Treatment with oral formulations of GS-441524

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Updated September 24, 2021

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levels, but somewhat delayed and only at about 40% peak levels of subcutaneous and intravenous routes (Pedersen NC, unpublished data, 2018).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. Therefore, the subcutaneous route was chosen for field testing in cats based on ease of administration and resulting blood levels.

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. Currently, Mutian, Aura and Lucky brands 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 several times higher 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]. 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. Newer information obtained from field use of the oral forms of GS-441524 of Mutian and Aura brands, indicate that this problem

may not be as serious as first believed as most forms of FIP respond equally well whether given pills or injections.

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. Steadily increasing numbers of cats are being treated with oral drug either for part or all of the treatment.

Formulation and Dosing

Suppliers of oral GS-441524 do not list the amount of active drug in their tablets or capsules. Some suppliers also provide pills with a higher concentration of GS-441524 for use in cats with ocular and neurological FIP to limit pills that must be given at one time. In addition, one supplier (Aura) has tablets labeled for administration every 12 hour (h) and yet another for every 24h. The 1 tablet/kg q12 h tablet contains one half as much GS-441524 as a 1 tablet/kg q24h tablet - the rationale being that the q12h dosing would prevent a fall-off in the blood concentration prior to 24h. This belief is inconsistent with the original pharmacokinetic data, which shows blood levels to be sustained at effective levels for at least 24h. Regardless, both the q12h and q24h Aura pills seem equally effective when given according to instructions, although most owners prefer dosing once a day.

All established oral preparations, except for Mutian, are tablets. Tablets are all quite small, while the Mutian capsule is considerably larger. This makes the tablets easier to administer. Mutian capsules are also liquid rather than powder filled and if cats bite down on them the contents may be lost. Adverse reactions have been reported for cats who rupture the capsules. Newer preparations such as Sweeper offer a soluble film form of GS-441524 to avoid difficulties in "pilling" some cats.

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.

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 dosge 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 the brands of injectable or oral GS-441524 used prior to such switching were not good. 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 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

Information on oral forms of GS-441524 is sparse regarding treatment outcomes but there are a growing number of brands that are available, attesting to the popularity of this form of treatment. Information on these brands is updated at the FIP Warrior CZ/SK website [7]. This website also contains excellent information on FIP and GS-441524 treatment.

The recommended dosages vary from brand to brand and do not always correspond to the equivalent dosage for injectable GS-441524. GS-441424 is absorbed from the intestine with about 50% efficiency as subcutaneous or intravenous administration. There is also a theoretical upward limit to absorption through the intestine, which would also limit the blood levels that can be obtained. Given the absorption limitations of oral GS-441524, one would expect the oral dosage to be around twice that of injections. However, most oral brands are recommended at an equivalent dosage to injections. This suggests that the actual concentration of GS-441524 in oral

preparations may be higher than for injectable GS-441524 as listed in the tables below and as provided by the FIP Warrior CZ/SK website.

Mutian capsules - This is the original and most well-known brand of oral GS-441524 and is sold in capsules containing 2.5, 5 and 10 mg of GS-441524.

Form of FIP	Recommended Dosage	Tablets q24h (10 mg tablet)
Wet FIP	6 mg/kg	0.6 tablet/kg
Dry FIP	8 mg/kg	0.8 tablet/kg
Ocular FIP	10 mg/kg	1.0 tablet/kg
Neurological FIP	12 mg/kg	1.2 tablet/kg

Aura- Aura is a long-established brand and is sold in tablets that are for administration ever 12 or 24 hours. The 12-hour pill is said to increase the bioavailability compared with 24-hour pilling. The therapeutic effect of q12 hour treatment is also thought to last a little longer than for q24 hour treatment. Treatment every 12 hours is also used in cases where very high blood levels are needed, such as difficult cases of neurological FIP. The actual amount of GS-441524 in each tablet is not given, but it appears that the one q12 hour tablet is equivalent to 2.5-3 mg/kg daily of the injection form of GS-441524, while one q24h tablet/kg daily is equivalent to 5-6 mg/kg daily injectable GS-441524.

Spark – Spark tablets contain 2.5 mg of GS-441524

Form of FIP	Recommended Dosage	Tablets q24h
Wet FIP	6 mg/kg	2 tablets/kg
Dry FIP	8 mg/kg	3.25 tablets/kg
Ocular FIP	10 mg/kg	4 tablets/kg
Neurological FIP	12 mg/kg	5 tablets/kg

Lucky - Lucky pills are sold in 6 and 12 mg sizes and are said to have an identical formulation to the comparable Aura tablet, although in a different shape.

Form of FIP	Recommended Dosage	Tablets q24h (12 mg tablet)
Wet FIP	6 mg/kg	0.50 tablet/kg
Dry FIP	8 mg/kg	0.67 tablet/kg
Ocular FIP	10 mg/kg	0.83 tablet/kg
Neurological FIP	12 mg/kg	1.00 tablet/kg

Capella – Capella has only recently offered an oral version of GS-441524. This brand's injectable product has a solid reputation and the oral form is also trusted and growing in popularity.

Kitty Care – This is another low-cost brand that now offers both injection and oral formulations of GS-441524.. Each tablet contains 6 mg of GS-441524.

Form of FIP	Recommended Dosage	Tablets q24h

Wet FIP	6 mg/kg	1 tablets/kg
Dry FIP	8 mg/kg	1.33 tablets/kg
Ocular FIP	10 mg/kg	1.67 tablets/kg
Neurological FIP	12 mg/kg	2 tablets/kg

Hero 16 -This is a well-recognized brand that comes in easy to use and scored tablets containing 16 mg of GS-441524. The oral dosage, with equivalent injectable dosage, is as follows:

	Recommended	
Form of FIP	**Dosage**	**Tablets q24h**
Wet FIP	6 mg/kg	0.38 tablet/kg
Dry FIP	8 mg/kg	0.50 tablet/kg
Ocular FIP	10 mg/kg	0.63 tablet/kg
Neurological FIP	12 mg/kg	0.75 tablet/kg

Rainman - This brand is popular in China and appears to have a good reputation in countries where it is used. It is sold in tablets containing 10 mg of GS-441524.

	Recommended	
Form of FIP	**Dosage**	**Tablets q24h**
Wet FIP	6 mg/kg	0.6 tablet/kg
Dry FIP	8 mg/kg	0.8 tablet/kg
Ocular FIP	10 mg/kg	1.0 tablet/kg
Neurological FIP	12 mg/kg	1.2 tablet/kg

Mary- Mary is sold in capsules containing 6 mg of GS-441524

	Recommended	
Form of FIP	**Dosage**	**Tablets q24h**
Wet FIP	6 mg/kg	1.00 tablet/kg
Dry FIP	8 mg/kg	1.33 tablet/kg
Ocular FIP	10 mg/kg	1.67 tablet/kg
Neurological FIP	12 mg/kg	2.00 tablet/kg

Additional brands- Panda 6 mg, Pany 5 mg, Sweeper 6 mg, Sweeper film 6mg

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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