Most of the products used in dogs and cats are dictated by products used in humans. However, there have been 2 insulins that have been modified or relabeled for use in dogs and cats. One such product, Vetsulin (Merck, vetsulin.com), was very similar to the intermediate-acting insulin, Lente, which is used in humans, but is currently unavailable in the U.S. because it did not meet stability specifications. Merck Animal Health is working to resolve this issue.

DEFINITIONS
Many insulins used in dogs and cats were developed for use in humans. In general, their effects in dogs and cats include a more rapid onset and shorter duration of action.

- **Rapid-acting/short-acting insulin**: Insulin preparation with onset of action (after SC injection) from 0.5 to 1.5 H after injection and peak action about 2 to 4 H after administration.
- **Intermediate acting insulin**: Insulin preparation with onset of action from 1.5 to 2 H after injection and peak action between 2 and 11 H after administration; often combined with rapid- or short-acting insulin.
- **Long-acting insulin**: Insulin preparation with onset of action less than 3 H after injection and peak action between 4 and 26 H after administration; often combined, when needed, with rapid- or short-acting insulin.
FOCUS ON PHARMACOLOGY

InSulIn TypeS & AdmInISTrATIOn

Rapid- & Short-Acting

- **Regular**: Insulin preparation with an onset of action in dogs and cats from 0.5 to 1.5 H after SC injection, peak action about 0.5 to 4 H, and duration of action 1 to 4 H after administration. Regular insulin can also be given IM and IV.

- **Aspart**: This product’s onset of action is very rapid; it can only be administered SC. Onset of action is < 0.25 H, peak action 0.5 to 1.5 H, and duration of action 3 to 4 H. It is mainly used in humans to control postprandial hyperglycemia.

- **Lispro**: This product description is exactly the same as for insulin aspart.

Intermediate-Acting

- **Lente**: After SC injection, this insulin preparation has an onset of action from 0.5 to 2 H after injection, peak of action between 4 and 11 H, and duration of action 14 to 24 H. Lente insulin was the parent drug for the veterinary preparation, Vetsulin, which is not currently available in the U.S., but is available in Europe and Canada as Caninsulin.

- **Neutral Protamine Hagedorn (NPH)**: This insulin is absorbed from SC injection approximately 0.5 to 2 H after injection, with peak action at 2 to 10 H and duration of action at 4 to 18 H. The shorter end of the ranges are usually typical in the cat.

Long- & Prolonged-Acting

- **Glargine**: This ultra long-acting insulin is only recommended for cats. It is only given SC and has a maximum effect ranging from 8 to 26 H, with a duration of action that is often less than 24 H, requiring administration every 12 H.

- **Detemir**: A relatively new insulin with ultra-long activity. Has been used in dogs and cats and found to be effective for 24 H; however, giving 2 divided doses SC per day is recommended. In addition, due to its potent hypoglycemic capability, using lower insulin doses than usual is suggested.

- **Protamine Zinc (PZI)**: PZI acts more like an intermediate-acting insulin in the cat, calling for a split dosage (Q 12 H) treatment schedule. Its maximum effect occurs in 4 to 12 H and duration of action is frequently less than 24 H. It is sold only as a veterinary product (ProZinc, boehringer-ingelheim.com) and cali-

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### Table 1. Overview of Insulin Activity in Dogs & Cats

<table>
<thead>
<tr>
<th>Type</th>
<th>Derivation</th>
<th>Onset of Action</th>
<th>Peak Activity</th>
<th>Duration</th>
<th>Route</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-Acting/Short-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>Recombinant human analog</td>
<td>0.5–1.5 H</td>
<td>2–4 H</td>
<td>1–4 H</td>
<td>SC</td>
<td>Humulin R (lilly.com), Novolin R (novonordisk.com)</td>
</tr>
<tr>
<td>Aspart</td>
<td>Recombinant human analog</td>
<td>&lt; 0.25 H</td>
<td>0.5–1.5 H</td>
<td>3–4 H</td>
<td>SC</td>
<td>NovoLog (novonordisk.com)</td>
</tr>
<tr>
<td>Lispro</td>
<td>Recombinant human analog</td>
<td>&lt; 0.25 H</td>
<td>0.5–1.5 H</td>
<td>3–4 H</td>
<td>SC</td>
<td>Humalog (lilly.com)</td>
</tr>
<tr>
<td><strong>Intermediate-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lente</td>
<td>Porcine insulin zinc suspension + acetate buffer</td>
<td>0.5–2 H</td>
<td>4–11 H</td>
<td>14–24 H</td>
<td>SC Q 12 H</td>
<td>Vetsulin* (vetsulin.com)</td>
</tr>
<tr>
<td>Neutral Protamine Hagedorn (NPH)</td>
<td>Recombinant human analog + protamine</td>
<td>0.5–2 H</td>
<td>2–10 H</td>
<td>4–18 H</td>
<td>SC Q 12 H</td>
<td>Humulin N (lilly.com), Novolin N (novonordisk.com)</td>
</tr>
<tr>
<td><strong>Long-Acting/Prolonged-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>Recombinant human analog</td>
<td>&lt; 1.5 H</td>
<td>8–26 H</td>
<td>&lt; 12 H</td>
<td>SC Q 12 H</td>
<td>Lantus (sanofi.us)</td>
</tr>
<tr>
<td>Detemir</td>
<td>Recombinant human analog</td>
<td>&lt; 2 H</td>
<td>5–10 H</td>
<td>12–14 H</td>
<td>SC Q 12 H</td>
<td>Levemir (novonordisk.com)</td>
</tr>
<tr>
<td>Protamine Zinc</td>
<td>Recombinant human analog</td>
<td>&lt; 0.75–3 H</td>
<td>4–12 H</td>
<td>9–12 H</td>
<td>SC Q 12 H</td>
<td>ProZinc§ (boehringer-ingelheim.com)</td>
</tr>
</tbody>
</table>

* Approved by the FDA for use in veterinary patients; however, it is not currently available in the U.S.
§ Approved by the FDA for use in cats
The rest of the insulin products mentioned previously are routinely available in 100 U/mL concentrations.

### Mixtures
- **NPH + Regular**: This product contains the combined features of regular crystalline insulin and NPH insulin. Its purpose is to offset the postprandial hyperglycemia that occurs in humans. Since this is rarely a concern in dogs and cats, its use in veterinary patients is rare. Early onset hypoglycemia is a concern because of the rapid-acting component.
- **Lente + Regular**: This product is no longer manufactured in the U.S.

### Measurement
- **Present standard** is 24 U per mg; the standard was set to assure uniformity among insulin doses. A U is based on absolute weight of insulin prepared from a recrystallized composite sample.
- **U-100 syringes versus U-40 syringes**: It is important to use insulin syringes that are calibrated for the particular insulin concentration being administered to the patient. Mixing the 2 and using a correction factor might cause confusion for the pet owner and lead to under- or overdosing.
- **Vetsulin & ProZinc** must be administered with U-40 syringes. These syringes are only available by mail order unless the veterinarian has a local source.

### U-100 syringes
- Available in 0.3-, 0.5-, and 1-mL capacities. These are readily available due to their routine use in human diabetic patients.

### Table 2. Insulin Administration

<table>
<thead>
<tr>
<th>Patient Insulin Syringe</th>
<th>Starting Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maintenance Therapy (Dogs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting NPH (Humulin N) U-100</td>
<td>0.5 U/kg SC Q 12 H</td>
<td>Insulin most commonly used at this time in dogs</td>
</tr>
<tr>
<td>Intermediate-acting Lente (Vetsulin) U-40</td>
<td></td>
<td>Currently unavailable for dogs in the U.S.</td>
</tr>
<tr>
<td>Long-acting Detemir (Levimir) U-100</td>
<td>No current dose recommendations</td>
<td>Detemir has demonstrated efficacy in a few canine studies but clinical experience with the use of long-acting insulin analogs in dogs is limited.</td>
</tr>
<tr>
<td><strong>Maintenance Therapy (Cats)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting Glargine (Lantus) Detemir (Levimir) U-100 U-100</td>
<td>0.25–0.5 U/kg SC Q 12 H</td>
<td>Because the overall metabolic effect of detemir is greater than glargine, a lower starting dose is suggested.</td>
</tr>
<tr>
<td>Long-acting Protamine Zinc Insulin (ProZinc) U-40</td>
<td>0.2–0.7 U/kg SC Q 12 H</td>
<td>Approved for cats in the U.S.</td>
</tr>
<tr>
<td>Intermediate-acting Lente (Vetsulin) U-40</td>
<td></td>
<td>Currently unavailable for cats in the U.S.</td>
</tr>
<tr>
<td>Intermediate-acting NPH (Humulin N) U-100</td>
<td>0.25–0.5 U/kg SC Q 12 H</td>
<td>Not a first-tier insulin choice for cats: short duration of action limits usefulness in cats; pronounced peak effect increases hypoglycemic risk in some cats</td>
</tr>
<tr>
<td><strong>Induction of Therapy and/or Diabetic Ketoacidosis (Dogs &amp; Cats)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting Regular (Humulin R) U-100</td>
<td>Continuous rate infusion (CRI) or intermittent IM protocol; can be used SC in noncritical patients</td>
<td>Regular insulin is used for stabilization of complicated diabetes and induction of insulin therapy. Stable, newly-diagnosed diabetic patients may begin maintenance therapy immediately.</td>
</tr>
</tbody>
</table>
ABSORPTION
Factors That Affect Absorption
1. **ph (stable at 7.4)** is a key factor with insulin glargine because this insulin requires an acidic solution to allow for its slow absorption from the injection site.

2. **Crystal size** was the key factor affecting the absorption of ultralente, lente, and semi-lente insulins when they were commercially available. The larger crystal size delayed absorption and allowed for longer duration of action.

3. **Zinc binding** allows insulin stabilization for gradual absorption.

4. **Protein (protamine) binding**—protamine is a protein that allows for delayed insulin absorption from the SC injection site.

Factors That Affect Time of Absorption
1. **Volume**: For example, 1 mL of U-40 is absorbed more slowly than 0.4 mL of U-100.

2. **Unit dosage**: As the total insulin dose increases, so does the absorption rate.

3. **Site of injection**: Injection into a body part that moves allows faster absorption.

4. **Local blood flow**: Damaged skin (eg, scars, inflammation) may have unpredictable effects on absorption.

Considerations for Administration
- Some obese patients may require larger insulin doses due to fewer numbers of peripheral receptor sites.
- Cachectic patients may be very insulin sensitive.
- Certain co-existing endocrinopathies, such as acromegaly and Cushing’s disease, can increase dosage requirements.
- Sepsis can require an increased insulin dose during early stages of diabetes due to increased stress hormone and cytokine production, but impaired gluconeogenesis in the later stages can cause marked insulin sensitivity.

DRUG INTERACTIONS
Drugs that decrease hypoglycemic effects:
- Corticosteroids
- Diltiazem
- Dobutamine
- Thiazides

Drugs that increase hypoglycemic effects:
- Beta-blockers
- Salicylates
- Tetracyclines

OVERDOSES
**In-Clinic**
- **Intravenous**: Glucagon CRI, 0.5–13 ng/kg/min, or IV glucose, 0.5 gm/kg IV

**At-Home**
- **Oral**: Karo syrup, 1 mL/kg PO if patient is conscious
- **Intramuscular**: Glucagon injection, 0.03 mg/kg IM

NPH = neutral protamine Hagedorn; PZI = protamine zinc insulin

*These drug-related effects are primarily documented in humans except for those caused by corticosteroids, which are specifically documented in dogs/cats.

References

Resources
- AVMA Diabetic Pets handout for pet owners: avma.org (select Animal Health Brochures under Public Resources)
- National Pet Diabetes Month (November 2011): Petdiabetesmonth.com

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