commercially available injection has a pH adjusted to 3.2–4 and an osmolality of 101 mOsm/L.

Inamrinone may also be known as: amrinone, Win-40680, *Amcoral®, Inocor®, Vesistol®,* and *Wincoram®*.

Storage/Stability/Compatibility

The commercially available injection should be stored at room temperature and protected from light. It is stable for 2 years after manufacture.

Inamrinone lactate for injection is reportedly **compatible** with 0.45% or 0.9% sodium chloride injection, propranolol HCl, verapamil HCl. It is reportedly **incompatible** with solutions containing dextrose or sodium bicarbonate. Compatibility is dependent upon factors such as pH, concentration, temperature and diluent used; consult specialized references or a hospital pharmacist for more specific information.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Inamrinone Lactate for Injection: 5 mg/mL (as lactate) in 20 mL amps; generic (Abbott Hospital); (Rx)

INSULIN INJECTION, REGULAR (CRYSTALLINE ZINC)
INSULIN, ISOPHANE SUSPENSION (NPH)
INSULIN, PROTAMINE ZINC SUSPENSION (PZI)
INSULIN, PORCINE ZINC SUSPENSION (LENTE)
INSULIN, GLARGINE

(***in***-su-lin)

HORMONE

Note: Insulin preparations available to the practitioner are in a constant state of change. It is highly recommended to review current references or sources of information pertaining to insulin therapy for dogs and cats to maximize efficacy of therapy and reduce the chance for errors.

Prescriber Highlights

- Pancreatic hormone used to treat diabetic ketoacidosis, uncomplicated diabetes mellitus, & as adjunctive therapy in treating hyperkalemia
- Contraindications: No absolute contraindications
- Adverse Effects: Hypoglycemia, insulin-induced hyperglycemia ("Somogyi effect"), insulin antagonism/resistance, rapid insulin metabolism, & local reactions to the "foreign" proteins
- Do not confuse insulin types, strengths, syringes
- Drug Interactions

Monograph by Dinah Jordan, PharmD, DICVP

Uses/Indications

Insulin preparations have been used for the adjunctive treatment of diabetic ketoacidosis, uncomplicated diabetes mellitus, and as adjunctive therapy in treating hyperkalemia. Insulin treatment in veterinary species has been primarily in dogs and cats. Experience using insulin in other veterinary species is limited.

Regular insulin is commonly used for stabilization of the diabetic patient and is the only formulation appropriate for intravenous administration (IV); it is also administered by intramuscular (IM) and subcutaneous (SC) injection. Only regular insulin should be used in patients with diabetic ketoacidosis or diabetic coma. Regular insulin is preferred in patients with poor tissue perfusion, shock, or cardiovascular collapse, or in patients requiring insulin for the treatment of severe, life-threatening hyperkalemia causing cardiotoxicity (*i.e.,* >8 mEq/L).

Pharmacology

Eliciting multiple biological responses, insulin initiates its actions by binding to cell-surface receptors, present in varying numbers in virtually all mammalian cells. This binding results in a cascade of intracellular events which can be studied in detail by consulting a physiology text.

Insulin is the primary hormone responsible for controlling the uptake, utilization, and storage of cellular nutrients. Insulin affects primarily liver, muscle, and adipose tissues, but also exerts potent regulatory effects on other cell types as well. Insulin stimulates carbohydrate metabolism in cardiac, skeletal, and adipose tissue by facilitating the uptake of glucose by these cells. Other tissues, such as brain, nerve, intestinal, liver, and kidney tubules, do not require insulin for glucose transport. Liver cells do need insulin to convert glucose to glycogen (for storage), and the hypothalamus requires insulin for glucose entry into the satiety center. Insulin has a direct effect on fat and protein metabolism. The hormone stimulates lipogenesis, increases protein synthesis, and inhibits lipolysis and free fatty acid release from adipose tissues. Insulin promotes an intracellular shift of potassium and magnesium. Exogenous insulin elicits all the pharmacologic responses usually produced by endogenous insulin.

Pharmacokinetics

Insulin is metabolized mainly by the liver and kidneys (also muscle and fat to a lesser degree) by enzymatic reduction to form peptides and amino acids. About 50% of the insulin that reaches the liver via the portal vein is destroyed and never reaches the general circulation. Insulin is filtered by the renal glomeruli and is reabsorbed by the tubules, which also degrade it. Severe impairment of renal function appears to affect the rate of clearance of circulating insulin to a greater extent than hepatic disease. Hepatic degradation of insulin operates near its maximal capacity and cannot compensate for diminished renal breakdown of the hormone. The half-life of endogenous insulin is less than ten minutes in normal subjects and in patients with uncomplicated diabetes.

Note: The pharmacokinetics of various insulin formulations can vary widely from published values between species, among individuals within a species, and within the same individual patient from day to day. Therefore, the values should only be used as a general reference guide.

Regular insulin injection: When the recombinant human insulin product is given IV to dogs and cats, it has an immediate onset of action, with maximum effects occurring at 0.5–2 hours; duration of action is 1–4 hours. Following IM administration, onset is 10–30 minutes; peak 1–4 hours; and duration 3–8 hours. After subcutaneous administration, onset is generally 10–30 minutes; peak from 1–5 hours; duration 4–10 hours.

Although the kinetics of all insulin products vary markedly for the individual product between species, regular insulin appears to exhibit the most similar properties.

Isophane insulin suspension (NPH): NPH is administered by the subcutaneous route only. Following SC administration of the recombinant human insulin product, onset is 0.5–2 hours in dogs and cats; peak is 2–10 hours in dogs and 2–8 hours in cats; and duration is 6–18 hours in dogs and 4–12 hours in cats.

Porcine insulin zinc suspension (Lente): Lente is classified as intermediate-acting; it has two peaks of activity following subcutaneous administration (the first at around 4 hours and the second at around 11 hours). The duration of activity varies between 14 and 24 hours. The peak(s), duration of activity, and dose required to adequately control diabetic signs will vary between dogs. Following SC administration of the recombinant human insulin lente product, onset is 0.5–2 hours in dogs and cats. Pharmacokinetics of the purified pork product are similar to the human product.

Protamine zinc suspension (PZI): Following SC administration, onset is 1–4 hours in dogs and cats; peak is 4–8 hours; duration is 6–28 hours in dogs; 6–24 hours in cats.

Insulin glargine injection: Following SC injection, the acidic solution is neutralized, and microprecipitates are formed which slowly release small amounts of insulin glargine. This action results in a relatively constant concentration/time profile over 24 hours with no pronounced peak in humans. A small Australian study compared equal doses of insulin glargine, PZI (mixed beef/pork), and purified pork lente insulin in 9 healthy cats. Results showed no significant difference in onset of action or nadir glucose concentrations among the insulins; time to reach nadir glucose concentration was longer for glargine (~16 hours) vs. PZI (~6 hours) and lente (~4.5 hours). Duration was significantly shorter for lente than for glargine or PZI, with glargine and PZI not significantly different. The study in healthy cats also showed there were definite peaks in insulin concentration and glucose lowering effects of glargine. (Marshall and Rand 2004)

Contraindications/Precautions/Warnings

Because there are no alternatives for insulin when it is used for diabetic indications, there are no absolute contraindications to its use. If animals develop hypersensitivity (local or otherwise) or should insulin resistance develop, a change in type or species of insulin should be tried. Pork insulin is identical to canine insulin and is considered the insulin source of choice for diabetic dogs. Human insulin has a low potential for producing insulin antibodies in dogs (~5%), while beef/pork insulin produces antibody formation in a higher percentage of dogs (~45%) and is associated with insulin resistance and poor or erratic glycemic control. Dogs known to have a systemic allergy to pork or pork products should not be treated with *Vetsulin®*. Beef/pork insulin is considered the source of choice in cats, although the incidence of insulin antibody production is low and approximately the same in cats treated with either beef/pork or human insulin. Overt insulin resistance caused by insulin antibodies occurs in less than 5% of cats treated with recombinant human insulin.

Do not inject insulin at the same site day after day or lipodystrophic reactions can occur.

Adverse Effects

Adverse effects of insulin therapy may include hypoglycemia (see overdosage below), insulin-induced hyperglycemia ("Somogyi effect"), insulin antagonism/resistance, rapid insulin metabolism, and local reactions to the "foreign" proteins.

Reproductive/Nursing Safety

In humans, the FDA categorizes all human insulin and purified pork insulin as category ***B*** for use during pregnancy (*Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.*) In humans, the FDA categorizes insulin glargine as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

Insulin is compatible with nursing.

Overdosage/Acute Toxicity

Overdosage of insulin can lead to various degrees of hypoglycemia. Signs may include weakness, shaking, head tilting, lethargy, ataxia, seizures, blindness, bizarre behavior, and coma. Other signs may include restlessness, hunger, and muscle fasciculations. Prolonged hypoglycemia can result in permanent brain damage or death.

Mild hypoglycemia may be treated by offering the animal its usual food. More serious symptoms (such as seizure) should be treated with oral dextrose solutions (*e.g.*, *Karo®* syrup) rubbed on the oral mucosa (not poured down the throat) or by intravenous injections of 50% dextrose solutions (small amounts, slowly administered—usually 2–15 mL). If the animal is seizuring, fingers should not be placed in the animal's mouth. Once the animal's hypoglycemia is alleviated (response usually occurs within 1–2 minutes), it should be closely monitored (both by physical observation and serial blood glucose levels) to prevent a recurrence of hypoglycemia (especially with the slower absorbed products) and to prevent hyperglycemia from developing. Future insulin dosages or feeding habits should be adjusted to prevent further occurrences of hypoglycemia.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving insulin and may be of significance in veterinary patients:

- **BETA-ADRENERGIC BLOCKERS** (*e.g.*, **propranolol**): Can have variable effects on glycemic control and can mask the signs associated with hypoglycemia
- **CLONIDINE; RESERPINE:** Can mask the signs associated with hypoglycemia
- **DIGOXIN:** Because insulin can alter serum potassium levels, patients receiving concomitant cardiac glycoside (*e.g.*, digoxin) therapy should be closely monitored; especially true in patients receiving concurrent diuretic therapy

The following drugs or drug classes may ***potentiate*** **the hypoglycemic activity of insulin:**

- **ALCOHOL**
- **ANABOLIC STEROIDS** (*e.g.*, **stanozolol, boldenone**)
- **ANGIOTENSIN CONVERTING ENZYME INHIBITORS** (*e.g.*, **captopril, enalapril**)
- **ASPIRIN** or **other salicylates**
- **DISOPYRAMIDE**
- **FLUOXETINE**
- **MONOAMINE OXIDASE INHIBITORS**
- **SOMATOSTATIN DERIVATIVES** (*e.g.*, **octreotide**)
- **SULFONAMIDES**

The following drugs or drug classes may ***decrease*** **the hypoglycemic activity of insulin:**

- **CALCIUM CHANNEL BLOCKERS** (*e.g.*, **diltiazem**)
- **CORTICOSTEROIDS**
- **DANAZOL**
- **DIURETICS**
- **ISONIAZID**
- **NIACIN**
- **PHENOTHIAZINES**
- **THYROID HORMONES** (can elevate blood glucose levels in diabetic patients when thyroid hormone therapy is first initiated)

Doses

Note: Treatment of diabetes mellitus and in particular, diabetic ketoacidosis is complex. Insulin is only one component of therapy; fluid and electrolytes, acid/base, and if necessary, antimicrobial therapy must also be employed. Adequate patient monitoring is mandatory. The reader is strongly encouraged to refer to more thorough discussions of treatment in veterinary endocrinology or internal medicine references for additional information.

- **DOGS:**

For adjunctive therapy of diabetic ketoacidosis:

a) Using Regular insulin, choose either the intermittent IM technique or low-dose IV infusion technique.

Intermittent IM technique: Initial Dose: 0.2 U/kg IM into muscles of the rear legs; repeat IM doses of 0.1 U/kg hourly. Initial doses may be reduced by 25–50% in animals with severe hypokalemia. Goal is to slowly lower blood glucose to 200–250 mg/dL over a 6–10 hour period. As blood glucose approaches 250 mg/dl, switch to IM regular insulin at 0.1–0.4 U/kg q4–6h or subcutaneous (if hydration status is good) q6–8h. Goal is to keep blood glucose in the 150–300 mg/dL range. Giving 5% dextrose IV is necessary during this stage.

Constant Low-Dose Infusion Technique: Initially give regular insulin at a rate of 0.05–0.1 U/kg/hr in an IV line separate from that for fluid therapy. Initial doses may be reduced by 25–50% in animals with severe hypokalemia. Adjust infusion rate based upon hourly blood glucose determinations. An hourly reduction in blood glucose by 50–100 mg/dL is ideal. Once blood glucose approaches 250 mg/dL switch to IM regular insulin every 4–6 hours or to subcutaneous regular insulin at 0.1–0.4 U/kg q6–8h if hydration status is good. Goal is to keep blood glucose in the 150–300 mg/dL range. Giving 5% dextrose IV is necessary during this stage. Alternatively, may continue IV infusion at a decreased rate until exchanged for a longer-acting product. (Nelson and Elliott 2003a)

For adjunctive treatment of severe hyperkalemia (>8 mEq/L):

a) Give *regular insulin* 0.25–0.5 U/kg slow IV bolus followed by 50% dextrose (4 mL/U of administered insulin); or give regular 0.5–1 U/kg in parenteral fluids plus 2 grams dextrose per unit insulin administered (Nelson and Elliott 2003b)

Insulin treatment of uncomplicated diabetes mellitus:

a) *Vetsulin®*: The initial recommended dose is 1 U insulin/kg body weight plus a body weight-dependent dose supplement (as shown in the table below) given SC once daily concurrently with, or right after a meal. Re-evaluation of the patient should be performed at appropriate intervals and insulin doses adjusted as needed. (*Vetsulin®* package insert)

DOSE	DOSE PLUS	DOSE SUPPLEMENT	INITIAL DOSE
<10 kg	(Weight in kg) x 1 U/kg	1 Unit	1 U/kg + 1 Unit
10–11 kg	(Weight in kg) x 1 U/kg	2 Units	1 U/kg + 2 Units
12–20 kg	(Weight in kg) x 1 U/kg	3 Units	1 U/kg + 3 Units
>20 kg	(Weight in kg) x 1 U/kg	4 Units	1 U/kg + 4 Units

Twice daily dosing may be required if the duration of action is insufficient. To calculate the twice daily dose, decrease the total once daily dose by 25% and give that calculated dose twice daily. For example, the new dose for a dog previously receiving 20 Units once daily would be 15 Units twice daily. (Intervet; Technical Services)

b) *NPH insulin of recombinant human origin:* give 0.25 U/kg SC every 12 hours. (Nelson 2007)

Note: More than 90% of dogs will require twice daily doses of intermediate acting insulin; therefore, initiating therapy with this regimen may result in better and easier glycemic control and fewer problems with hypoglycemia and the Somogyi effect). Dietary therapy is used concurrently. Following stabilization, diabetic dogs are typically evaluated every 7 days until an effective insulin protocol is established. (Nelson and Elliott 2003a)

c) *Insulin glargine:* Initiate dose of insulin glargine at 0.25 U/kg SC q12 hours in dogs with poor response to porcine zinc insulin or NPH. (Nelson 2007)

- **CATS:**

For adjunctive therapy of diabetic ketoacidosis:

a) Use the same protocol as described above in "a" for dogs (Nelson and Elliott 2003a)

Insulin treatment of uncomplicated diabetes mellitus:

Note: Cats are very unpredictable in their response to insulin therapy, and no single type of insulin is routinely effective in maintaining glycemic control, even with twice daily dosing. Cats should be closely monitored during the first month of insulin therapy.

a) *Using PZI:* Starting dose: 0.1–0.3 Units per pound body weight (0.22–0.6 Units/kg) SC every 12 to 24 hours (maximum starting dose should not exceed 3 total Units per cat every 12 hours); reevaluate every 7–14 days and adjust insulin dose as necessary to achieve regulation (*PZI-VET* product information)

b) *Using PZI:* Starting dose: 1 Unit per cat SC every 12 hours (Nelson 2007)

c) *Using Porcine insulin zinc (lente):* Starting dose: 1–2 Units per cat SC every 12 hours. Half of the cat's total daily caloric intake should be offered at the time of each insulin injection, and the cat should have access to any uneaten food until time for the next injection. Patients should be evaluated at appropriate intervals and insulin dose adjustments made accordingly. (Nelson and Elliott 2003a)

d) *Using Porcine insulin zinc (lente):* Starting dose: 0.25 U/kg twice daily if the blood glucose concentration is between 216–342 mg/dL and 0.5 U/kg twice daily if the blood glucose concentration is >360 mg/dL. (Rand 1997, Behrend 2007)

e) *Using Porcine insulin zinc (lente):* Starting dose: 1 Unit/cat twice daily for cats weighing less than 4 kg and 1.5–2 Unit/cat twice daily for cats weighing >4 kg can be used to initiate therapy (Reusch 2005, Behrend 2007)

f) *Using NPH:* Starting dose: 0.5 U/kg SC every 12 hours. (Boothe 2001)

g) *Using NPH:* Starting dose: 1–2 Units per cat SC every 12 hours (Cohn, Graves 2007)

h) *Using Insulin glargine* (Lantus)*:* 1 Unit per cat SC every 24 hours; increase to twice daily injections if subsequent blood glucose evaluations indicate less than 12 hours duration. (Nelson 2007)

i) *Using Insulin glargine* (Lantus)*:* 0.25–0.5 U/kg SC every 12 hours, not to exceed 3 Units per cat q12 hours starting dose (Peterson, Kintzer 2007)

Note: insulin glargine may have little or no effect on blood glucose in cats for the first 3 days after initiation of therapy. Dose increases are not recommended for the first week of therapy to avoid possible hypoglycemia. Some cats may require a decrease in dose, and some may achieve diabetic remission after one month of glargine therapy.

■ **BIRDS:**

Diabetes mellitus is most common in budgies, cockatiels, and toucans. Blood glucose levels in diabetic birds range from 600–2000 mg/dL (Definitive diagnosis requires persistently elevated blood glucose levels >800 mg/dL). Insulin therapy is sometimes hindered by the highly variable dose needed for individual birds, the development of insulin resistance, and the development of pancreatic atrophy and pancreatic insufficiency.

a) Insulin dose: Initially, 0.1–0.2 U/kg regular insulin. When stabilized, NPH insulin can be started. Dose range is 0.067–3.3 U/kg IM every 12–24 hours. (Oglesbee 2003) A blood glucose curve should be obtained. Determine blood glucose levels initially, then every 2–3 hours for 12–24 hours. The dose is adjusted based on blood glucose levels. Frequency varies from twice daily to once every several days. Bird should be placed on a low-carbohydrate diet. Clinical sign of successful treatment is weight gain. Monitor for hypoglycemia. Treat hypoglycemia with oral or injectable dextrose or oral corn syrup. (Rupley 1997)

■ **FERRETS:**

Treatment of diabetes mellitus:

a) NPH 0.5–1 Unit per ferret SC twice daily. Goal of therapy is negative ketones and a small amount of glucose in the urine. (Quesenberry and Carpenter 2003)

b) NPH 0.1–0.5 IU/kg IM or SC twice daily to start; adjust to optimal dose. May require insulin to be diluted; monitor urine for glucose/ketones. (Williams 2000)

■ **CATTLE:**

For adjunctive treatment of ketosis:

a) PZI insulin 200 Units (total dose) SC once every 48 hours (Smith 2002a)

■ **HORSES:**

For diabetes mellitus:

a) True diabetes mellitus rarely occurs in horses. Most cases are a result of pituitary tumors that cause hyperglycemia secondary to excessive ACTH or growth hormone. A case is cited where an animal received 0.5–1 Unit/kg of PZI insulin and the hyperglycemia was controlled. Patients with hyperglycemia secondary to a pituitary tumor are apparently insulin-resistant (Merritt 1987).

b) PZI insulin 0.15 U/kg IM or SC twice daily (Robinson 1987)

For treatment of hyperlipemia in ponies:

a) For a 200 kg pony: PZI 30 U (total dose) IM every 12 hours on odd days (given with 100 grams glucose orally once daily); PZI 15 U (total dose) IM every 12 hours on even days (given with 100 grams galactose orally once daily) until hyperlipemia resolves. (Smith 2002a)

Monitoring Parameters

- Blood glucose
- Patient weight, appetite, fluid intake/output
- Blood, urine ketones (if warranted)
- Glycosylated hemoglobin and fructosamine [goal = fructosamine <450 micromol/L] (if available and warranted)

Client Information

- Keep insulin products away from temperature extremes. If stored in the refrigerator, allow to come to room temperature in syringe before injecting.
- Clients must be instructed in proper techniques for withdrawing insulin into the syringe, including rolling the vial, not shaking before withdrawing into syringe, and using the proper syringe size with insulin concentration (*e.g.*, not confusing U-40 insulin/syringes with U-100 insulin/syringes).
- Proper injection techniques should be taught and practiced with the client before the animal's discharge.
- The symptoms of hypoglycemia should be thoroughly reviewed with the owner.
- A written protocol outlining monitoring procedures and treatment steps for hypoglycemia should be sent home with the owner.
- When traveling, insulin should not be left in carry-on luggage that will pass through airport surveillance equipment. Generally, insulin stability is not affected by a single pass through surveillance equipment; however, longer than normal exposure or repeated passes through surveillance equipment may alter insulin potency.

Chemistry and Biosynthesis

The endocrine component of the pancreas is organized as discrete islets (islets of Langerhans) that contain four cell types, each of which produces a different hormone. Insulin is produced in the beta cells, which comprise 60–80% of the islet. Insulin is a protein consisting of two chains, designated A and B, with 21 and 30 amino acids respectively that are connected by two disulfide bonds. The amino acid composition of insulin has been determined in various species of animals. The insulin of dogs, pigs, and certain whales (sperm and fin) is identical in structure; sheep insulin is identical to goat. Cattle, sheep, horses, and dogs differ only in positions 8, 9, and 10 of the A chain. Porcine insulin differs from human insulin by one amino acid [alanine instead of threonine at the carboxy terminal of the B chain (*i.e.*, in position B 30)], and bovine insulin differs by two additional alterations in the A chain (threonine and isoleucine in positions A8 and A10 are replaced by alanine and valine, respectively). Of the domestic species, feline insulin is most similar to bovine insulin, differing by only 1 amino acid (at position 18 of the A chain). Human insulin differs from rabbit insulin by a single amino acid. There is a single insulin gene and a single protein product in most mammalian species (multiple insulins appear to occur frequently among fishes).

For therapeutic purposes, doses and concentrations of insulin are expressed in Units (U). One unit of insulin is equal to the amount required to reduce the concentration of blood glucose in a fasting rabbit to 45 mg/dl (2.5 mM). All commercial preparations

of human insulin currently manufactured in the U.S. are supplied in solution or suspension at a concentration of 100 U/mL, which is approximately 3.6 mg of insulin per milliliter; likewise, one unit of insulin equals about 36 micrograms of insulin.

Insulin is a small protein; human insulin has a molecular weight of 5808. Insulin secretion is a tightly regulated process designed to provide stable concentrations of glucose in blood during fasting and feeding. This regulation is achieved by the coordinated interplay of various nutrients, gastrointestinal and pancreatic hormones, and autonomic neurotransmitters. The primary stimulus for secretion of endogenous insulin is glucose.

Regular insulin is a rapid-acting sterile solution prepared by precipitating insulin in the presence of zinc chloride to form zinc insulin crystals. Regular insulin 100 U/mL is a clear and colorless or almost colorless solution. Discoloration, turbidity, or unusual viscosity indicates deterioration or contamination.

Isophane insulin, more commonly known as *NPH*, is an intermediate-acting, sterile suspension of zinc insulin crystals and protamine sulfate in buffered water for injection.

Porcine Lente insulin is a sterile aqueous suspension of purified pork Lente insulin consisting of 30% amorphous zinc insulin and 70% crystalline zinc insulin. It is available only as a U-40 insulin concentration and is a cloudy or milky suspension of a mixture of characteristic crystals and particles with no uniform shape.

Protamine zinc suspension (PZI) is composed of 90% beef/10% pork insulin combined with zinc and protamine (a protein extracted from salmon testes), which slow the release of the insulin into tissues. PZI is clear (not cloudy) with white sediment (no clumps), that when mixed gently, looks like watery milk. It is available only as a U-40 insulin concentration.

Insulin glargine is a long-acting human insulin analog produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *E. coli*. It differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine, and two arginines are added to the C-terminus of the B chain. The injection consists of insulin glargine dissolved in a clear aqueous fluid. It is available only as a U-100 insulin concentration.

All human, purified pork, and beef/pork insulin products have a neutral pH of approximately 7–7.8, while insulin glargine has an acidic pH of approximately 4.

Stability/Storage/Compatibility

Manufacturers of insulin recommend that all insulin products be stored in the refrigerator but protected from freezing temperatures (do not store at temperatures <36°F or <2°C). Freezing may alter the protein structure, decreasing potency. Particle aggregation and crystal damage may be visible to the naked eye or may require microscopic examination. Higher temperature (>86°F or >30°C) extremes and direct exposure to sunlight should be avoided (such as might occur when insulin is stored in a car glove compartment or on a window sill), since insulin transformation products and fibril formation may occur. Although the manufacturers recommend a maximum of 30 days storage at room temperature, studies have actually shown that regular insulin maintains stability of 24–30 months at 25°C. One study showed a 5% loss of biological potency after about 36 months at 25°C.

According to the manufacturer's label, insulin glargine has a discard date of 28 days after the initial puncture of the vial (consistent with all human-labeled insulin products) and stored at room temperature, although clinical reports indicate that opened vials stored in the refrigerator can be used for up to 6 months; discard vial immediately if there is any discoloration. Bacterial contamination and precipitation associated with pH change can cause cloudiness (Marshall and Rand 2006).

For animals requiring small doses of glargine, the 3 mL cartridge may be preferable to the 10 mL vial to prevent the need for extended use beyond the recommended discard date.

Flocculation of NPH human insulin may appear 3–6 weeks after opening the vial. Deterioration in glycemic control may appear before frosting of the vial. If unexplained hyperglycemia is observed, a new vial of insulin should be used.

Regular and NPH insulin may be stored in plastic or glass syringes under refrigeration for 5–7 days without loss of potency. One study found no degradation after 14 days storage under refrigeration. Other sources state that prefilled insulin syringes are stable for 30 days when stored in the refrigerator. It is generally accepted that syringes of insulin can be stored for 28 days under refrigeration without fear of potency loss.

Regular insulin is reportedly physically **compatible** with following drugs/solutions: normal saline, TPN solutions (4% amino acids, 25% dextrose with electrolytes and vitamins; must occasionally shake bag to prevent separation), bretylium tosylate, cimetidine HCl, lidocaine HCl, oxytetracycline HCl, and verapamil HCl. Regular insulin may be mixed with other insulin products (except for glargine) used in veterinary medicine (*e.g.*, NPH, PZI, etc.).

Regular insulin is reportedly physically **incompatible** when mixed with the following drugs/solutions: aminophylline, amobarbital sodium, chlorothiazide sodium, cytarabine, dobutamine HCl, nitrofurantoin sodium, pentobarbital sodium, phenobarbital sodium, phenytoin sodium, secobarbital sodium, sodium bicarbonate, sulfisoxazole sodium, and thiopental sodium. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluent used; consult specialized references for more specific information.

Diluting insulin: Other than for immediate use, insulin should only be diluted using product-specific sterile diluents supplied by the manufacturer. Diluents for Regular insulin (*Humulin R*) and NPH insulin (*Humulin N*) and sterile vials can be obtained by telephoning the manufacturer. Diluted insulin is stable for 4 (preferred) to 6 weeks and should be stored in the refrigerator. For immediate use, insulin products (except glargine) can be diluted with normal saline for injection, but the potency cannot be predicted after 24 hours. **Insulin glargine must not be diluted or mixed** with any other insulin or solution because the prolonged action is dependent on its pH.

Adsorption: The adsorption of regular insulin to the surfaces of IV infusion solution containers, glass and plastic (including PVC, ethylene vinyl acetate, polyethylene, and other polyolefins), tubing, and filters has been demonstrated. Estimates of loss of potency range from 20–80%, although reports of 20–30% are more common. The percent adsorbed is inversely proportional to the concentration of the insulin, and may include other factors such as the amount of container surface area, the fill volume of the solution, the type of solution, type and length of administration set, temperature, previous exposure of tubing to insulin, and the presence of other drugs, blood, etc. The adsorption process is instantaneous, with the bulk of insulin adsorption occurring within the first 30–60 minutes. To saturate binding sites and deliver a more predictable dose to the patient through an IV infusion, it is recommended that the first 50 mL be run through the IV tubing and discarded.

Insulin Syringes: Syringes are designed for use with a specific strength of insulin, with the needle covers color-coded according to strength. U-40 syringes have a red top, while U-100 syringes have an orange top. U-40 syringes contain ½ cc (equivalent to 0.5 mL) and have 20 unit marks. Measuring U-40 insulin to the one unit mark in a U-40 syringe will contain 1U of insulin. U-100 syringes are available in 3/10cc, ½cc, and 1cc size. Measuring U-100 insulin to one mark in a U-100 syringe will contain 1U of insulin.

Tuberculin syringes can also be used, but are not generally recommended because the potential for confusion is substantial. If using 100U/mL or TB syringes to measure 40U/mL insulin doses:

- Determine the required dose in units.
- If using U-100 insulin syringes (orange top), multiply the required Units of U-40 insulin by 2.5 (*e.g.* If required dose is 10 units, 10 x 2.5=25 units).
- If using TB syringes, multiply the required Units of U-40 insulin x 0.025 (*e.g.*, If the required dose is 10 Units, 10 x 0.025= 0.25 mL).

Reuse of Insulin Syringes: Reuse of disposable insulin syringes has been suggested to reduce client costs. However, disposable insulin syringes are usually siliconized, and reuse can result in contamination of vials of insulin with silicone oil, causing a white precipitate and impairment of biological effects.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Porcine insulin zinc suspension 40 U/mL in 10 mL vials, intermediate-acting; *Vetsulin®* (Intervet) in U.S.; *Caninsulin®* (Intervet) in Canada & Europe; (Rx). FDA approved for use in dogs.

Protamine zinc insulin (beef 90%/pork 10%) 40 U/mL in 10 mL vials; long-acting; *PZI VET®* (IDEXX); (Rx). Not fully FDA approved, but distribution is allowed under the Medically Necessary Veterinary Products Policy for use in cats.

HUMAN-LABELED PRODUCTS:

Note: partial listing; includes only those products generally used in veterinary medicine.

Insulin Injection, ***Regular*** *— (short-acting):*

Human (rDNA): 100 U/mL in 10 mL vials; *Humulin® R* (Eli Lilly); *Novolin®R & Novolin R® Prefilled* (Novo Nordisk); (OTC)

Isophane (Neutral Protamine Hagedorn; ***NPH****) — (intermediate-acting):*

Human (rDNA) 100 U/mL in 10 mL vials, 5 x 1.5 mL prefilled syringes & 5 x 3 mL pen insulin delivery devices; *Humulin®N* (Lilly); *Novolin®N & Prefilled* (Novo Nordisk); (OTC)

Human (rDNA) Cartridges (suspension) 100 U/mL in 5 x1.5 mL & 5 x 3 mL; *Novolin N® PenFill* (Novo Nordisk); (OTC)

Combination: Insulin Isophane & Regular Injection (suspension):

Human (rDNA) 100 U/mL 70% isophane insulin (NPH) & 30 % insulin injection (regular) in 5 x 3 mL disposable pen insulin delivery devices, 10 mL vials & 5 x 1.5 mL prefilled syringes; *Humulin® 70/30* (Lilly); *Novolin® 70/30 & Prefilled* (Novo Nordisk); (OTC)

Human (rDNA) Cartridges (suspension): 100 U/mL; 70% isophane insulin (NPH) & 30% insulin injection (regular) in 5 x 1.5 & 5 x 3 mL; *Novolin® 70/30 PenFill* (Novo Nordisk); (OTC)

Human (rDNA) Injection (suspension): 100 U/mL; 50% isophane insulin (NPH) & 50% insulin injection (regular) in 10 mL vials; *Humulin® 50/50* (Lilly); (OTC)

Insulin Glargine Injection—(long-acting):

Human (rDNA) 100 U/mL in 10 mL vials & 3 mL cartridge system for use with *OptiClik*; *Lantus®* (Aventis); (Rx)

INTERFERON ALFA, HUMAN RECOMBINANT

(in-ter-***feer***-on) Roferon-A®, Intron-A®

IMMUNOMODULATOR

Prescriber Highlights

- Cytokine used to alleviate clinical effects of certain viral diseases; little scientific info available to document safety/efficacy in small animals
- Cautions: Preexisting autoimmune disease, severe cardiac disease, pulmonary disease, "brittle" diabetes, Herpes infections, hypersensitivity to the drug, or CNS disorders
- Adverse Effects: In cats, adverse effects are apparently uncommon with PO; higher dosages given parenterally may cause malaise; fever, allergic reactions, myelotoxicity & myalgia are possible

Uses/Indications

Interferon alfa use in veterinary medicine in the past has primarily been centered on its oral/buccal administration in cats to treat non-neoplastic FeLV disease. Oral interferon may also be of benefit in the treatment of ocular herpes infection.

Feline interferon-omega has recently become available in several countries and it may be found significantly useful in treating viral diseases in both cats and dogs. A separate monograph for this agent, follows this one.

Pharmacology/Actions

The pharmacologic effects of the interferons are widespread and complex. Suffice it to say, that interferon alfa has antiviral, antiproliferative, and immunomodulating effects. Its antiproliferative and antiviral activities are thought to be due to its effects on the synthesis of RNA, DNA, and cellular proteins (oncogenes included). The mechanisms for its antineoplastic activities are not well understood, but are probably related these effects as well.

Pharmacokinetics

Interferon alfa is poorly absorbed after oral administration due to its degradation by proteolytic enzymes and studies have not detected measurable levels in the systemic circulation, however, there may be some absorption via upper GI mucosa.

Interferon alfa is widely distributed throughout the body, although it does not penetrate into the CNS well. It is unknown if it crosses the placenta. Interferon alfa is freely filtered by the glomeruli, but is absorbed by the renal tubules where it is metabolized by brush border or lysosomes. Hepatic metabolism is of minor importance. The plasma half-life in cats has been reported as 2.9 hours.

Contraindications/Precautions/Warnings

When used parenterally, consider the risks versus benefits in patients with preexisting autoimmune disease, severe cardiac disease, pulmonary disease, "brittle" diabetes, Herpes infections, hypersensitivity to the drug, or CNS disorders.

Adverse Effects

When used orally in cats, adverse effects are apparently uncommon. Higher dosages given parenterally to cats may cause malaise; fever, allergic reactions, myelotoxicity, and myalgia are possible. Cats given human interferon-alfa parenterally may develop significant antibodies to it after 7–8 weeks of treatment. When used systemi-