From:

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Re: Uniprim® Oral Granules
Case Id: ON-062321-23241
Date of Response: Jun 23, 2021 2:31:15 PM

Case Information:

Date Submitted	Jun 23, 2021 1:28:48 PM
Species	Chickens/Broiler Breeder
Number of Animals	20000
Location of Animals	[redacted]
Reason for Use	Treatment
Additional Information	Please provide both meat and egg withdrawals.

Drugs Administered

Drug Trade Name	Generics	Route	Dose	Diseases
Uniprim® Oral Granules	• sulfadiazine • trimethoprim	Oral - Feed	750 g of uniprim per ton of feed: Sulfadiazine 249.75 ppm/Trimethoprim 50.25 ppm. Continuously for 7 days.	• **Alimentary:** colibacillosis

Response and Recommendation: *Meat: 3 days, Eggs: 21 days or more*

As sulfadiazine and trimethoprim are not approved for poultry in Canada, there are no MRLs for these drugs in poultry. Therefore, any amount of sulfadiazine or trimethoprim detected in the meat or eggs of chickens is a residue violation. Trimethoprim is usually administered with a sulfonamide but is excreted faster. Consequently if no residues of sulfonamide are detectable, no residues of trimethoprim would be expected. So, CFIA's detection program focuses on sulfonamides. We have been provided with depletion data for sulfadiazine/ trimethoprim in chickens at a dose of 25-30 mg/kg from the US manufacturer of Uniprim. The methodology of the analysis is unknown and may not be as accurate as the methodology employed by the CFIA, but it does give us data to model the elimination of sulfadiazine from chickens and we use the means plus 3 standard

deviations. We find a liver elimination half-life of 4 hours, which corresponds to a literature reference of a plasma elimination half-life of 2 hours. By modelling the US data from the highest tissue levels (liver), we believe that a 72 hour (3 days) withdrawal interval will be sufficient to prevent detectable residues of sulfadiazine in chickens at this dose. For eggs, we were able to find a published reference and it is from Egypt and published in an obscure journal (Atta A., El-zeini SA; Depletion time of trimethoprim and sulfadiazine from eggs of laying hens receiving trimethoprim/sulfadiazine combination. Food Control; 2001; 12:269-274). But we have reservations about extrapolating from this work. The drug was a different formulation than the Uniprim product you are using and was given in water, so we cannot compare their dosage with yours. While they did use an HPLC method of analysis, their limit of detection was 20 ng/g for both drugs. The CFIA laboratory usually screens eggs for antimicrobials with the Charm II test. But the Charm II test is notorious for false positives and in their own survey, of 10 Charm positive for sulfas, only one turned out to be real (Quon, D. Monitoring of domestic and imported eggs for veterinary drug residues by the CFIA. J. Agric. Food Chem. 2000; 48: 6421-6427). However, the CFIA's has a very sensitive confirmatory methodology for sulfas. In the Egyptian study, sulfa residues were detected up to 4 days in yolk (LOD= 15 ppb) and 5 days in albumen (LOD: 20 ppb) following administration of trimethoprim/sulfadiazine at 200 mg/L of drinking water for 5 days and they were detected up to 6 days in yolk and 7 days in albumen following administration of trimethoprim/sulfadiazine at 400 mg/L of drinking water for 5 days. We believe that you should use a longer withdrawal than 8 days, we are just not sure what to recommend in this case and are scrambling to find usable data to make specific recommendations. Sulfa drugs always make us concerned as they are notorious for sticking to equipment and causing cross-contamination and because they are very easy for the CFIA to detect. Ideally, it would be best to screen eggs from treated birds prior to releasing them for human consumption. If you can't screen the eggs, then you should be recommending a "greatly extended" withdrawal interval on the order of 21 days or more. We are sorry that we can't be more specific at this time.

Therefore, the Canadian gFARAD recommends a withdrawal interval of 3 days for meat and 21 days or more for eggs, which should be sufficient so that detectable residues are not found. Furthermore, this recommendation for residue avoidance does not address the risks of developing or transmitting antimicrobial resistance from treated animals to other animals or humans following the extralabel use of this antimicrobial. Because the Canadian gFARAD withdrawal recommendation is not an official withdrawal time and is based on data that has not been reviewed nor approved by the Veterinary Drugs Directorate or the Canadian Food Inspection Agency, responsibility for residue violations rests with the attending veterinarian.

To review this request in CgFARAD:
https://farad.usask.ca/cgfarad/vet/viewRequest?id=23241&langen