A CLINICIAN'S BRIEF SUPPLEMENT

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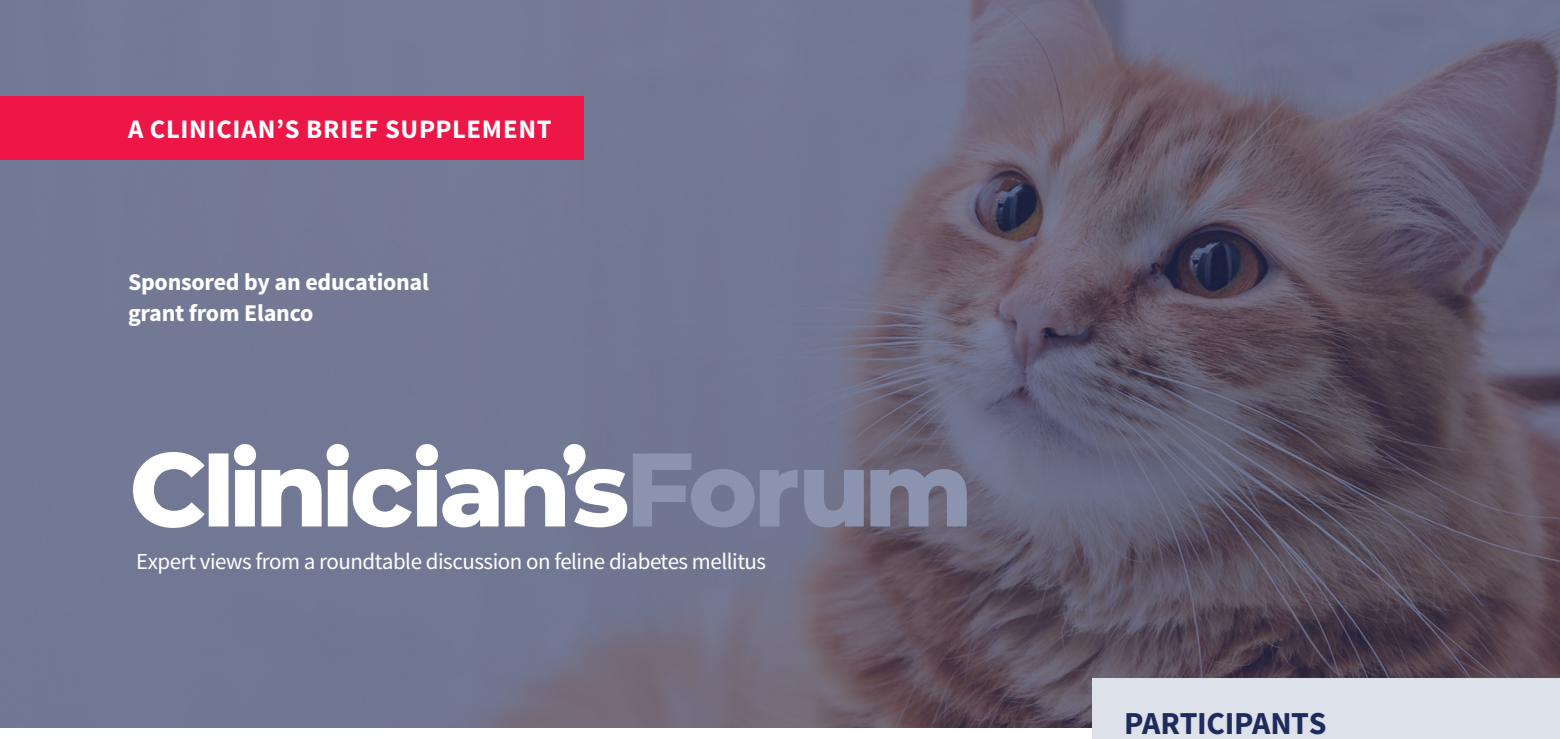

Clinician's Forum

Expert views from a roundtable discussion on feline diabetes mellitus

The Once-Daily, Single-Dose Tablet for Treatment of Feline Diabetes Mellitus

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Diabetes mellitus (DM) is a common endocrine disease of middle aged and older cats. Bexacat™ (bexagliflozin tablets), an innovative sodium-glucose cotransporter-2 (SGLT2) inhibitor, is a once-daily oral tablet for achieving glycemic control in otherwise healthy cats with DM not previously treated with insulin. Bexacat can be used to achieve glycemic control in a subset of cats with DM, thereby avoiding some of the potential challenges of using insulin. Knowing how this drug works, understanding the patient selection process, and being familiar with monitoring protocols are key to the successful implementation of Bexacat in practice.

BHBA = beta-hydroxybutyrate
DKA = diabetic ketoacidosis
DM = diabetes mellitus
eDKA = euglycemic diabetic ketoacidosis
fPL = feline pancreas-specific lipase
GFR = glomerular filtration rate
SGLT2 = sodium-glucose cotransporter-2

Dr. Marks: Let's talk about diabetes in cats. How does it differ from dogs? And what do we mean by diabetic remission when talking about our feline patients?

Dr. Mott: When we talk about dogs with diabetes, their disease is most similar to type 1 diabetes in people, meaning they're insulin-deficient and cannot produce insulin. Dogs typically require exogenous insulin for the rest of their life once they become diabetic. Many cats, however, have a disease that's more similar to advanced type 2 diabetes in people, so they have both insulin resistance and beta cell dysfunction. In some cases, though, beta cell dysfunction is reversible if glucose toxicity is controlled. These cats are then able to start secreting insulin, and if they can secrete enough endogenous insulin,

they may go into remission, which, by definition, means that they're insulin-independent for at least 4 weeks.

Dr. Marks: The mainstay of diabetic treatment has historically been insulin therapy. Bexacat is an innovative alternative for the right patients. What is Bexacat, and how does it work as compared with insulin?

Dr. Ward: Bexacat is in the SGLT2 inhibitor family that has been around in human medicine for quite some time. They work very differently than insulin. When we give a diabetic patient an insulin injection, basically, what we're doing is lowering their blood glucose by allowing the cells to uptake that glucose. SGLT2 inhibitors work by blocking glucose reabsorption in the kidney and allowing glucose to be excreted through the urine. So, instead of glucose being put into the cells like we see with insulin therapy, we lower the blood sugar by causing glucose to be excreted through the kidneys.

Dr. Marks: How can patients with polyuria and polydipsia improve on a drug that causes glucosuria?

> **"SGLT2 inhibitors work by blocking glucose reabsorption in the kidney and allowing glucose to be excreted through the urine.**
>
> ***—Dr. Ward***

Dr. Mahony: Bexacat, like all SGLT2 inhibitors, lowers blood glucose levels by promoting renal excretion of glucose. In diabetic people and healthy cats, osmotic diuresis from glucosuria leads to polyuria; this doesn't appear to happen in diabetic cats. In the pivotal field study for Bexacat, polyuria improved in 75% and polydipsia in 81% of cats, possibly due to the improvement in blood glucose concentrations, resulting in less glucose for excretion as compared with untreated cats.[1]

Dr. Marks: Which cats are ideal Bexacat candidates?

Dr. Scott-Moncrieff: The ideal Bexacat candidate is a newly diagnosed diabetic cat that is otherwise healthy, meaning, in addition to being newly diagnosed, they have no evidence of anorexia, lethargy, dehydration, or vomiting. Their minimum database also needs to exclude other underlying diseases such as more severe chronic kidney disease, hepatic disease, et cetera.

Dr. Mott: When they're in the examination room, they should be healthy and stable. I think of these as the cats that come in and their owners have no idea they're diabetic because, overall, they're doing well at home. They may be urinating outside of the box or having increased urination, and the owners are bringing them in for that complaint but they are otherwise fine. On physical examination, these cats should be hydrated and have pretty unremarkable physical examinations. Those are the patients that I typically think of as being good candidates for bexagliflozin once they've passed the required screening.

Dr. Scott-Moncrieff: And they definitely need that screening, because the cat can look healthy and have a normal physical examination and then have either an elevated feline pancreas-specific lipase (fPL) or an elevated beta-hydroxybutyrate (BHBA) or both. But the starting point is that healthy-looking cat.

Dr. Mahony: In the pivotal trial, they excluded cats with IRIS stage 3 or higher kidney disease as well as liver disease. And like we mentioned, we also have to screen candidates for evidence of elevated fPL or BHBA. Those are also things that may disqualify a patient from being a good Bexacat candidate.

Dr. Mott: It's really important that, if you do the screening and initiate bexagliflozin, it's done right away. We sometimes see cats that are diagnosed with diabetes, and then several weeks later the decision is made to start treatment. In those cases, they really should be screened again, because their status can change in a short period of time, so even though they were a candidate for bexagliflozin a couple of weeks ago, they may no longer be a good candidate.

Dr. Marks: Which tests need to be run to accurately determine which patients are candidates?

Dr. Scott-Moncrieff: The minimum database should include a baseline CBC, serum chemistry, urinalysis, and fPL. The other really important parameter that needs to be measured is serum ketones. Ideally, the most sensitive ketone that should be measured is BHBA, and that can be measured in the serum through a central laboratory or in the blood using a handheld ketone meter. Cats that have very high levels of BHBA are not good candidates for treatment with Bexacat.

Dr. Marks: Can cats receiving Bexacat go into remission? If so, what indicates remission?

Dr. Mott: In the pivotal study, remission was not something that was evaluated. Anecdotally, there were some cats that stopped receiving Bexacat for one reason or another and were reported to have gone into remission and not required insulin. The traditional definition of remission is that insulin therapy has been discontinued for at least 4 weeks and the cat remains euglycemic. In cats on Bexacat, the definition of remission will need to be remaining euglycemic without any diabetes treatment for a certain period of time. For these cats on Bexacat, we wouldn't know whether they're in remission unless we stop the drug. I think there's going to be a lot of research done in the future that can help with making this decision. On the human side, these drugs can have renal protective effects and cardiovascular improvements, so it may actually be beneficial for some of these cats, even if they've gone into remission, to stay on an SGLT2 inhibitor because their kidneys or heart or something else may be benefiting. I think, as investigation into use of SGLT2 inhibitors for other diseases occurs, in the future, we may find other uses for these drugs and better understand the effects they have on cats.

Dr. Marks: What concerns are there regarding giving Bexacat to cats that have been previously treated with insulin?

Dr. Ward: In the pivotal study, the cats were selected to include cats that hadn't been on insulin in the past, because cats need some insulin to prevent ketosis. When we're giving Bexacat or an SGLT2 inhibitor, we're not giving them insulin, so they have to be able to produce some insulin on their own, which means they have to have some degree of healthy beta cell mass that can actually secrete insulin. The problem is we don't have good testing to really predict which cats have retained good beta cell mass. So the easiest way to avoid using Bexacat or an SGLT2 inhibitor in cats that have lost all beta cell function would be to select patients that have not been insulin-treated. So we're assuming these are fairly newly diagnosed diabetics and they're going to have some healthy beta cells that are still producing some insulin on their own. Then, when we lower the blood glucose using the SGLT2 inhibitor, we hopefully will reverse the glucose toxicity on those beta cells and they're able to secrete insulin.

Dr. Marks: What is BHBA? Why do we need to test for it? How do we measure it? And how is this different from testing ketones in the urine?

Dr. Mahony: BHBA is the predominant keto acid in diabetic ketoacidosis (DKA). Cats treated with SGLT2 inhibitors must retain the capacity to secrete insulin or they may die of DKA or euglycemic DKA. We do not have a way of determining which cats have this ability and will respond well to SGLT2 inhibitors; therefore, we need to monitor cats closely for the development of ketones, especially in the first few weeks of treatment. BHBA is measured by sending a blood sample to the laboratory or using a handheld ketone meter. Urine ketone testing is less sensitive for the diagnosis of DKA because urine dipsticks detect acetoacetic acid, and a negative urine ketone test does not rule out DKA.

Dr. Marks: How important is it to run an fPL test before initiating treatment for diabetes mellitus?

Dr. Scott-Moncrieff: Pancreatitis is a documented complication of cats receiving SGLT2 inhibitors. In the pilot studies, there was a fairly high rate of pancreatitis in cats treated with bexagliflozin.[1] In the pivotal study, the cats were confirmed to have a normal fPL,[1] and that decreased the risk for pancreatitis in treated cats. I recommend cats be screened with a SNAP fPL test, and if that test is negative, then that's fine. If they are positive for the SNAP fPL, then they should have a spec fPL, which should be <5.3 µg/L, which is the top end of the gray zone. So if they're <5.3 µg/L, then they remain a candidate for treatment with bexagliflozin.

Dr. Marks: Let's talk more about DKA. How do we screen for DKA or euglycemic DKA (eDKA), and what are the clinical signs we should be looking for?

Dr. Mott: For DKA, we're usually going to document that ketones are present in the urine or, in the case of SGLT2 inhibitors, we're looking for an elevated BHBA and then typically a blood gas that shows acidosis. If a blood gas isn't available, then looking at total carbon dioxide content (TCO2) on serum chemistry can help determine acid-base status. Clinical signs that can be indicative of DKA, especially with SGLT2 inhibitors, are anorexia, hyporexia, lethargy, weight loss, and dehydration. If a cat is on an SGLT2 inhibitor and the owner has noted any of these signs, or anything

off with their pet, they should definitely be examined and screened more closely for the possibility of eDKA.

Dr. Marks: What is eDKA, and how is it different from more traditional or regular DKA?

Dr. Mott: eDKA is something that's brand new for us in veterinary medicine. This isn't something we've seen before. Cats that are on SGLT2 inhibitors can present euglycemic and in DKA. The SGLT2 inhibitor causes them to be euglycemic, but they still have all the other components of DKA. Even though they're euglycemic, they still need insulin. But because they're euglycemic, they're going to need some type of dextrose or carbohydrate source. For most of these cats, they're going to need to be on IV dextrose during their DKA treatment.

Dr. Marks: eDKA is such a new disease state, and veterinarians or emergency rooms may be unfamiliar with eDKA. What are some ways we can help educate veterinary professionals on eDKA?

Dr. Ward: There are stickers available from Elanco with a QR code that owners can put on their cat carrier. They function like an ID bracelet for a person with a disease and can be beneficial, particularly in an emergency setting. Owners need to be aware that their cat's on a medication that some people may not be familiar with, and having some information about that medication that they can take with their pet to an emergency visit can be beneficial. Emergency clinics should know that there's nothing scary about treating these eDKA patients versus traditional DKA patients, except A: being able to recognize the patient is in DKA despite normal blood glucose levels, and B: giving them glucose during treatment. Otherwise, I think emergency practitioners are going to be fine with this. They just need to have this awareness.

Dr. Scott-Moncrieff: When practitioners are starting out using Bexacat, I suggest they reach out to their emergency clinics and let them know about this new drug, because most people go to their local emergency clinic in a crisis and most practitioners have a relationship with their local emergency clinic. They may even be sharing care of patients. So, I think it comes down to good, open communication between the emergency clinic and the practitioners with this new drug.

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Dr. Mahony: Another thing worth adding is that sick cats can remain euglycemic for more than a week following discontinuation of Bexacat, likely due to decreased metabolism and excretion of the drug.

Dr. Marks: How should patients receiving Bexacat be monitored?

Dr. Mahony: Bexacat should be stopped in any cat exhibiting signs of illness, such as anorexia, lethargy, or vomiting, and any cats showing these signs should be assessed as soon as possible for DKA or eDKA. Cats starting Bexacat should be monitored closely for the first 8 weeks, beginning with a physical examination, weight check, and measurement of BHBA 3 to 5 days after starting treatment. A physical examination and weight check should be repeated at 2, 4, and 8 weeks after starting treatment, and an 8-hour blood glucose curve and BHBA and fructosamine levels should also be measured at each of these visits. Then, at least every 90 days thereafter, it is recommended to recheck the cat's weight; perform a physical examination; measure BHBA, fructosamine, and fPL; and obtain a serum chemistry profile that includes glucose level, liver enzymes, kidney values, cholesterol, and triglycerides.

Dr. Scott-Moncrieff: I think it's also really important to look at trends in the physical examination and laboratory work, because sometimes, cats may be doing very well and be stable but can also be developing slight increases in blood glucose, fructosamine, or BHBA, or perhaps they may start to lose weight. If they're feeling well, then it's okay to continue monitoring, but if these values continue to trend in the wrong direction, it's advisable to reevaluate and decide if that's the right treatment for the individual cat. If a cat gets to 8 weeks after starting bexagliflozin and doesn't have evidence of good glycemic control, if fructosamine and blood glucose are not within the recommended ranges, then it's time to think about transitioning to insulin.

Dr. Ward: When you're using an SGLT2 inhibitor like Bexacat, looking for ketones is going to be a lot more important than with an insulin-treated diabetic. In insulin-treated cats, we are mostly worried about blood glucose levels and making sure patients are not getting hypoglycemic or remaining too hyperglycemic. I think the paradigm is shifting a little bit now, and we're really going to be looking at ketones in our diabetic patients. That's why looking at the blood ketones and trends is

so helpful, because when you start seeing them go up, the cat might be starting to get into trouble. I think it's a little bit of a shift in our way of thinking about how to monitor these diabetics when using SGLT2 inhibitors versus when using insulin therapy.

Dr. Mott: When you do blood glucose curves on cats being treated with Bexacat as recommended by the label, their glucose levels tend to remain very consistent. Results will be different from what we are used to seeing in blood glucose curves in cats on insulin. I think blood glucose curves may be something that, with time, we'll find may be more information than is needed for assessing glycemic control.

Dr. Ward: I think the other thing too is that these cats don't get clinically hypoglycemic. That is another big concern with insulin and why we look at glucose so much and do these curves. These cats really don't get clinically hypoglycemic, so again, it's a change in paradigm on how we've been monitoring these guys.

Dr. Scott-Moncrieff: In the cats that I've treated with bexagliflozin, they do sometimes have fairly low blood glucose levels that may raise concern out of context, but not clinical hypoglycemia. Sometimes the blood glucose level is actually in the 60s or high 50s, which was also reported in the pivotal study and was unassociated with clinical signs.[1] I have noticed that cats on bexagliflozin with owners who are using a Freestyle Libre tend to have low readings. I wouldn't panic if cats have mild hypoglycemia that is not associated with clinical signs. In fact, you can put a Freestyle Libre on healthy cats and their blood glucose can run in the upper 50s, low 60s, and people can sometimes get a little bit frightened by that.

Dr. Mott: With cats on Bexacat, continuous glucose monitoring may be more data than is needed to assess glycemic control. Monitoring BHBA is going to be more beneficial.

Dr. Marks: Let's shift to comorbidities associated with the diabetic patient. One of them, of course, is urinary tract infections. Are cats receiving Bexacat more likely to have UTIs?

Dr. Scott-Moncrieff: The Bexacat studies were not designed to answer that question. The field study for bexagliflozin didn't compare treatment with Bexacat to treatment with insulin. There was a rate of ≈10% of cats that had urinary tract infections documented, but it's really difficult to know if that's an increase as compared with insulin-treated cats. My sense is there's very little difference in the rate of clinical UTIs between Bexacat-treated cats and insulin-treated cats. The field studies required urinalysis and urine culture every time the cats came in, and even when positive cultures were documented, the majority of those cats didn't have evidence of clinical signs of UTIs. Regarding risk for UTIs, you'd think that the risk would be higher with the degree of glucosuria induced by SGLT2 inhibitors, but again, insulin-treated cats may also have glucosuria for a large amount of the day. Bexagliflozin-treated cats also tend to have a pretty high urine specific gravity, so that probably plays a role in decreasing the risk for UTI.

Dr. Marks: What should we know regarding using Bexacat in feline patients that have kidney disease?

Dr. Mott: In the pivotal study, cats that were stage 1 or stage 2 IRIS chronic renal disease were included. Those that were stage 3 or 4 were excluded.[1] We know that a lot of the cats with stage 1 or 2 did well on bexagliflozin.

Dr. Ward: We're talking a lot about the data from this pivotal study because that's what we know about Bexacat, but I anticipate we'll know so much more about this drug in the next few years. I'm sure that people are planning some clinical trials already that are going to look at things like the risk for UTIs and the degree of chronic kidney disease for which it's safe to use this drug. Certainly, in people, it looks like SGLT2 inhibitors may have a renal protective effect, but I don't think we know the answers to that now, but maybe in a couple of years we will know more.

Dr. Scott-Moncrieff: In people, it comes down to what the glomerular filtration rate (GFR) is, because you do need a certain GFR to be able to get the drug to its site of action in the renal tubules. So that's really why the higher stage chronic kidney disease cats were excluded, because the drug has to get to the site of action.

Dr. Mahony: Another thing is that, because of the mechanism of action of SGLT2 inhibitors and their ability to cause osmotic diuresis, mild elevations in creatinine, BUN, and SDMA are not unexpected. If they continue to increase, then Bexacat might need to be discontinued.

Dr. Marks: When should Bexacat be discontinued and insulin therapy initiated instead?

Dr. Ward: We've talked a lot about DKA and eDKA. If that happens, you've got to stop Bexacat and put them on insulin. The recommendations from the study were to not put them back on Bexacat after DKA or eDKA.[1] During the study, if patients had a history of being ketotic, they were not started on Bexacat, so I think ketosis is probably the number one reason why you would want to get a cat off Bexacat—or, of course, if you're not achieving diabetic control.

Dr. Scott-Moncrieff: I think any time a cat is systemically unwell, they need to at least temporarily be taken off the drug. If they're vomiting, if they're anorexic, if they're dehydrated or have severe diarrhea, the drug needs to be discontinued. Once you determine the cause of those clinical signs, you can decide if the drug needs to permanently discontinued, because there are obviously cats that have a transient illness that then resolves, and those cats can potentially go back on bexagliflozin. There are other cats for which it clearly is not a good choice. Again, if they develop DKA or eDKA, pancreatitis, or some other severe illness that's causing insulin resistance, then I would be much more inclined to permanently transition them to insulin.

Dr. Mahony: I think it is worth advising our clients that cats that do well initially on Bexacat may experience worsening glucose control in the future due to progressive loss of pancreatic beta cell function, and a transition to insulin may be required at that time.

Dr. Ward: When people start running glucose curves on these cats on Bexacat, their glucose control is so beautiful and they seem to do so well that you might just want to put them on autopilot and never monitor them, but we really can't do that. You've got to recheck them every 90 days or so and see how they're doing, and even though they may look stable glucose-wise, there may be other things happening.

Dr. Marks: Are there any recommendations on the relationship of a specific low-carb diet or feeding times in relationship to administration of Bexacat?

Dr. Mott: Giving Bexacat doesn't have to be related to feeding, so it can be given with or without food, whereas insulin therapy is typically tied to a feeding schedule. In the pivotal study, diet was not a variable that was controlled or looked at. But we have seen that cats seem to have a response to SGLT2 inhibitors, regardless of diet. As for whether low carbohydrate is beneficial, that will have to be looked at in the future. In people, if you are diabetic and you're on an SGLT2 inhibitor, they do not recommend going on a low-carbohydrate diet or a ketogenic diet, as that can actually put them at greater risk for DKA.

Dr. Marks: What are some practical reasons practitioners should consider Bexacat?

Dr. Mott: Bexacat potentially offers more freedom for owners of cats with diabetes. We know that having a cat with diabetes is challenging for an owner. There's a lot of time and effort that they need to dedicate to managing this disease. With Bexacat, they're giving a tablet once a day, making treatment simple. It doesn't have to be associated with eating, and it's given regardless of what the glucose level is. So we don't even necessarily have to have these clients measuring glucose before they give Bexacat. This offers a lot of freedom from measuring glucose levels prior to each dose. The other thing with bexagliflozin is, in the margin of safety study, they showed that, even if a cat gets a double dose of bexagliflozin, those cats are extremely unlikely to become hypoglycemic.[1] With Bexacat, if a double dose occurs, that cat does not have to be rushed into the emergency room. I think, for owners, there can be a lot more freedom and less stress with cats that are good candidates for bexagliflozin.

Dr. Scott-Moncrieff: To add to that, some people are needle-shy and don't like to give injections or are not willing to give injections, so the fact that you can mix it in the food and don't even need to pill the cat is a really big advantage. It also allows for less anxiety around boarding or having a housesitter.

Dr. Ward: There's also less anxiety around hypoglycemia with Bexacat. Again, you hate to say that it never happens, but it's rare, and I think that really helps owners as well. I look at it in terms of how many cats will get treated now that may not have gotten treated in the past or maybe would have been euthanized. But now, there's an alternative, and maybe we'll be able to save more cats that might have otherwise not been treated.

Dr. Marks: Client communication is always critical, especially when we have a first-time diabetic that's been diagnosed. What are some expectations and practical verbiage that we can give to help veterinary staff to best educate about this drug?

Dr. Mahony: I think we have to emphasize that our concern now is the formation of ketones—the fact

that this drug will only work effectively if a cat is able to produce insulin and that we need to monitor the cat's ketones, attitude, and appetite very closely. We need to hear from the owners as soon as they have any concerns, because these cats can go downhill very quickly, and we want to be able to recognize this and get these cats in straightaway for evaluation.

Dr. Scott-Moncrieff: I do think it's worthwhile letting owners know that, at some point in the future, their cat may still require treatment with insulin. If they know there's possibly a need for insulin again later down the road, then it won't be a huge shock to them if and when that happens. And, certainly, if a cat isn't doing well with Bexacat, you don't want to delay the transition to insulin too long because, as Dr. Mahony said, they can go from mildly ill to really unwell and needing intensive care within a few days. So it's important for owners to be aware that intervention, sooner rather than later, is critical. You don't want to waste any time if your cat shows signs of concern.

Dr. Marks: What might practitioners need to have on hand to treat patients with Bexacat, if anything?

Dr. Scott-Moncrieff: If they're interested in using Bexacat in their practice going forward, having a BHBA monitor is important. Getting that on hand, ahead of time, would be worthwhile. And also getting Bexacat on hand before they have that first case, because what you don't want to do is have a big lag between making the diagnosis in a cat that's eligible and ordering in the drug and then having to wait, because then you have to reassess and make sure that they haven't gone from nonketotic to ketotic in that time period. So you don't want to make the diagnosis on a Friday and then have to wait till the next Tuesday or Wednesday to get the drug and meter in hand. In addition, making sure they have all the supportive materials to educate the owner is important. There are all sorts of good handouts that Elanco put together as far as educating the owner about this drug and what to be looking out for.

Dr. Mahony: Owners typically need the most support during the first 2 weeks of treatment. Should it happen, most incidences of DKA occur relatively quickly after starting the drug. It's important to get the cat back in for a 3- to 5-day checkup, so there needs to be flexibility in your schedule to see the cat and make sure everything is going fine. If you were heading out on vacation after initiating treatment, notify a colleague that you just started a patient on Bexacat and arrange for follow-up.

Dr. Mott: I think the other thing is that there may be clients who want to measure BHBA at home. And this is something they can do. It's a portable ketone monitor, and it's really just like a glucometer. If the cat is lethargic or having a decreased appetite or any of those signs, they can actually measure that and then give their veterinarian a call and report the BHBA level.

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>
> ***—Dr. Scott-Moncrieff***

Dr. Scott-Moncrieff: I also think there needs to be some flexibility in the timing of reevaluations, because we say 2 to 5 days and then again in 14 days, but it depends on the cat. If you see them 2 days after starting the drug and BHBA is trending up, you probably don't want to wait until 14 days to see them again.

Dr. Ward: I've heard from practitioners that they're nervous about using the handheld BHBA monitor, which I think we're all recommending because it's so much easier than sending a serum sample out to get the BHBA measured. But we need to remember that this is still a new test and new equipment for many veterinarians. However, these monitors are very inexpensive to get, and the samples are really easy to run. I would say, if a practitioner is prepping themselves to use this drug in their clinic, it would be really helpful if they got themselves a BHBA monitor. The Precision Extra is the one that's validated for use in the cat.[2] I will almost guarantee they're going to fall in love with it. It's so much easier and more accurate than looking at a urine sample. Once they're comfortable with that, it's going to be one less hurdle when it comes to using the new drug for the first time.

Dr. Marks: With the advent of low-stress handling techniques and some of the tricks we know to help preserve the physical and emotional health of our patients, what are some tips we can give to our cat caregivers on the best ways to make administering Bexacat as easy as possible?

Dr. Mahony: Bexacat is very palatable, so it is easy to administer. Most cats seem to take it readily, and a tasty tablet, of course, is much easier than having to give an injection.

Dr. Scott-Moncrieff: One other note might be that it's

a little unusual to have a drug like this that is not dosed per kilogram; it's 15 milligrams per cat. So it's important that people don't make the mistake of thinking it's 15 milligrams per kilogram. And we should also point out that cats need to be 3 kilograms or heavier for that 15-milligram dose to be appropriate and to be a candidate for receiving Bexacat.

Key Takeaways

- Bexacat (bexagliflozin tablets), an SGLT2 inhibitor, has been introduced as a once-daily oral option for achieving glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.
- The ideal candidate for Bexacat is a newly diagnosed diabetic cat with no obvious clinical signs of disease that has been shown to be free of liver disease, serum ketones, pancreatitis, and severe renal disease.
- Close monitoring is required to assess response to treatment and to ensure that eDKA, a condition not seen with traditional insulin therapies, does not develop. Any cat with clinical signs of illness should always be screened for eDKA.
- Many aspects of traditional therapy, including adherence to a strict treatment schedule, administration of injections, and concerns of hypoglycemia, can be avoided with Bexacat, which has an oral formula that has been shown to be highly palatable.

Dr. Mott: This is an exciting time in veterinary medicine, now that we have other options available when treating a subset of our diabetics. I think we're going to see SGLT2 inhibitors used in a lot of different aspects of veterinary medicine as we become more familiar with them, and potentially in other species as well.

Dr. Scott-Moncrieff: And to follow up on that, I would say watch this space, because I think there's going to be so much more to come. If we have this conversation again in 2 years' time, hopefully there'll be so much more that we know about this class of drugs in our domestic species. It will be very interesting, I think, to see how this continues to evolve.

Dr. Ward: I think this medication is going to open up treatment to groups of cats that may have otherwise been euthanized. Nothing makes me sadder than seeing a cat that could be treated but the owners just couldn't do it for any number of reasons. This drug will allow so many more of these cats to be treated and have an improved quality of life. ●

References

1. Hadd MJ, Bienhoff SE, Little SE, et al. Safety and effectiveness of the sodium-glucose cotransporter inhibitor bexagliflozin in cats newly diagnosed with diabetes mellitus. *J Vet Intern Med*. 2023;37(3):915-924.
2. Zeugswetter FK, Rebuzzi L. Point-of-care β-hydroxybutyrate measurement for the diagnosis of feline diabetic ketoacidaemia. *J Small Anim Pract*. 2012;53(6):328-331.

Bexacat™

(bexagliflozin tablets)

15 mg flavored tablets
For oral use in cats only
Sodium-glucose cotransporter 2 (SGLT2) inhibitor

CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Before using Bexacat, please consult the product insert, a summary of which follows:

WARNING: DIABETIC KETOACIDOSIS/EUGLYCEMIC DIABETIC KETOACIDOSIS

- **Cats treated with Bexacat may be at an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis (see Adverse Reactions). As diabetic ketoacidosis and euglycemic diabetic ketoacidosis in cats treated with Bexacat may result in death, development of these conditions should be treated promptly, including insulin administration and discontinuation of Bexacat (see Monitoring).**
- **Due to the risk of developing diabetic ketoacidosis or euglycemic diabetic ketoacidosis, do not use Bexacat in cats with diabetes mellitus who have previously been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus (see Contraindications).**
- **Bexacat should not be initiated in cats with anorexia, dehydration or lethargy at the time of diagnosis of diabetes mellitus or without appropriate screening tests (see Animal Safety Warnings).**

INDICATION

Bexacat is indicated to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.

DOSAGE AND ADMINISTRATION

Always provide the Client Information Sheet with the prescription.

Dosing Instructions

Administer one tablet by mouth to cats weighing 6.6 lbs (3.0 kg) or greater once daily, at approximately the same time each day, with or without food, and regardless of blood glucose level.

Monitoring

- Sudden onset of hyporexia/anorexia, lethargy, dehydration, or weight loss in cats receiving Bexacat should prompt immediate discontinuation of Bexacat and assessment for diabetic ketoacidosis, regardless of blood glucose level.
- During treatment with Bexacat, blood glucose, fructosamine, serum β-hydroxybutyrate (BHBA), serum feline pancreas-specific lipase (fPL), liver parameters, serum cholesterol and triglycerides; and body weight and clinical signs should be routinely monitored.
  - Increasing or persistently elevated feline pancreas-specific lipase or liver parameters should prompt further evaluation for pancreatitis and/or hepatic disease and consideration for discontinuing Bexacat.
  - BHBA is the predominate ketoacid in diabetic ketoacidosis. Bexacat should be discontinued if a notable reduction in BHBA is not observed after initiation of Bexacat, or if BHBA persistently rises after an initial reduction.
  - Cats with increasing or persistently elevated cholesterol and triglyceride levels may be at an increased risk for developing diabetic ketoacidosis or euglycemic diabetic ketoacidosis.
  - Bexacat should be discontinued if poor glycemic control, as described below, develops.
- During the first 8 weeks after initiation of Bexacat, assessment of glycemic control and clinical improvement should be evaluated.
  - A physical examination, an 8-hour blood glucose curve, serum fructosamine and body weight should be assessed at 2, 4 and 8 weeks.
  - Cats demonstrating poor glycemic control, including weight loss, an average blood glucose concentration from an 8-hour blood glucose curve ≥ 250 mg/dL, and/or a fructosamine indicating poor glycemic control should be closely monitored.
  - Bexacat should be discontinued, and initiation of insulin considered in cats demonstrating poor glycemic control, as described above, at 8 weeks.
- Cats may present with diabetic ketoacidosis and a normal blood glucose concentration (euglycemic diabetic ketoacidosis). Delay in recognition and treatment of diabetic ketoacidosis and euglycemic diabetic ketoacidosis may result in increased morbidity and mortality.
- Development of diabetic ketoacidosis and euglycemic diabetic ketoacidosis requires the following actions:
  - Discontinuation of Bexacat
  - Prompt initiation of insulin therapy
  - Administration of dextrose or other carbohydrate source, regardless of blood glucose concentration
  - Appropriate nutritional support should be promptly initiated to prevent or treat hepatic lipidosis.

For more information refer to **CONTRAINDICATIONS** and **WARNINGS.**

CONTRAINDICATIONS

- Do not use Bexacat in cats with diabetes mellitus who have previously been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus. The use of Bexacat in cats with insulin-dependent diabetes mellitus, or the withdrawal of insulin and initiation of Bexacat, is associated with an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis and death.
- Due to risk of severe adverse reactions, do not use Bexacat in cats with evidence of hepatic disease or reduced renal function.

WARNINGS

User Safety Warnings

Not for use in humans. Keep out of reach of children. Consult a physician in case of accidental ingestion by humans.

Animal Safety Warnings

- Bexacat should not be initiated in cats with:
  - Anorexia, dehydration, or lethargy at the time of diagnosis of diabetes mellitus, as it may indicate the presence of other concurrent disease and increase the risk of diabetic ketoacidosis.
  - An fPL level > 5.3 mcg/L, diagnostic imaging consistent with pancreatitis, a history of pancreatitis, or current clinical signs suggestive of pancreatitis.
  - Laboratory values consistent with diabetic ketoacidosis, including elevated urine or serum ketones, and metabolic acidosis (high anion gap, or decreased bicarbonate, pH, or partial pressure carbon dioxide [$PaCO_2$] levels).
  - A BHBA > 37 mg/dL, or if BHBA is > 25 mg/dL and the cat has a history of renal disease or metabolic acidosis.
- Persistent plasma bexagliflozin concentrations and reduced clearance of Bexacat, represented as the presence of plasma half-lives in excess of 24 hours, may result in prolonged clinical effects such as glucosuria and/or euglycemia despite discontinuation of Bexacat in some cats with hepatic disease and/or reduced renal function, including cats with clinically undetectable disease at the time of Bexacat initiation. Reduced clearance of Bexacat may contribute to persistent glucosuria, resulting in an osmotic diuresis and dehydration that requires appropriate hydration support. These cats may require hospitalization, which may be protracted, for sequalae such as diabetic ketoacidosis, euglycemic diabetic ketoacidosis, or hepatic lipidosis.
- Cats should be screened for urinary tract infections and treated, if indicated, when initiating Bexacat. Treatment with Bexacat may increase the risk for urinary tract infections (see **Adverse Reactions**). Cats treated with Bexacat should be monitored for urinary tract infections and treated promptly. Consider discontinuation of Bexacat in cats with recurrent urinary tract infections.
- Bexacat may cause increased serum calcium concentrations. Bexacat should be discontinued in cats with persistent increases in serum total calcium or ionized calcium because of increased risk of forming calcium containing uroliths (see **Adverse Reactions**).
- Long term use of Bexacat may increase the risk of urothelial carcinoma (see **Adverse Reactions**).
- Keep Bexacat in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS

- Bexacat should be discontinued in cats who develop diarrhea unresponsive to conventional therapy.
- Consider temporary discontinuation of Bexacat in cats during times of decreased caloric intake, such as surgery or decreased appetite, as administration of Bexacat in these cats may increase the risk of diabetic ketoacidosis or hepatic lipidosis.
- The osmotic diuretic effects of Bexacat may contribute to inappropriate urination in some cats (see **Adverse Reactions**).
- Polyphagia as a compensatory response to caloric wasting from glucosuria may persist in up to 80% of cats, despite evidence of adequate glycemic control, and may lead to progressive weight gain.
- Approximately 20-30% of cats may have persistent polyuria and/or polydipsia secondary to Bexacat-induced osmotic diuresis and may be a risk factor for dehydration-associated diabetic ketoacidosis.
- The concurrent use of volume depleting drugs in cats treated with Bexacat has not been evaluated.
- The safety of Bexacat in breeding, pregnant, and lactating cats has not been evaluated.

ADVERSE REACTIONS

Field Study

Eighty-four cats with newly diagnosed diabetes mellitus were enrolled in a 180-day multicenter field effectiveness and safety study. Safety data were evaluated in 84 cats treated with at least one dose of Bexacat. All cats received one tablet, once daily, regardless of body weight or blood glucose level. Seventy-two of the 84 enrolled cats completed the study. The most common adverse reactions included elevated blood urea nitrogen (BUN), vomiting, elevated urine specific gravity (USG), elevated serum fPL, diarrhea, anorexia, lethargy, and dehydration. The adverse reactions seen during the field study are summarized in Table 1 below.

Table 1. Adverse Reactions (n=84)

Adverse Reaction	Number (%)
Elevated BUN*	46 (54.8)
Vomiting	42 (50.0)
Elevated USG†	33 (39.3)
Elevated fPL‡	33 (39.3)
Diarrhea	32 (38.1)
Anorexia	31 (37.0)
Lethargy	17 (20.2)
Dehydration	16 (19.0)
Elevated symmetrical dimethylarginine (SDMA)	13 (15.5)
Weight loss	13 (15.5)
Urinary tract infection	12 (14.3)
Elevated ALT and/or AST§	11 (13.1)
Hypercalcemia	8 (9.5)
Behavioral changes**	6 (7.1)
Proteinuria	5 (6.0)
Elevated creatinine	4 (4.8)
Elevated creatine kinase	4 (4.8)
Inappropriate urination	4 (4.8)
Death	3 (3.6)
Diabetic ketoacidosis	3 (3.6)
Pancreatitis	3 (3.6)
Euglycemic diabetic ketoacidosis	2 (2.4)
Hepatic lipidosis	2 (2.4)
Elevated alkaline phosphatase	2 (2.4)
Elevated total bilirubin	2 (2.4)
Constipation	2 (2.4)

* Most cats had elevations < 1.5 times the upper limit of normal (ULN).
† Elevations were predominantly attributable to dehydration and/or glucosuria.
‡ Most cats had one or more isolated elevations, followed by a return to previous values.
§ Of nine cats with elevations ≥ 1.5X ULN, 2 cats developed diabetic ketoacidosis and were transitioned to insulin. One cat developed diabetic ketoacidosis and hepatic lipidosis resulting in death (euthanasia). One cat developed anemia, progressive weight loss and fPL elevations resulting in death.
** Observations included hiding, agitation, aggression, vocalization, and anxious behavior.

Nine serious adverse reactions associated with Bexacat administration occurred during the study, including three cats who died or were euthanized. Of the three cats who died or were euthanized, two cats became clinically ill within 5 doses of Bexacat administration (range 3 to 5 doses). One cat with euglycemic diabetic ketoacidosis and hepatic lipidosis was euthanized due to further deterioration of its clinical condition, despite supportive treatment. One cat demonstrating anorexia, lethargy, dehydration, azotemia, and hypokalemia was euthanized without supportive treatment. One cat, who demonstrated a lack of effectiveness, anemia and hepatic lipidosis died on Day 77 despite supportive treatment and additional diagnostics. Six of the nine cats had serious adverse reactions that did not result in death or euthanasia. Five cats were treated for their clinical conditions and transitioned to insulin. Serious adverse reactions in these cats were associated with the following conditions (number of cats): euglycemic diabetic ketoacidosis (1); lack of effectiveness, diabetic ketoacidosis, elevated liver parameters (1); diabetic ketoacidosis (1); diabetic ketoacidosis and pyelonephritis (1); and lack of effectiveness, weight loss, dehydration (1). One cat with constipation and pancreatitis received supportive treatment and remained on Bexacat (bexagliflozin tablets).

Pilot Field Study

Eighty-nine cats with newly diagnosed diabetes mellitus were enrolled in a 56-day multicenter pilot field effectiveness and safety study, with continued use for up to 180 days. All cats received one tablet, once daily, regardless of body weight or blood glucose level. Safety data were evaluated for all 89 cats treated with at least one dose of bexagliflozin. The most common adverse reactions included elevated blood urea nitrogen (BUN), elevated urine specific gravity (USG), elevated serum feline pancreas-specific lipase, vomiting, diarrhea/loose stool, hyporexia/anorexia, lethargy, elevated serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), and urinary tract infections. The adverse reactions seen in the pilot study are summarized in Table 2 below.

Table 2. Adverse Reactions (n=89)

Adverse Reaction	Number (%)
Elevated BUN*	51 (57.3)
Elevated USG†	43 (48.3)
Elevated fPL‡	39 (43.8)
Vomiting	39 (43.8)
Diarrhea/Loose Stool	29 (32.6)
Hyporexia/Anorexia	28 (31.4)
Lethargy	16 (18.0)
Elevated ALT and/or AST§	13 (14.6)
Urinary tract infection	13 (14.6)
Dehydration	10 (11.2)
Elevated symmetrical dimethylarginine (SDMA)	10 (11.2)
Behavioral changes**	9 (10.1)
Ketosis/Ketonuria	8 (9.0)
Weight loss	8 (9.0)
Proteinuria	8 (9.0)
Pancreatitis	7 (7.9)
Death	6 (6.7)
Anemia	6 (6.7)
Hepatopathy	6 (6.7)
Hypercalcemia	4 (4.5)
Elevated creatine kinase	4 (4.5)
Inappropriate urination	4 (4.5)
Peritonitis	3 (3.4)
Constipation	3 (3.4)
Elevated creatinine	2 (2.2)
Euglycemic diabetic ketoacidosis	2 (2.2)
Diabetic ketoacidosis	2 (2.2)
Hemolytic anemia	2 (2.2)
Elevated total bilirubin	2 (2.2)

* Most cats had elevations ≤ 1.5X upper limit of normal (ULN).
† Elevations were predominantly attributable to dehydration and/or glucosuria.
‡ Most cats had one or more isolated elevations, followed by a return to previous values.
§ Most elevations were ≤ 2X ULN. One cat had marked ALT and AST (9X and 6X upper limit of normal, respectively) elevations on Day 28. Following discontinuation of bexagliflozin, the liver enzymes decreased within 24 hours and returned to within reference range in 10 days.
** Observations included hiding, hyperactivity, vocalization, and abnormal behavior.

Twenty cats (22%) had at least one blood glucose value < 65 mg/dL recorded during 8-hour blood glucose curves. No clinical signs of hypoglycemia were observed and bexagliflozin dosing was not adjusted in any cat due to documented hypoglycemia. Nine serious adverse reactions associated with bexagliflozin administration occurred during the study, including six cats who died or were euthanized. Of the six cats who died or were euthanized, five became clinically ill within receiving 5 doses of bexagliflozin (range 1 to 5 doses). Four of the cats were euthanized due to further deterioration of their clinical condition despite supportive treatment. One cat died despite supportive treatment. Deaths were associated with the following conditions (number of cats): necrotizing pancreatitis and pancreatic abscess (1), pancreatitis and hepatic lipidosis (1), euglycemic diabetic ketoacidosis and severe hepatic lipidosis (1), pancreatitis and hepatic abscesses (1), diabetic ketoacidosis (1), and persistent polyuria and polydipsia and quality of life concerns (1).

Three of nine serious adverse reactions that did not result in death or euthanasia included the following (number of cats): acute hepatocellular injury (1), immune-mediated hemolytic anemia (1), and euglycemic diabetic ketoacidosis with concurrent pancreatitis and hepatopathy (1). Two cats with serious adverse reactions demonstrated persistent bexagliflozin blood plasma levels and elimination half-lives after discontinuation of bexagliflozin. One cat with renal and liver values within the reference range at screening was euthanized due to a continued decline in clinical condition despite treatment for euglycemic diabetic ketoacidosis and severe hepatic lipidosis. The second cat, noted to have IRIS (International Renal Interest Society) stage II renal disease and liver values within the reference range at screening, recovered following treatment for marked liver enzyme elevations above the reference range on Day 28.

Extended Use Field Study

One hundred twenty-five cats with diabetes mellitus that had previously completed a bexagliflozin field study were enrolled in a multicenter extended use field study. Cats were enrolled in the study for a range of 7 to 1064 days, with a mean of 329 days. Safety data were evaluated for all 125 cats treated with at least on dose of Bexacat (bexagliflozin tablets). All cats received one tablet, once daily, regardless of body weight or blood glucose level. Forty-nine of the 125 enrolled cats were withdrawn from the study due to adverse reactions, serious adverse reactions, death/euthanasia, lack of effectiveness, suspected diabetic remission, withdrawal of owner consent, or lost to follow up. The most common adverse reactions were similar to those noted in the previous field studies and included elevated USG (35.2%), vomiting (27.2%), elevated fPL (26.4%), anorexia (24.0%), diarrhea (22.4%), urinary tract infections (17.6%), lethargy (16.8%), and death (16.0%).

Twenty serious adverse reactions associated with Bexacat administration occurred during the study, all resulting in death or euthanasia. Clinical signs of hypoglycemia were observed in two of these cats. Deaths were associated with the following conditions (number of cats), with some cats experiencing multiple comorbidities (necropsy was not granted in all cases): euglycemic diabetic ketoacidosis (8); diabetic ketoacidosis (4); hepatic lipidosis (5); pancreatic necrosis/peripancreatic fat saponification (3); urothelial carcinoma (2); hypercalcemia, recurrent calcium containing cystic calculi (1); lack of effectiveness, weight loss, anorexia (1); lethargy, weight loss, pallor (1); chronic renal disease, glomerulonephritis (1); chronic enteropathy (1); hypoglycemia, possible pancreatitis (1).

CONTACT INFORMATION

To report suspected adverse events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), contact Elanco US Inc at 1-888-545-5973.

For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

EFFECTIVENESS

Field Study

Eighty-four cats diagnosed with diabetes mellitus were enrolled in a 180-day multicenter field effectiveness and safety study. Enrolled cats included purebreds and mixed breeds, ranging in age from 3 to 19 years, and weighing between 7.3 to 24.3 lbs (3.3 to 11.3 kg). Cats received one tablet, once daily, regardless of body weight or blood glucose level. Treatment success was defined as improvement in at least one blood glucose variable (blood glucose curve mean or fructosamine) and improvement in at least one clinical sign of diabetes mellitus (polyuria, polydipsia, polyphagia, or body weight [weight gain or no weight loss]).

Of 77 cats included in the effectiveness-evaluable population:

- 64 cats (83.1%) were considered a treatment success on Day 56.
- The lower bound two-sided 90% confidence interval was 74.5%. Effectiveness was demonstrated if the lower bound of the confidence interval was > 66%.
- Mean blood glucose curve mean decreased from 284 mg/dL on Day 0 to 143 mg/dL on Day 56.
- Mean fructosamine levels decreased from 544 µmol/L prior to Day 0 to 295 µmol/L on Day 56.
- Improvements in the clinical signs of polyuria, polydipsia, polyphagia, and body weight on Day 56 were observed in 53 (68.8%), 57 (74.0%), 44 (57.1%), and 42 (54.6%) cats, respectively.
- 66 cats (85.7%) completed the 180-day study.

Pilot Field Study

Eighty-nine cats diagnosed with diabetes mellitus were enrolled in a 56-day, multicenter pilot field effectiveness and safety study with continued use for up to 180 days. Enrolled cats included purebreds and mixed breeds, ranging in age from 3 to 17 years and weighing 6.4 to 22.9 lbs (2.9 to 10.4 kg). Cats received one tablet, once daily, regardless of weight. Treatment success was defined as improvement in at least one blood glucose variable (blood glucose curve mean or fructosamine) and improvement in at least one clinical sign of diabetes mellitus (polyuria, polydipsia, polyphagia, or body weight [weight gain or no weight loss]). Of the 72 cats included in the effectiveness-evaluable population, 58 (80.6%) were considered treatment successes on Day 56.

STORAGE CONDITIONS Bexacat should be stored at room temperature 68 to 77 ˚F (20 to 25 °C).

HOW SUPPLIED

Flavored tablet each containing 15 mg bexagliflozin; 30 or 90 tablets per bottle.

Approved by FDA under NADA # 141-566
Manufactured for: Elanco US Inc, Greenfield, IN 46140

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