of robust data supporting most of the known psychotropic drug-drug interactions. As a result, clinicians are often uncertain with interpreting the clinical relevance of these psychotropic drug interaction warnings since most are based on inferred mechanistic data or assumed therapeutic drug class interactions. At a minimum, facilities may want to ensure that the ten interactions listed in Table 1 are included in clinical alerts to providers and continue to consider increased monitoring for effects of other psychotropic drug interaction pairs. Post-marketing studies are necessary to evaluate the real-world safety of concurrent psychotropic use in order to ensure optimal clinical support systems and to reduce alert fatigue, where possible.

Highlights: Review of evidence supporting psychotropic drug-drug interactions

- In a systematic review of 58 "major" or "contraindicated" psychotropic drug-drug interactions, 31% were not supported by primary literature, while 88% included studies of less than 100 patients.
- According to the study, there are only ten psychotropic drug-drug interaction pairs that are supported by one or more clinical trials of at least a combined 50 patients, with the data being formally evaluated using statistics.
Use of acid suppressants (i.e., proton pump inhibitors, histamine-2 receptor antagonists) is identified as a potential risk factor for multidrug-resistant microorganism colonization according to recently published data. It is hypothesized that acid suppressants increase the risk of multidrug-resistant colonization through three possible mechanisms: (1) reduction of gastric acid secretion that increases survival of viable exogenous bacteria from stomach to intestine, (2) alteration of the intestinal microbiota composition resulting in reduced species diversity, and (3) gastric acid resistance of certain strains (i.e., extended-spectrum β-lactamases-producing Escherichia coli sequence type 131) resulting in penetration ease through the gastric acid barrier.

A systematic review and meta-analysis of twelve qualified observational studies (cross-sectional (n=7), case control (n=3), cohort studies (n=2)) (n=22,305 patients) was recently conducted to determine whether gastric acid suppression is linked to an increased risk of intestinal colonization with multidrug-resistant microorganisms, including multidrug-resistant Enterobacteriaceae, methicillin- or vancomycin-resistant Staphylococcus aureus, multidrug-resistant Pseudomonas or Acinetobacter species, and vancomycin-resistant enterococci. Multidrug-resistant microorganisms of the Enterobacterales order often will produce extended-spectrum β-lactamases, carbapenemases, or plasmid-mediated AmpC β-lactamases.

Based on the results of the analysis that was adjusted for potential confounders, acid suppression was associated with an increased odds by approximately 75% (odds ratio (OR)=1.74; 95% confidence interval (CI), 1.40 to 2.16) of intestinal colonization for both multidrug-resistant Gram-negative Enterobacteriaceae and vancomycin-resistant Gram-positive enterococci.

Of note, the investigators included studies in their review pertaining to urinary tract infections which are caused by Enterobacteriaceae microorganisms that often colonize the intestinal tract; inclusion and exclusion of these studies did not change the study conclusions. None of the studies on methicillin- or vancomycin-resistant Staphylococcus aureus were eligible for inclusion in this meta-analysis; likewise, there were no eligible randomized clinical trials included.

Compared to proton pump inhibitors, the use of histamine-2 receptor antagonists does not seem to be associated with multidrug-resistant microorganism colonization based on preliminary data from this meta-analysis (OR=1.33; 95% CI, 0.86 to 2.08); of note, this statement is supported by only four studies with a large CI for the odds ratio and should, therefore, be interpreted with caution. According to two studies, there was no association between the duration of acid suppressant use and increased vancomycin-resistant enterococci colonization.

Since observational studies cannot prove causation, providers should apply the study conclusions with caution but still weigh the risks and benefits of acid suppressant use, particularly proton pump inhibitors, for each patient in order to curb the increase of antimicrobial resistance in accordance with antimicrobial stewardship efforts.

**Highlights:** Acid suppressants and multidrug-resistant microorganism colonization

- Acid suppressant use is associated with an increased risk for multidrug-resistant microorganism colonization based on the meta-analysis of twelve observational studies involving over 22,000 patients.
- Acid suppressive medications, particularly proton pump inhibitors, should be used only when clinically necessary and avoided if deemed unnecessary for a specific patient.
PAIN MANAGEMENT STEWARDSHIP

Nonopioid and Opioid Effects on Chronic Noncancer Pain

The Agency for Healthcare Research and Quality published two comparative effectiveness reviews of trials involving oral and topical nonopioid and opioid pharmacologic treatments (including medical cannabis) for chronic noncancer pain, including chronic headache, fibromyalgia, inflammatory arthritis, low back pain, neuropathic pain, osteoarthritis, and sickle cell disease. The investigators evaluated the magnitude of benefit and harm effects for nonopioid (185 studies) and opioid (162 studies) pharmacologic therapies relative to short-, intermediate-, and long-term treatment durations for chronic noncancer pain. To determine the magnitude of effect, investigators set numerous predefined thresholds. For example, a small effect on pain may be defined as a mean between-group difference of 0.5 to 1 point on a visual analog scale, while a moderate effect on pain may involve a mean difference of 10- to 20-points on a 0- to 100-point visual analog scale. Key positive findings on efficacy are presented in Table 1. Limited intermediate- and long-term studies evaluating other nonopioid or opioid treatment options were insufficient for drawing conclusions. According to these reviews, nonopioid drugs (serotonin-norepinephrine reuptake inhibitors, pregabalin/gabapentin, and nonsteroidal anti-inflammatory drugs (NSAIDs), particularly) are associated with small-to-moderate improvements in pain and function in the short-term in patients with specific types of chronic pain; for some patients, medication class-specific adverse events led to treatment discontinuation, including serious cardiovascular or gastrointestinal effects with NSAIDs. In the short-term, opioids showed no difference in efficacy when compared to nonopioids. Studies show that opioids are associated with dose-dependent harm, especially with short-term use; concomitant use with benzodiazepines and gabapentinoids increase overdose risks.

In selecting nonopioid and opioid treatments, patient characteristics must be considered. In order to appropriately interpret and apply the presented information, providers should refer to the published reviews in their entirety which provide additional details on medications evaluated, strength of supporting evidence and a table summarizing medication-specific adverse events. Conclusions from both reviews are consistent with current understanding of analgesics.

### Highlights: Noncancer pain treatment options
- Small-to-moderate improvements in pain and/or function are reported with only short-term nonopioid and opioid use for chronic noncancer pain.
- Adverse events resulted in medication discontinuation, particularly with nonsteroid anti-inflammatory drugs and higher opioid doses.

### Table 1. Efficacy of Nonopioid and Opioid Options for Short-Term (one to less than six months) Treatment of Pain

<table>
<thead>
<tr>
<th>Indication: Medication(s)</th>
<th>Magnitude of improvement (outcomes)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropathic pain</strong>: Duloxetine, gabapentin/pregabalin (pain only), oxcarbazepine</td>
<td>Small (pain, function)</td>
</tr>
<tr>
<td><strong>Fibromyalgia</strong>: Duloxetine, gabapentin/pregabalin, milnacipran</td>
<td></td>
</tr>
<tr>
<td><strong>Inflammatory arthritis</strong>: Nonsteroidal anti-inflammatory drugs</td>
<td></td>
</tr>
<tr>
<td><strong>Osteoarthritis</strong>: Duloxetine, Nonsteroidal anti-inflammatory drugs</td>
<td></td>
</tr>
<tr>
<td><strong>Low back pain</strong>: Duloxetine (pain only)</td>
<td>Moderate (pain)</td>
</tr>
<tr>
<td><strong>Neuropathic pain</strong>: Duloxetine</td>
<td></td>
</tr>
<tr>
<td><strong>Osteoarthritis</strong>: Diclofenac improvement moderately more than celecoxib</td>
<td>Moderate (pain and function)</td>
</tr>
<tr>
<td>Opioids</td>
<td>Small (pain, function, sleep quality)</td>
</tr>
</tbody>
</table>
Inpatient Antiretroviral Stewardship Programs

The Infectious Diseases Society of America (IDSA), the HIV Medicine Association (HIVMA), and the American Academy of HIV Medicine (AAHIVM) recently published a joint policy paper on the role of antiretroviral stewardship programs (ARVSPs) in inpatient practice settings to reduce risks of antiretroviral (ARV) therapy-related errors during hospitalization and at transitions of care for patients living with human immunodeficiency virus (HIV). Occurring up to a reported 86% of the time, inpatient ARV-related errors may include ARV drug regimen omission, incorrect ARV dose or schedule, and missed ARV drug-drug interactions which can lead to risks of adverse drug events, treatment failure, and drug resistance. The guidance document is modeled after multidisciplinary, institution-specific antimicrobial stewardship programs (ASPs) currently required by Joint Commission standards and supported by the Centers for Disease Control and Prevention. Antiretrovirals are typically prescribed in the outpatient setting and continued in the inpatient setting. Although associated with risks for viral resistance, the management and monitoring of antiretrovirals are not currently included in most inpatient or outpatient antimicrobial stewardship programs.

In garnering appropriate leadership support and oversight for ARVSPs, the guidance document defines ARV expertise, which generally includes recent HIV-focused clinical patient care, continuing education, and documented experience or board certification, as minimum criteria established by HIVMA or AAHIVM.

The joint policy paper provides a detailed overview of the three key evidence-based strategies for reducing ARV-related medication errors and clinically significant drug interactions as summarized below:

- Clinical checklists for safe prescribing practices applied upon admission and at order entry.
- Computerized physician order entry order sets to guide ARV prescribing, in addition to administration recommendations (e.g., take with food); electronic order entry alerts regarding ARV-focused best-practice advisories and contraindicated drug combinations, with reference links to supporting electronic drug information resources.
- Collaborative prospective physician-pharmacist reviews of hospitalized patients living with HIV upon admission and/or throughout hospital stay.

The following recommendations are jointly endorsed by IDSA, HIVMA, and AAHIVM in support of expanded stewardship in the area of ARV management:

- Accrediting, quality assurance, and regulatory bodies can broaden the scope of stewardship definitions to include ARV management.
- Institutions should incorporate ARV-focused stewardship into infrastructure of existing ASPs.
- Institution should refer to existing professional organizations focused on HIV management in order to maintain updated institutional treatment and prevention protocols.
- Institutions should develop processes, including formulary management, to ensure uninterrupted ARV therapy from admission through transition to outpatient care.

Optimal clinical services for the pharmacologic management of ARVs should evolve to include not only evidence-based selection of an ARV based on patient-specific factors, but also careful selection of concomitant drug therapy to manage concurrent infectious and noninfectious complications and comorbidities. The development and implementation of a multidisciplinary ARVSP may be a critical initial step to ensuring appropriate medication management for patients living with HIV in the inpatient setting.

**Highlights:** Recommendations for antiretroviral stewardship programs in the inpatient setting

- The Infectious Diseases Society of America, the HIV Medicine Association, and the American Academy of HIV Medicine recently published a joint policy paper on the role of antiretroviral stewardship programs (ARVSPs) in inpatient practice settings.
- Three key evidence-based strategies for reducing ARV-related errors include using clinical checklists, electronic order sets and order entry alerts, and physician-pharmacist prospective medication reviews.
- The joint policy paper challenges institutions and authoritative bodies to incorporate ARVSPs into existing infrastructure of antimicrobial stewardship programs.
### RECENT NEW DRUG APPROVALS

**U.S. Food and Drug Administration**

<table>
<thead>
<tr>
<th>Generic (Brand)</th>
<th>Dosage form</th>
<th>Indication</th>
<th>Approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegfilgrastim-apgf (Nyvepria)</td>
<td>Injectable, subcutaneous</td>
<td>To decrease the incidence of infection in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia</td>
<td>June 10, 2020</td>
</tr>
<tr>
<td>Inebilizumab-cdon (Uplizna)</td>
<td>Injectable, intravenous</td>
<td>To treat neuromyelitis optica spectrum disorder in adults who have antibodies against aquaporin-4</td>
<td>June 11, 2020</td>
</tr>
<tr>
<td>Insulin glargine (Semglee)</td>
<td>Injectable, subcutaneous</td>
<td>To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus</td>
<td>June 11, 2020</td>
</tr>
<tr>
<td>Insulin lispro-aabc (Lyumjev)</td>
<td>Injectable, subcutaneous</td>
<td>To improve glycemic control in adults with diabetes mellitus</td>
<td>June 11, 2020</td>
</tr>
<tr>
<td>Lurbinectedin (Zepzelca)</td>
<td>Injectable, intravenous</td>
<td>To treat adults with metastatic small cell lung cancer that has spread during or after treatment with platinum-containing therapy</td>
<td>June 15, 2020</td>
</tr>
<tr>
<td>Triheptanoin (Dojolvi)</td>
<td>Liquid, oral</td>
<td>To treat pediatric and adult patients with molecularly-confirmed long-chain fatty acid oxidation disorders</td>
<td>June 30, 2020</td>
</tr>
</tbody>
</table>

### References

References

Clinical Updates

Follow-on Biologic: Long-Acting Analogue Glargine

- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. The "deemed to be a license" provision of the BPCI act: questions and answers guidance for industry. [guidance][updated 2020 Mar, cited 2020 Jul 14]. Available at: https://www.fda.gov/media/135838/download.

The Evidence Behind Clinically Significant Psychotropic Drug-Drug Interactions


Antimicrobial Stewardship

Acid Suppressant Impact on Multidrug-Resistant Microorganism Colonization


Pain Management Stewardship

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Medication Safety

Inpatient Antiretroviral Stewardship Programs


References


