## Compatibility Reference Guide

### Testing Methods
- Admixture stability with SMOFlipid was tested by visual inspection, pH, large-diameter lipid globule size distribution (PFAT5), and mean lipid droplet diameter in compliance with USP <729> standards. No microbiological or chemical tests were conducted.
- Results are only valid for the branded products listed at the time of testing.

### SMOFlipid
Lipid Injectable Emulsion, USP 20%

<table>
<thead>
<tr>
<th>Macronutrients*</th>
<th>Aminosyn® II 15% Amino Acid Injection</th>
<th>Plenamine™ 15% Amino Acids Injection</th>
<th>Clinisol 15% Amino Acid Injection</th>
<th>ProSol 20% Amino Acid Injection</th>
<th>Travasol 10% Amino Acid Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino Acid Solution (g/L)</td>
<td>32-91</td>
<td>32-91</td>
<td>32-91</td>
<td>35-111</td>
<td>28-67</td>
</tr>
<tr>
<td>SMOFlipid 20% (g/L)</td>
<td>12-67</td>
<td>12-67</td>
<td>12-67</td>
<td>14-74</td>
<td>9-56</td>
</tr>
<tr>
<td>Dextrose 70% (g/L)</td>
<td>88-342</td>
<td>88-342</td>
<td>88-343</td>
<td>103-371</td>
<td>68-297</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trace Elements &amp; Adult Multivitamins</th>
<th>Infuvite Adult Injection (Baxter)</th>
<th>Addamel N (Fresenius Kabi)</th>
<th>Electrolytes*</th>
<th>Sodium</th>
<th>Potassium</th>
<th>Calcium</th>
<th>Magnesium</th>
<th>Chloride</th>
<th>Acetate</th>
<th>(inorganic) Phosphate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 10 mL</td>
<td>0 to 10 mL</td>
<td>0 to 10 mL</td>
<td>0 to 10 mL</td>
<td>0 to 15 mEq/L</td>
<td>0 to 15 mEq/L</td>
<td>0 to 15 mEq/L</td>
<td>0 to 15 mEq/L</td>
<td>0 to 300 mEq/L</td>
<td>0 to 15 mEq/L</td>
<td>0 to 15 mEq/L</td>
</tr>
</tbody>
</table>

| Extended Stability | 9 days total storage: 7 days storage at 2°-8°C, then 2 days at 20°-25°C | 9 days total storage: 7 days storage at 2°-8°C, then 2 days at 20°-25°C | 8 days total storage: 7 days storage at 2°-8°C, then 1 day at 20°-25°C | 8 days total storage: 7 days storage at 2°-8°C, then 1 day at 20°-25°C | 8 days total storage: 7 days storage at 2°-8°C, then 1 day at 20°-25°C |

*The range does not necessarily reflect the minimum concentration of each macronutrient to ensure stability.
*Addamel N (for adults) is not FDA-approved for use in the U.S. Per 10 mL, it contains: iron (1.1 mg), zinc (6.5 mg), copper (1.26 mg), chromium (0.01 mg), fluoride (0.95 mg), and molybdenum (0.019 mg).
*The electrolyte salts used were sodium chloride, potassium acetate, calcium chloride, magnesium sulfate, and sodium phosphates. Any significant change in additions to the admixture compared to what has been evaluated in this study may affect stability/compatibility.
*The same limits are valid when additions of organic phosphate, sodium glycerophosphate (Glycophos) are used. Glycophos is not FDA-approved for use in the U.S.

### Additives & Storage
- Additions to the PN admixtures should be evaluated by a pharmacist for compatibility. If it is deemed advisable to introduce additives, use strict aseptic techniques to avoid microbial contamination.
- Infuse admixtures containing SMOFlipid immediately. If not used immediately, store admixtures under refrigeration at 2°C to 8°C (36°F to 46°F) for no longer than 24 hours. Infusion must be complete within 24 hours after removal from refrigeration. Discard any remaining admixture.

If you have any questions, please contact medical information at 1.800.551.7176 (option 4) or email Nutrition.MedInfo.USA@fresenius-kabi.com.
SMOFLIPID (lipid injectable emulsion), for intravenous use

INDICATIONS AND USAGE
SMOFLIPID is indicated in adult and pediatric patients, including term and preterm neonates, as a source of calories and essential fatty acids for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.

DOSAGE AND ADMINISTRATION
The recommended daily dosage is 1 to 2 grams per kg per day and should not exceed 2.5 grams/kg per day. Reduced dosage or dilution (≤ 6.25%) is recommended in infants with high risk of new or ongoing nephrotoxicity. Allow 10% to 15% of the daily required calories to be provided by parenteral nutrition.

When SMOFLIPID 1000 mL is supplied as a Pharmacy Bulk Package for admixing only and not for direct infusion.

Prior to administration, transfer to a separate I-PN container for individual patient use. Use a non-vented, non-DUSP 12-gauge 1-inch T-line in-line administration. Protect the admixed PN solution from light.

Table 1: Recommended Pediatric Dosage

<table>
<thead>
<tr>
<th>Pediatric age group</th>
<th>Initial dose</th>
<th>Maximum dose</th>
<th>Duration of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 2 years of age (excluding preterm and term neonates)*</td>
<td>0.5 to 1 g/kg/day</td>
<td>3 g/kg/day</td>
<td>20 to 24 hours for preterm and term neonates</td>
</tr>
<tr>
<td>2 to &lt;12 years</td>
<td>1 to 2 g/kg/day</td>
<td>3 g/kg/day</td>
<td>12 to 24 hours for patients 1 month to 2 years</td>
</tr>
<tr>
<td>12 to 17 years</td>
<td>1 to 2 g/kg/day</td>
<td>2.5 g/kg/day</td>
<td>12 to 24 hours</td>
</tr>
</tbody>
</table>

* The neonatal period is defined as including term, post-term, and preterm newborn infants. The neonatal period for term and post-term infants is the day of birth plus 27 days. For preterm infants, the neonatal period is defined as the day of birth through the expected age of delivery plus 27 days (i.e., 44 weeks postnatal-age).

CONTRAINDICATIONS
- Known hypersensitivity to fish, egg, soybean, or peanut protein, or to any of the active ingredients or inorganic acids in SMOFLIPID
- Severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglycerides >1000 mg/dL)
- Hypersensitivity Reaction: Reactions have been observed between soybean and peanut protein.

WARNINGS AND PRECAUTIONS
- Risk of Parenteral Nutrition-Associated Liver Disease (PNALD) and Other Hepatobiliary Disorders: PNALD, or intestinal failure associated liver disease (IFALD) can be associated with parenteral nutrition with or without phytosterols, and may progress to steatohepatitis with fibrosis and cirrhosis (possibly leading to chronic hepatic failure). In the etiology of PNALD, multifactorial, however, intravenously administered phytosterols (plant sterols) contained in plant-derived lipid emulsion, including SMOFLIPID, have been associated with development of PNALD.

In a randomized study of neonates and infants expected to be treated with PN for at least 28 days, parenteral nutrition-induced alkalosis (PNAC), a precursor to PNALD, developed less frequently in SMOFLIPID-treated patients than in 100% soybean oil lipid emulsion-treated patients.

Monitor liver tests in patients treated with SMOFLIPID and consider discontinuation or dosage reduction if abnormalities occur.

Other Hepatobiliary Disorders
- Hyperlipidemia disorders including cholestasis and cholelithiasis have developed in some parenteral nutrition-treated patients without preexisting liver disease. Monitor liver tests when administering SMOFLIPID. Patients developing signs of hepatobiliary disorders should be assessed early to determine whether these conditions are related to SMOFLIPID use.
- Death in Preterm Neonates: Deaths in preterm neonates after infusion of lipid injectable emulsions containing only soybean oil have been reported in the medical literature. Autopsy findings in these preterm neonates included intravascular lipid accumulation in the lungs. Preterm and small-for-gestational-age neonates, who may rapidly accumulate lipids, accompanied by prolonged plasma clearance (resulting in higher lipid levels), may result in this adverse reaction.

Perform frequent checks of the intravenous catheter insertion site for edema, redness, and discharge.

Fat Overload Syndrome: This is a rare condition that has been reported with intravenous lipid emulsions, and is characterized by a sudden deterioration in the patient's condition (e.g., fever, avascular necrosis, thrombocytopenia, coagulation disorders, hyperlipidemia, hepatomegaly, deteriorating liver function, and central nervous system manifestations such as coma). A reduced or limited ability to metabolize lipids, accompanied by severe engorgement of plasma clearance (resulting in higher lipid levels), may result in a syndrome. Although fatal overdose syndrome has been most frequently observed when the recommended doses (e.g., 8 grams/day or 15% infusion rate) exceeded, cases have also been described when the lipid formulation was administered according to instructions.

If signs or symptoms of fat overload syndrome occur, stop SMOFLIPID. The syndrome is usually reversible when the infusion of the lipid emulsion is stopped.

Rebound Lipemia: Adverse events associated with parenteral nutrition in malnourished patients may result in rebound syndrome, which is characterized by the intracellular shift of potassium, phosphorus, and magnesium as patients become anabolic. Thrombocytopenia and fluid retention may also develop. To prevent these complications, clinicians are recommended to maintain hydration and prevent excessive increases in serum triglycerides.

Hypertriglyceridemia: The use of SMOFLIPID is contraindicated in patients with hypertriglyceridemia with serum triglyceride concentrations >1000 mg/dL.

Patients with conditions such as inherited lipid disorders, obesity, diabetes mellitus, or metabolic syndromes have a higher risk of developing hypertriglyceridemia with the use of SMOFLIPID. In addition, patients with hypertriglyceridemia may have worsening of their hypertriglyceridemia with the use of SMOFLIPID. Adverse events may further increase such risk.

Evaluate patients' capacity to metabolize and eliminate the infused lipid emulsion by measuring serum triglycerides before the start of infusion (baseline value) and regularly throughout therapy. If triglyceride levels are above 400 mg/dL in adults, stop the SMOFLIPID infusion and monitor serum triglyceride levels to avoid clinical complications of hypertriglyceridemia such as pancreatitis. In pediatric patients with hypertriglyceridemia, lower triglyceride levels (i.e., below 400 mg/dL) may be associated with increased risk of lipidosis. Therefore, in patients at risk of new or ongoing nephrotoxicity, clinicians should avoid potential complications of hypertriglyceridemia such as pancreatitis, lipid pneumonitis, and neurologic changes, including ketonuria.

In adults, repeated measurement of serum triglycerides in patients with hypertriglyceridemia, assess high-risk patients for their overall energy intake including other sources of lipids and dextrose, as well as concomitant drugs that may affect lipid and dextrose metabolism.

- Essential Fatty Acid Deficiency: Treatment-emergent moderate of severe essential fatty acid deficiency (EFAD) defined as the triene (Mead acid) to balance (arachidonic acid) ratio 1:2 and 1:4, respectively, were not observed in pediatric clinical trials of SMOFLIPID up to 28 days. However, cases of EFAD have been reported in adults and pediatric patients in the postmarketing period with the use of SMOFLIPID. The median time to onset was greater than 28 days among cases that reported time to onset. Monitor patients for laboratory evidence (e.g., abnormal fatty acid levels) and clinical symptoms of EFAD (e.g., skin manifestations and poor growth) because these signs may emerge before laboratory evidence of EFAD is confirmed. Laboratory tests (e.g., measurement of Mead acid to balance) should be adequate to diagnose EFAD, and assessment of individual fatty acid levels may be needed. Ensure patients are receiving recommended doses of SMOFLIPID to prevent EFAD.

- Monitoring/Laboratory Tests: Throughout treatment monitor serum triglycerides, fluid and electrolyte status, blood glucose, liver and kidney function, coagulation parameters, and complete blood counting including platelets.

Drug Interactions
- SMOFLIPID contains soybean oil which may interfere with some laboratory blood tests (e.g., hemoglobin, lactate dehydrogenase (LDH), bilirubin, and oxygen saturation) if blood is sampled before lipids have cleared from the bloodstream. Conduct these blood tests at least 6 hours after stopping the infusion.

- SMOFLIPID contains vitamin K that may counteract anticoagulant activity.

ADVERSE REACTIONS
- Most common adverse drug reactions (%) of adult patients who received SMOFLIPID from clinical trials were hypokalemia, vomiting, hypoglycemia, anemia, nausea, and headache.

- Less common adverse reactions in 1% of pediatric patients who received SMOFLIPID were dyspnea, leukocytosis, diarrhea, pneumonia, cholestasis, dysgeusia, increased blood alkaline phosphatase, increased gamma-glutamyltransferase, increased aspartate aminotransferase, increased alanine aminotransferase, fluid overload, hypertension, hypertriglyceridemia, and rash.

- Less common adverse reactions in 1% of pediatric patients who received SMOFLIPID were decreased hematocrit, metabolic acidosis, increased blood triglycerides, infection, increased blood alkaline phosphatase, increased alanine aminotransferase, fluid overload, hypertension, hypertriglyceridemia, and rash.

- The following adverse reactions have been identified during post-approval use of SMOFLIPID in countries where it is regulated. Cardiac disorders: CAD (coronary artery disease) in conditions such as diabetes, hypertension, sepsis, dyspnea, pulmonary hypertension, and anemia, and device-related infection.

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176, option 5, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- SMOFLIPID contains soybean oil which may interfere with some laboratory blood tests (e.g., hemoglobin, lactate dehydrogenase (LDH), bilirubin, and oxygen saturation) if blood is sampled before lipids have cleared from the bloodstream. Conduct these blood tests at least 6 hours after stopping the infusion.

- SMOFLIPID contains vitamin K that may counteract anticoagulant activity.

OVERDOSAGE
- An overdose, fat overload syndrome may occur. Stop the SMOFLIPID infusion until triglyceride levels have normalized and symptoms have abated. The effects are usually reversible by stopping the lipid infusion. If medically appropriate, further intervention may be indicated. Lipids are not dialyzable from plasma.