

Guidance for the owners of dogs with Addison's disease in making the transition from Florinef to Zycortal and prednisone (or its equivalent)

This document has been written to guide owners of dogs with Addison's disease through the transition from Florinef to Zycortal.

1) Introduction: Why the change ?

Florinef is a drug which has both mineralocorticoid and glucocorticoid activity. It replaces both the aldosterone and cortisol that a dog with Typical Addison's can no longer make. Licensed as a drug for humans, it has also been used for dogs as there has been no dog specific drug alternative until now, with the launch of Zycortal. Production of Florinef was discontinued at the end of February 2016. (Fludrocortisone acetate, which has replaced Florinef, is being produced but at a much higher cost to dog owners)

Zycortal is produced by Dechra UK and was first registered to them in 2014, with a license running until 2024. It is an injectable drug which has only mineralocorticoid activity. It replaces only the aldosterone our Adogs can no longer produce, hence when making the change over to Zycortal, it is important to remember to give a small daily dose of glucocorticoid such as prednisolone.

Zycortal was launched in the UK at the BSAVA congress in Birmingham in April 2016, with sessions being run about Addison's disease, helping to raise awareness of this disease. It is a drug specifically for the management of Addison's disease in dogs and due to the Cascade system in the UK, must be prescribed ahead of a human drug (e.g. Florinef) to treat the same disease.

Percorten (DOCP) which has the same active substance as Zycortal (desoxycortone pivalate) has been used successfully in managing Addison's in other parts of the world for many years now and the experience of owners using this drug for their dogs is now being used to aid owners transitioning to Zycortal from Florinef. There will be no need to apply for a special licence to use Zycortal as people who have been importing Percorten into the UK have had to do. In addition current UK Percorten users may decide to switch to Zycortal which will be cheaper for them.

2) How does Zycortal work ?

Zycortal is a 25mg/ml prolonged-release suspension for injection for dogs. Its aim is to maintain balance of the electrolytes whereas Florinef balanced the electrolytes as well as provided a cortisol replacement to deal with stress. The Zycortal product information states giving an initial starting dose of 2.2 mg / kg, testing the electrolytes firstly at 10 days, then again at around 25 days in order to determine the next dose. After this first 'cycle' it is only necessary to check the lytes just prior to giving the next dose. When you first start using Zycortal, you will need to continue to give the normal dose of florinef for 24 hours after the first injection, before stopping it. The day after the first injection, once you stop the florinef, you will then start to give the required dose of pred each morning.

One of the most important things about using Zycortal effectively and efficiently is to make sure the lytes results are used to determine the next dose. You are aiming to have well balanced lytes throughout the cycle just as you did each day with Florinef. Basically, if the K is below the middle of its reference range at the end of the cycle, then you know too high a dose has been given last time, so you need to reduce it. Always remember that Zycortal raises the Na and lowers the K.

You should be aiming for an Na:K ratio of around 30 to 32. If the lytes are well balanced as in both the Na and the K being close to the middle of their respective reference ranges, then you know you have reached your optimum dose. Some vets may think a ratio anywhere within the 'normal' range of 27 - 40 is ok, but many years of experience from thousands of Addison dogs owners across the world, tells a very different tale. In addition, to give an example, the following pairs of values of the Na and K, all give the same ratio of 30.2, but which set of results would you prefer and which one would suggest to you need to give the next dose of Zycortal or which set of values could be a cause of concern ? N.B. Reference ranges for the Na and K are also important.

Na:148, K:4.9

Na:145, K:4.8

Na:139, K:4.6

Na:129.9, K:4.3

Zycortal does not suddenly stop working, so if you missed giving a dose by a day or so, the Zycortal will still be working

3) Does my dog need a daily dose of prednisone (or its equivalent) and if so how much ?

All dogs having Zycortal will need a daily dose of glucocorticoid to replace the cortisol the adrenal glands are no longer making and this is one of the noted bonuses of using Zycortal rather than Florinef as you will now be able to control the amount of glucocorticoid your dog gets. The glucocorticoids most likely to be prescribed are prednisone or prednisolone, though there may be other options (see the chart in Ref 2). Initially as you are transitioning from Florinef to Zycortal, you need to take into account the amount of glucocorticoid within the Florinef that your dog is already taking plus any additional daily pred. Each 0.1 mg Florinef has the glucocorticoid activity equivalent to approximately 0.25 mg pred. As an example, if your dog is taking 0.8mg Florinef daily, they are taking the equivalent of 2 mg prednisolone - so to calculate the starting dose of pred, for each 0.1 mg Florinef your dog is currently taking you will need to multiply that by 0.25 and add this to any daily pred. This is only the starting dose and over time you will be able to taper that down according to the clinical signs of your dog until you find the best lowest dose for your dog. It is very important that you eventually reduce this to the best lowest effective dose for your dog. Dogs with Addison's only need a replacement dose of pred - to replace the cortisol they can no longer make - and NOT a therapeutic dose. Making sure the dog does not start off on too high a dose of pred will make a huge difference. It has been documented by both vets and owners of dogs with Addison's disease, that some dogs as large as 100 lb only need 1 mg pred per day.

4) Will my vet let me give the injections myself at home ?

Giving injections at home to our dogs is not something all vets are familiar with in the UK. However, a precedent has been set by owners of dogs with diabetes, who have to give insulin injections every day. This is something you need to be comfortable with and have the discussion with your vet about. Some practices are likely to be much happier about this than others, some practices also do not charge if a vet nurse gives the injection rather than a vet. Note it has to be stored at a temperature below 30 deg C and above freezing. It must not be kept in a fridge.

5) What happens if I don't need a whole vial of Zycortal at one go ?

Zycortal comes in vials of 4 ml / 100mg. At present this is the only sized vial. The product has a shelf life of 3 years from production but once opened, the in-use shelf life is 4 months. It is very likely though, that once you find the best lowest dose for your dog, it can last more than 4 injections. Only time will tell if it will last for a longer period as the Percorten does. Initially, if you take your dog to the vet for the injection and your vet practice has more than one dog using Zycortal and it is being stored correctly, it may work out cheaper to be charged by the ml rather than by the vial, especially for owners of smaller dogs. This would avoid wastage, so do ask your vet if this is an option.

6) Where can I buy Zycortal myself ?

Vets will order Zycortal for you unless you have a different arrangement. You can buy Zycortal online from internet pharmacies such as viovet.co.uk or vetmedic.com and this is likely to be a cheaper option than from your vet, but you will need a prescription from your vet to do this so make sure you figure this into your costs. At the time of writing this, Viovet were selling a 4 ml vial for £54.21.

7) What problems might I encounter

Zycortal is a new drug to the vets in the UK and Europe and hence the vets here are not au fait with using it and nor will most of them be familiar with the Low Dose Protocol research study carried out for Percorten (see Ref 5), so the first challenge will be in persuading your vet to dose according to the lytes and not according to the weight going forwards and indeed the product information does state clearly in cases of hypokalaemia (low potassium), hypernatremia (high sodium) or a ratio > 32, to lower the dose of Zycortal or extend the time between injections. However, experience of people using Percorten with their dogs, shows a clear preference to lowering the dose rather than extending the time between doses in order to maintain a more consistent balance of the lytes throughout the cycle and in doing so, avoid highs and lows which is very important in order to keep a dog feeling well all of the time.

In a clinical trial of Zycortal, very common adverse reactions were noted as polydipsia (excessive thirst) and polyuria (excessive urination) but these are very likely to be avoided if the dose of both the Zycortal and the pred (or its equivalent) are optimised for your dog and the best lowest dose of each found. Some vets are concerned that once Zycortal is in the system, you cannot take it out so if the wrong dose was given, what happens ? Well if a lot too much Zycortal was given, your dog might display symptoms of hypokalaemia (low potassium) or hypernatremia (high sodium) and if too little were given the opposite - hyperkalaemia (high potassium) and /or hyponatremia (low sodium) could occur. If the latter were to occur it can easily be rectified by giving the next dose earlier and adjusting the amount given and should the former occur, your dog should be treated symptomatically and the next dose adjusted as needs. It does emphasise the need to make sure your vet determines the dose according to the lytes results of your dog as each dog is different.

8) What should I do now ?

- Familiarise yourself with the facts about Zycortal.
- Arrange an appointment with your vet to discuss a plan going forward, make sure it takes place well before you finish your last Florinef. Have your questions ready!
- Go armed with knowledge, even take a copy of the Percorten low dose protocol with you but be prepared for your vet to not feel comfortable using it at this stage. It should however, give your vet food for thought once they have more experience in using Zycortal.
- Ask your vet questions:
 - will the vet agree to dosing according to the lytes ?
 - Will the vet support you giving the injections at home (if that is what you wish to do) ?
 - Will the cost of giving the injection be cheaper if a vet nurse gives it instead of the vet ?
 - Will your vet either price match internet prices of Zycortal or give you a prescription to buy your own ?
 - How will they decide what dose of pred (or its equivalent) to prescribe for your dog ?

For many people, this is a worrying period of travelling into the unknown, but it is also a time for embracing the change in the medication for your dog, comfortable in the knowledge that this is a UK produced drug which most, if not all dogs with Typical Addison's will be changing over to, in the coming weeks and which is essentially the same drug, Percorten (DOCP), that has been used successfully across other parts of the world for many, many years. Zycortal will enable your dog to continue to live a good happy life.

Lastly, remember the adage "There are no problems, only solutions".

Update May 2016

I have added this update as it is now almost 2 months since Zycortal was released in the UK and some dog owners are already onto the second cycle of Zycortal whilst many are still waiting to begin.

What has been learnt in these two months ?

- The dogs that have started using Zycortal are doing well, which is very encouraging.
- Some of the dogs that have been started on the full recommended dose are experiencing PU/PD, some also experiencing lethargy which may be due to the potassium dropping too low and/or the high dose of pred many have been started on. Owners are having discussions with their vets to make sure that the next dose is based upon the lytes results so that appropriate reductions are made in the dose where necessary. Using the ratio on its own is not appropriate as shown in point 2 above.
- The stated starting dose of pred for a dog changing from Florinef to Zycortal in most cases has not been reflective of the amount of glucocorticoid they were getting from the Florinef and unwanted side effects are being felt from lethargy or conversely hyperactivity, excessive urination and thirst, with a few showing signs of aggression. Once the dose of pred has been lowered these symptoms have disappeared once again. Where owners have a vet who has been in agreement with a lower starting dose of pred, one akin to what their dog was getting from the Florinef, there have been no unwanted side effects. The general dose which is working best at this point, seems to be that using the guide as stated above, of each 0.1 mg florinef having the equivalent to 0.25 mg pred.
- The cost varies hugely across the UK, both for the lytes testing and also for the cost of the injection. Some vets are working closely with their clients to make sure this drug is well affordable, enabling them to do the injections themselves in their own homes and giving them a prescription to purchase the Zycortal from reputable online sites. Other vets are not being so helpful, charging much more and not enabling their clients to give the injections themselves, despite the fact that owners of diabetic dogs have to do this each day. It is important to remind the vet, that Addison's is a lifelong disease and thus a lifelong financial commitment.
- Surprisingly, some vets have made the change to Zycortal but NOT prescribed any daily pred. All dogs with Typical Addison's using Zycortal must have some daily glucocorticoid and this is stated clearly in the guidance.
- Good news is coming in from owners whose dogs go to the charities such as the PDSA and RSPCA, that they too are now on board with making the changeover.

Summing up: The experience varies a lot across the UK depending upon how much the vet already knows about Zycortal and how willing they are to use the experience obtained from thousands of dog owners using the equivalent drug, Percorten, across the world, in

determining and adjusting the dose of both Zycortal and Prednisone. It depends also, upon how willing the vet is in listening to and working with, the owners in deciding how things move forward. One thing is very clear, it is important that there is an agreement not to give more Zycortal or pred than a dog needs to thrive, be happy and live a good, long life.

References

1) EMA CVMP Assessment report for Zycortal -

<http://tinyurl.com/zjq87ql>

2) Chart comparing the relative activity of steroids - prednisone equivalent 0.25 mg steroid activity in each 0.1 mg Florinef - also showing other alternatives to prednisone

<http://patient.info/doctor/corticosteroids-and-corticosteroid-replacement-therapy>

3) Noah's Compendium - a valuable resource of drugs in the UK including data sheets

<http://tinyurl.com/zmrnkxf>

4) Zycortal Freedom of Information Summary Feb 2016

<http://tinyurl.com/gsgfmqc>

5) Percorten Low dose protocol abstract from Wiley

<http://tinyurl.com/jdcenok>

6) Everything you need to know about Zycortal including the Summary for the public

<http://tinyurl.com/jzyy9fu>

7) Summary of Zycortal product information for vets which includes the information found on the product insert

<http://tinyurl.com/jtdajob>

8) Viovet - Zycortal product information and where to buy Zycortal from online

<http://tinyurl.com/zbhwk4n>

Pam Johnson - April 2016 (May 2016)

Please note that I am not a vet, but I have been helping out on Addison's support groups for over 18 years, having had my own standard poodle with Addison's disease who thrived for 12 years on Florinef and had he still been here today I would have been in the same position as yourself, changing over to Zycortal. If you have any feedback on your experience with Zycortal, please get in touch at Teesidebubbles@aol.com