FIP treatment with oral formulations of GS-441524

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The initial field testing of GS-441524 for FIP treatment involved subcutaneous injection. This route of administration was based on prior pharmacokinetic (PK) studies done on laboratory cats. Intravenous and subcutaneous routes of injection yielded similar high blood levels that were sustained at virus inhibitory concentrations for over 24 hours. Oral administration was also found to provide blood levels, peaking at 2 hours, but reaching only about 40% peak levels of subcutaneous and intravenous routes (Pedersen NC, unpublished data, 2018). However, dogs which have a longer intestinal tract evolved for omnivorous diets, can absorb up to 85% of GS441524 by the oral route [1, 5]. Dogs have often been used as surrogates for humans in oral absorption studies, so oral absorption in humans is also likely to be higher than in cats.

Chinese suppliers of GS-441524 copied the diluent, drug concentration, subcutaneous route of administration that were used in the initial published field trial. The first company to offer GS441524 on the unapproved market was Mutian. Mutian was also the first to research and offer an oral form of the drug. Mutian researchers found that effective blood levels of GS-441524 could be achieved by merely increasing the concentration of the drug in their oral preparations. Other companies (e.g., Aura, Lucky) subsequently offered their own versions of orally administered GS-441524. However, ss of September 2021, Mutian no longer lists oral GS preparations (of any form) on their website. Currently, Aura, Lucky, and Capella are the most used oral forms of GS441524 in the US.

Current brands of capsules/tablets are sold as supplements and their labels list several common innocuous chemical compounds and medicinal herbs and do not list GS-441524 as one of the ingredients. This is probably done to avoid scrutiny by customs. Regardless of the list of ingredients, the active component in all oral products is GS-441524. The exact concentration of GS-441524 in the various oral products is kept secret by the sellers, but it is obviously higher (1.5 – 2 times?) than would be needed if the drug were given by the subcutaneous route.

We were initially critical of the oral route for two reasons. First, oral forms were more wasteful of what was initially a rare and expensive resource. Second, published research on oral absorption of nucleosides (GS-441524 is a nucleoside) document a concentration limit or ceiling for oral absorption [2-5]. Results with EIDD-1931, a related nucleoside showed bioavailability drop from 56 to 36% as the oral dosage increased [6]. This limitation would make it theoretically difficult to achieve the extremely high blood concentrations required to treat certain forms of FIP (e.g., neurological) and/or to overcome the problem of acquired drug resistance. Oral bioavailability can also be significantly decreased by certain substances in the diet, and cat owners are notorious for using a large range of dietary supplements, some of which could negatively affect the treatment.

It appears that more and more owners and veterinarians are embracing oral GS-441524 for part or all the treatment. The cost of oral GS-441524 preparations has steadily declined over the last

two years and quality increased. The problem of injection site reactions, coupled with more effective oral preparations of GS-441524, have encouraged the oral treatment and increasing numbers of cats are being cured with oral drug either for part or all their treatment.

Formulation and Labeling

Most established oral preparations are smaller tablets, which are easier to administer than larger capsules. Newer preparations such as Sweeper offer a soluble film form of GS-441524 to avoid difficulties in "pilling" some cats.

The actual amount of GS-441524 in a tablet/capsule and seller recommended dosage for oral medications varies greatly by form of FIP, the seller, and experience of owner and FIP treatment groups. Therefore, the actual amount (mg) of GS-441524 in a pill or capsule is not usually given. In lieu of an actual amount of GS-441524 in a pill or capsule, seller dosages are often based on the number of pills needed per kg of weight, e.g., 1 pill/kg *per os* (P0) every (q)24 hour (h) for cats with wet or dry FIP and no ocular or neurological involvement. The amount of GS-41524 in such one such pill given PO q24h is equivalent to the 4-6 mg/kg SC q24h dosage, but the actual amount of GS in the one pill may be twice the amount as in 1 ml of injectable GS to compensate for decreased bioavailability by the PO route.

In addition, one supplier (Aura/Spark) has tablets labeled for administration q12h and another for q24h dosing. The 1 tablet/kg PO q12 h tablet contains half as much GS-441524 (presumably 4-6 mg) as a 1 tablet/kg PO q24h tablet (presumably 10 mg) - the rationale being that the q12h dosing will prevent a fall-off in the blood concentration prior to 24h. However, effective blood levels after a single PO or SC dose are both sustained for 24h or more. At dosages equivalent to 10-15 mg/kg SC q24h there may be another advantage in q8h or q12h dosing over q24h, as it may help to circumvent the absorption ceiling. Therefore, dividing PO doses into q8h or q12h increments is often used for cats with dosages equivalent to 10-15 mg/kg SC q24h or higher.

Dosing

GS-441524 for cats wet or dry FIP and no neurological or ocular signs the recommended starting dosage is 4-6 mg/kg SC q24h. The injection dosage for cats with ocular disease is 8 mg/kg SC q24h and cats with neurological disease 10 mg/kg SC q24h. If a cat starts treatment for wet FIP and then develops ocular disease, the dosage is immediately increased to 8 mg/kg SC q24h, and if neurological signs develop it is increased to 10 mg/kg SC q24h. Failure to cure FIP at dosages higher than 15 mg/kg SC q24h are indicative of drug resistance. The PO dosages equivalent to 4-6, 8 and 10 mg/kg SC q24h, are 10, 16, and 20 mg/kg PO q24h. (Note: some oral preparations are labeled as SC equivalents but actually contain up to twice the labelled mg of GS) The recommended treatment is 12 weeks, with dosage increases when deemed necessary. However, it is recognized that some cats can be cured in 6 weeks with either form of GS-441524, more in 8-10 weeks, and almost all in 12 weeks. Young cats with abdominal wet FIP tend to respond the fastest, cats with dry FIP slower, and cats with neurological FIP the slowest. Therefore, the "universal" recommendation is to treat every cat with FIP, regardless of form, for a minimum of 12 weeks. The daily PO dosage can be divided q12h, which may be advantageous when treating

at the higher dosages in order to avoid the absorption ceiling. SC and PO treatments may alternate q12h in order to avoid large injection volumes.

Oral GS dosing is less exact than with injections. Tablets are difficult to divide, as they tend to crumble, so cutting in half is often the best that can be done. When a calculated PO dosage falls between the labeled tablet dosage it is recommended to always round up to the nearest half tablet.

Administration

All oral brands have similar instructions for administering capsules or tablets. Fasting for half an hour before and after giving the medication is generally recommended. A small amount of treat may encourage cats to take them, and many cats will consume them when put on a plate with a coating treat (e.g., Churu).

Cost

The price of oral GS has significantly decreased in the last year. Nevertheless, the relative cost of oral GS-441524 is 20-40% higher (depending on the supplier) than their injectable version.

Factors affecting oral vs. injection

Cats currently experiencing vomiting/regurgitation and diarrhea are generally considered poor candidates for oral GS-441524. Therefore, cats with serious gastro-intestinal disease are often started on injections, at least until the problems are resolved. Most people, especially in the past, have started with injectable GS-441524. The injection form is cheaper, and the dosage is more accurately managed. Absorption of GS-441524 is also more reliable by the subcutaneous than oral route, which is often a critical factor in the initial treatment of cats that are severely ill and unstable at the onset. Whether or not a cat continues injectable GS-441524 is often conditioned on the ability of the owner to do injections in the most effective manner, the willingness of the cat to adapt to the injection pain, and the occurrence of injection site sores. Oral medication is often a welcome respite for owner and feline patient in such situations. Some substances given PO may interfere with GS-441524 absorption. Therefore, the inclusion of other drugs and dietary supplements should be avoided if not essential to the FIP treatment.

Comparison of treatment success between injectable and oral GS-441524

Assuming that dosages are accurately calculated, and dosing properly done, the success rate with oral GS-441524 currently mirrors that of injectable formulations. Nevertheless, differences in responses between oral and injectable GS-441524 have been reported. A small number of cats have not responded well to oral GS-441524 as initial treatment or have led to relapses when replacing injections. Alternatively, switching cats to oral GS-441524 at an equivalent dosage has resolved disease that was not responding well to injections. It is difficult to assign these dramatic differences in response to the drug form, as GS-441524 given by subcutaneous or oral routes ends up in the bloodstream and ultimately in the tissues. It is more likely that it is due to the brands of injectable or oral GS-441524 used prior to such switching were not good or that there

were issues with absorption or administration. Indeed, there have been many cases when switching to a different oral or injectable brand immediately improved the response.

It was assumed that only the injectable form of GS-441524 could achieve the extremely high blood and cerebrospinal fluid levels necessary to effectively treat neurological disease, especially in situations where the virus has evolved variable degrees of drug resistance. However, oral brands such as Aura/Lucky have been quite effective on many cats with neurological FIP. This has also included some cats who were failing to respond to an extremely high dosage of injectable GS441524. More and more cats with neurological FIP are being cured with entirely oral treatment. This is either due to more experience with oral treatment in difficult cases of FIP, or equally likely, to the increased quality of oral formulations.

Summary of currently available brands of oral GS-441524

Note: Labeling and GS content reflects the information given by the supplier and have not been independently verified.

Mutian - This is the original and most well-known brand of oral GS-441524. It has been sold in several different forms, including multiple forms of tablets and capsules. In early 2021 Mutian switched to a tablet form, labeled as 200 mg or 50 mg of "Mutian" or "Xraphconn" - these deliver an equivalent SC dose of 10 and 2.5 mg of GS-441524 respectively. The tablets are considerably larger (8.5 mm diameter) than those of other suppliers. More recently a new capsule formulation has been sporadically available. As of September 2021, Mutian's website no longer offers the PO option. For all Mutian oral forms, dosing is specified by the supplier as: 100 mg/kg "Mutian" for wet/dry FIP, 150 mg/kg Mutian for ocular FIP, and 200 mg/kg for neurological FIP.

Aura/Spark- Aura is a long-established brand and is sold in tablets that are for administration every 12 or 24 hours. They are marketed in q12h and q24h versions, however there is no formulation difference (i.e., extended release, etc.) between the two versions. The actual amount of GS-441524 in each tablet is not given, but the labeling and effective dose is as follows:

Labeled As:	Equivalent injectable dose	Dosing Instructions
Aura 12h -1 kg	approx. 2.5 mg/kg	Wet/Dry: one tablet per kg twice daily Ocular: 1.5 tablets per kg twice daily Neurological: 2 tablets per kg twice daily
Aura 24h – 1 kg	approx. 5 mg/kg	Wet/Dry: one tablet per kg daily Ocular: 1.5 tablets per kg daily Neurological: 2 tablets per kg daily
Aura 12h – 3 kg	approx. 7.5 mg/kg	Wet/Dry: one tablet per 3 kg twice daily Ocular: 1.5 tablets per 3 kg twice daily Neurological: 2 tablets per 3 kg twice daily

Aura 24h – 2 kg	approx. 10 mg/kg	Wet/Dry: one tablet per 2 kg twice daily Ocular: 1.5 tablets per 2 kg twice daily Neurological: 2 tablets per 2 kg twice daily

Equivalent oral dosage for >10 mg/kg daily of injectable GS are increased proportionally. Pills can be combined regardless of the 12/24h labeling using the effective injectable dose – for example a 2.5 kg cat with wet FIP could take one 24h – 2 kg tablet and one 12h -1 kg daily.

Lucky - Lucky pills are labeled as 24h – 1kg (5-6 mg/kg SC equivalent dose) or 24h – 2kg (approx. 10-12 mg/kg SC equivalent dose) and are said to have an identical formulation to the comparable Aura tablet, although in a different shape. For FIP cases without ocular or neurological symptoms, you would give one 1kg pill per day per kg of cat weight or one 2kg pill per each 2 kg, rounded up to nearest half pill. Multiply the number of pills per day by 1.5 for ocular or by 2 for neurological forms.

Labeled As:	Equivalent injectable dose	Wet/dry dosing instructions (dosing is doubled for neuro/ocular)
Lucky 24h – 1 kg	approx. 5-6 mg	one tablet per kg daily
Lucky 24h – 2 kg	approx. 10-12 mg	one tablet per 2 kg daily

Capella – Capella makes two sizes of tablets, a 1kg (5-6 mg SC equivalent dose) and 2 kg (10-12 mg SC equivalent dose). For FIP cases without ocular or neurological symptoms, you would give one 1kg pill per day per kg of cat weight or one 2kg pill per each 2 kg and round up to nearest half pill. Multiply the number of pills per day by 1.5 for ocular or by 2 for neurological forms.

Kitty Care – This is another low-cost brand that now offers both injection and oral formulations of GS-441524. Each tablet is presumed to contain the equivalent of 6 mg of SC administered GS-441524.

Hero 16 -This is a well-recognized brand that comes in easy to use and scored tablets labelled to be given at one tablet per 2 kg of weight, like the Capella 2kg tablet. Each tablet presumably contains 16 mg of GS-441524.

Rainman - This brand is popular in China and appears to have a good reputation in countries where it is used. It is sold in 1 kg and 2 kg tablets presumed to contain the equivalent of 5-6 mg and 10-12 mg of SC GS-441524 respectively.

Mary- Mary is sold in capsules presumably containing the equivalent of 6 mg of SC GS-441524

Additional brands- Panda, Pany, Sweeper, Sweeper film

Referenced studies on GI absorption of nucleosides related to GS-441524 and GS-441524

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After oral administration EIDD-1931 is quickly absorbed as evidenced by plasma T-max-values ranging between 0.5 and 1.0 h.Exposures are high (C-ma-xvalues range between 30 and 40μM) and are dose dependent, but significantly less than dose proportional. The observation of decreasing bioavailability with increasing dose may indicate capacity limited absorption, a phenomenon that has been reported for other nucleosides (de Miranda et al., 1981). EIDD-1931, like most endogenous nucleosides and xenobiotic nucleoside analogs, is a highly polar, hydrophilic molecule (cLog P =−2.2) and therefore likely to require functional transporters to cross cell membranes. This dependence would explain the capacity limited uptake seen in the pharmacokinetic studies done using the CD-1 mice. Earlier reports also indicated that nucleoside uptake into mouse intestinal epithelial cells is primarily mediated by sodium dependent concentrative nucleoside transporters (Cass et al., 1999; Vijayalakshmi and Belt, 1988).

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