

An update on treatment of FIP in the UK

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The above specialists have come together to run the 'FIP advice' email address (fipadvice@gmail.com) answering queries on the new treatments on a voluntary basis and disseminating information to vets and vet nurses in the UK. So far, they have answered over 700 emails on the advice line

Introduction

The UK has had nucleoside analogue antivirals legally available to vets for the treatment of FIP in cats since August 2021. In that time many cats and kittens have been treated successfully. However, our knowledge is constantly evolving as are our recommended protocols. The antivirals available are from a special manufacturer in the UK and comprise oral GS-441524 (50mg tablets) and injectable remdesivir (Figures 1 and 2). This article has been created to support practitioners in the use of these antivirals in the management of FIP. It is worth remembering that treatment needs to be tailored to the individual cat based on response, compliance and client finances. An information sheet on FIP is available for cat owners from International Cat Care describing treatments <https://icatcare.org/app/uploads/2022/05/FIP-pet-owner-brochure-FINAL-V2-1.pdf>

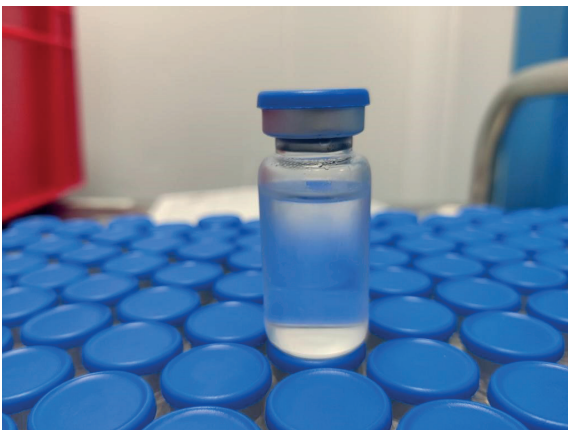


Figure 1: Remdesivir for intravenous or subcutaneous injection

Treatment protocols (updated January 2023)

Initially, when only injectable remdesivir was available, protocols were based on using only remdesivir for 12 weeks. With the subsequent availability of oral GS-441524, protocols evolved to include an initial period of injectable remdesivir (from a few days to 2 weeks) before a switch to oral GS-441524 to complete

the 12-week course. Although injectable remdesivir is still useful for the treatment of extremely dehydrated sick cats who cannot tolerate receiving oral GS-441524, treatment courses comprising only oral GS-441524 for the full 12-week course are now being increasingly used with success.

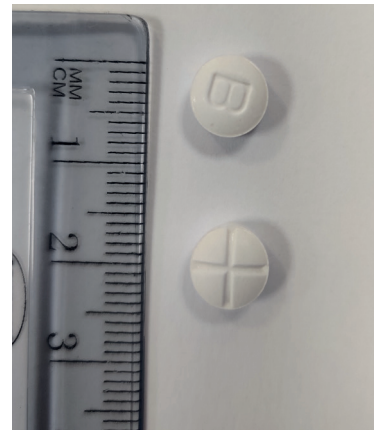


Figure 2: Oral GS-441524 tablets

Reasons for the use of oral GS-441524 over injectable remdesivir include:

- Better compliance with oral medications over injectables due to ease of administration - pain can occur with subcutaneous remdesivir
- Cost of treatment; as oral GS-441524 is cheaper than remdesivir to purchase, and there are additional costs of giving injections in the cost of needles, syringes, sharps disposal, wastage etc.
- Early recognition and treatment of FIP cases well enough to tolerate oral medication
- Client and cat preferences for route of administration
- When a cat has been started on injectable remdesivir but can be switched to oral GS-441524, this change can be made directly; remdesivir is given one day and GS tablets the next day
- No apparent difference in success has been seen between cats treated with only oral GS-441524 to those given a combination of remdesivir and GS-441524 or remdesivir only

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Suggested dosages, benefits and limitations of the drugs are provided below. Recommended drug dosages (Table 1) depend upon clinical presentation – i.e. whether there is an effusion present or not and whether there is ocular and/or neurological involvement – this is due to variation in the tissue penetration of the drugs. Where there is doubt, use of the higher dosage is preferable.

Please note that these dosages of oral GS-441524 are higher than quoted in some publications – this is because these publications have used illegal preparations of so-called GS-441524 in which the amount of active agent given to the cats was not confirmed and was likely to be higher than suggested by the manufacturers. The dosages provided below are based on experience using a reputable oral

preparation of known GS-441524 content. Thus, extrapolation is not applicable to other oral preparations where the active component and/or its concentration are not known or given by the manufacturer.

Oral GS-441524 only treatment protocol:

Cat is deemed well enough to receive oral medications

An oral GS-441524 treatment only protocol is recommended if the cat can tolerate oral medications and/or injections are not tolerated and/or financial constraints exist:

1. Once (or twice if very high neurological dosage needed) daily oral GS-441524 (see Table 1 for dosages) continued until at least day 84 (i.e. full 12-week treatment course).

Table 1: Summary of dosage recommendations for remdesivir and GS-441524

| Clinical presentation | GS-441524 – oral | Remdesivir – by intravenous or subcutaneous injection |
|--|--|---|
| Cats with effusions and without ocular or neurological signs | 10-12 mg/kg once daily | 10 mg/kg once daily |
| No effusion and without ocular or neurological signs | 10-12 mg/kg once daily | 12 mg/kg once daily |
| Ocular signs present (effusive and non-effusive) | 15 mg/kg once daily | 15 mg/kg once daily |
| Neurological signs present (effusive and non-effusive) | 10 mg/kg twice daily (i.e. 20 mg/kg/day given as a divided dose q 12 hours) | 20 mg/kg once daily |

NOTE ON WEIGHING CATS: It is very important to weigh cats weekly during treatment, using accurate scales – weight gain and/or growth in kittens will occur with successful treatment necessitating an increase in dose to ensure that the dosage of antiviral administered is still appropriate for the type of FIP being treated as in Table 1.

Combined injectable & oral treatment protocols:

Cat has very severe disease (e.g. anorexic, dehydrated, cat usually will be hospitalised to allow for appropriate supportive care to be given)

1. Initial treatment can be given with once daily **intravenous remdesivir** (Table 1) for a few days. This provides a loading dose of the drug in cats that

Potential adverse effects of remdesivir

Remdesivir seems well tolerated. However, the following adverse effects have been reported:

- Transient local discomfort/stinging on injection (see later on prevention);
- Development/worsening of a pleural effusion (not always proteinaceous) in the first 48 hours of treatment, sometimes requiring drainage;
- Cats may seem depressed or nauseated for a few hours after IV administration;
- Increases in ALT enzyme activity have been reported (unclear if due to underlying FIP disease or an adverse drug effect) but seem to resolve when treatment is stopped;
- Mild peripheral eosinophilia has been reported.

cannot receive oral medications, are too dehydrated to receive subcutaneous injections, or the gut is involved with FIP pathology/oedema such that oral drugs may not be well absorbed. On each day, dilute the remdesivir dose required to a total volume of 10ml with saline and administer slowly over around 30 minutes manually or with a syringe driver.

2. Can change to once daily **subcutaneous remdesivir** at the same dosage (Table 1) once cat is hydrated but still not able to accept oral medications
3. Remdesivir can be given for the number of days that medication using injectables is needed. More recently this has comprised just a few days early in treatment e.g. 1st 2-3 days of treatment.
4. Change to once daily (or twice daily if very high neurological dosage is needed) **oral GS-441524** (Table 1) as soon as oral medication can be tolerated and **continue until at least day 84**.

However, injectable remdesivir (usually switching from intravenous to subcutaneous administration when cat is rehydrated) can be given for the full 84 day treatment course, if this is the only antiviral available and/or oral medication is not possible.

Less severe disease (normal hydration, eating)

1. If an injectable is required but the cat has less severe disease, treatment can be started with once daily **subcutaneous remdesivir** (Table 1) and continued for the duration that injectables are needed.

Subcutaneous remdesivir is given as the formulation in the vial – no dilution is required.

2. Change to once daily (or twice daily if very high neurological dosage is needed) **oral GS-441524** (Table 1) as soon as oral medication can be tolerated and continue **until at least day 84**.

Options for cost limited clients – please note that treatment must be given using the recommended formulations and dosages for the full 84 days to increase likelihood of full clinical resolution. Only take the options below if absolutely necessary, as relapse may occur, which then requires longer treatment, increasing costs;

- Give oral GS-441524 or injectable remdesivir for as many days as the owner can afford before switching to oral mefloquine 62.5 mg 2-3 times weekly (large cat, give 3 times a week) or 20-25 mgs orally once daily if reformulation of tablets into 20 or 25 mg tablets is possible e.g. PCCA Ltd. for completion of an 84-day treatment protocol; mefloquine is cheaper than GS-441524 and remdesivir but more research is needed to judge its effectiveness in this situation;
- If an increase in GS-441524 or remdesivir dosage is required (e.g. due to neurological disease appearing during treatment) but cannot be afforded, mefloquine treatment can be added as adjunct treatment, as this is cheaper, although more research is needed to judge the effect of this combination;
- Feline interferon omega or polyprenyl immunostimulant (VetImmune™) have been used in the period following the end of treatment with GS-441524 or remdesivir to try to support the cat's immune system during this transition phase and

prevent relapse, but further research is needed on this combination to judge if it is necessary. Currently there is no evidence to suggest they are needed.

- Mefloquine has sometimes been used in the period following the end of treatment with GS-441524 or remdesivir to try and reduce the chances of relapse occurring; further research is needed to judge if it is necessary. Currently there is no evidence to suggest it is needed and many cats do well after finishing treatment if they fully recovered during treatment.
- As ALT can rise during treatment with GS-441524 or remdesivir, some suggest the use of hepatoprotectants (e.g. SAME) during antiviral treatment but further research is needed on this combination to judge if it is necessary. Currently there is no evidence to suggest it is needed.
- Limit tests for monitoring – see below.

Are oral treatments given with or without food?

- **GS-441524** is given on an empty stomach after an overnight fast for a morning dose or after a few hours fast for an evening dose, washing down with a little water. Food can be given 1 hour after treatment. GS-441524 can be given with a small treat or crushed into a small amount of lick-e-lix if this makes administration possible;
 - **Mefloquine** is given with food, otherwise vomiting often results.
- Do not forget to support clients giving oral medications, as this can also be challenging. Direct clients to the iCatCare website for information and videos:

<https://icatcare.org/advice/how-to-give-your-cat-a-tablet/>

What can I do to help the owners give the subcutaneous remdesivir?

Injection with remdesivir can cause transient local discomfort. If a switch to oral GS-441524 is not possible, the following may help reduce discomfort and improve compliance:

- Ensure owners use a new needle each time to withdraw the drug from the bottle (this will reduce the risk of bacterial contamination of the bottle, as well as alcohol swabbing the reusable seal top of the bottle before entry of the needle);
- Ensure owners change the needle after withdrawing the drug from the bottle and before injection (puncturing the reusable seal will blunt the needle);
- Needle size preference varies; some prefer a 21G needle to make injecting quicker, others find a finer 23G needle is better tolerated, so it may be worth trying both if problems arise;
- Rotate the injection sites;
- Have remdesivir at room temperature before administration;
- Oral gabapentin (50 to 100 mg per cat) may be helpful and/or transmucosal or subcutaneous buprenorphine given at least 30-60 mins before the remdesivir injection to induce mild sedation/analgesia;
- The area to be injected can also be clipped to help owners locate the appropriate site to inject and so that topical EMLA cream can be applied 40 mins before injection, although surface desensitisation may not help as it is usually the remdesivir under the skin that causes discomfort;
- Ensure the full dose of injection is administered at each time-point and encourage owners to report any mishaps as this may influence decisions if relapse occurs;
- Encourage owners to make the injection experience more positive by using treats (e.g. Lick-e-lix, Dreamies) around the time of injection, or stroking, brushing, or playing with the cat if they are less food motivated. Suggest owners spend time each day with their cat positively engaged to avoid any damage to cat-owner relationships that can reduce compliance.

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What should I expect during treatment?

- In the first 2-5 days you should see an improvement in demeanour, appetite, resolution of pyrexia and reduction in abdominal (Figure 3) or pleural fluid if an effusion is present (note that in some cases pleural fluid can transiently worsen in the first couple of days – if the cat is at home, advise owner to measure resting respiratory rate, plus respiratory effort) – effusion typically resolves by 2 weeks;
- If an effusion is still present at 2 weeks, consider increasing dosage (by 3-5 mg/mg if possible) to one that is greater than that being used e.g. increasing the dosage from that used for cats with effusions only;
- Serum albumin increases and globulin decreases (i.e. they normalise) over 1-3 weeks, but note that globulins can initially increase when a large volume effusion is absorbed;
- Lymphopenia and anaemia may take longer to resolve, up to 10 weeks, and a lymphocytosis can be seen as a result of treatment;
- Mild peripheral eosinophilia is a common finding and may be a favourable marker for disease resolution, as it is in COVID patients;
- Mild elevations of ALT and, less frequently, ALP may be documents during treatment and should resolve once treatment is completed;
- Lymph node size reduces over a few weeks;
- If progress is not as expected, consider reviewing the diagnosis (see below) and/or increasing dosage.

What do I need to monitor during treatment?

- Ideally, serum biochemistry and haematology after 2 weeks and then monthly; alpha-1 acid glycoprotein (AGP) may be useful to predict remission (by returning to normal if elevated before treatment)
- However, for cost limited clients, monitoring weight, demeanour, effusions (e.g. by in-house scanning but abdominal girth measurement is a crude alternative for abdominal effusions), neurological

signs and/or key biochemical abnormalities only (e.g. measuring just globulin, bilirubin and/or spinning microhaematocrit tube for PCV/Total Proteins/colour of plasma) is adequate;

- NB. ALT enzyme activity may increase – it is not clear if this is due to FIP pathology vs. drug reaction, and it is not usually a reason to stop therapy. It is not known if the addition of hepatoprotective therapy (e.g. SAME) is helpful in these cases and currently there is no evidence to suggest it is needed.
- Point-of-care ultrasonography (POCUS) to monitor for effusion resolution and/or lymph node size is useful if available and affordable.
- Note there is no benefit to measuring coronavirus antibodies during treatment..

If I am seeing a positive response to treatment, when do I stop treatment?

- Not before 84 days (12 weeks);
- Confirm resolution of previous abnormalities (clinically, POCUS, serum biochemistry [including albumin to globulin ratio of > 0.6 and normal AGP if possible], and haematology);
- Only stop treatment once cat has been normal (clinically and on serum biochemistry and haematology) for at least 2 weeks.

If I am seeing no response or a partial response to treatment, what do I do?

- Ensure that you are still confident that the cat has FIP – review diagnosis, look for additional pathology, consider repeat sampling (e.g. external laboratory analysis of any fluid; cytology or biopsy of lymph nodes), AGP;
- If biochemical abnormalities (hyperglobulinaemia in particular) remain present after 6-8 weeks, then increase dose as for relapse (below);

What do I monitor after treatment?

- Advise the owner to monitor the cat closely for any clinical relapse – this monitoring should continue for 12 weeks after completion of treatment;

Neutering, parasiticides & vaccination during or after treatment for FIP

- Neutering is ideally performed a month after treatment is completed if the cat has responded well. However, if leaving the cat unneutered is causing stress e.g. attempts to escape or distress when queens are on heat, neutering during therapy may be preferred, ideally when the cat is doing well on treatment with at least another 4 weeks' of treatment remaining. Some measure AGP to confirm it is normal before neutering;
- There is no contraindication to routine worming and flea treatment for cats on GS-441524 or remdesivir;
- No information is available on vaccination of cats receiving treatment for FIP although analysis of treated cases suggests that cats can be safely vaccinated after or during successful treatment without causing relapse. Vaccines should be administered as is normally recommended for the cat depending on its environment and risk (see WSAVA Vaccination Guidelines for general guidelines on vaccination). If urgent vaccination is required whilst the cat is being treated, due to risk of infectious disease, vaccines can be given if the cat is well as vaccination is still likely to be protective. If only two vaccines have been given, consider providing a third dose of vaccine after completion of FIP treatment;
- If veterinary visits and procedures are necessary, clinic stays should be minimised, and Cat Friendly Clinic protocols and handling implemented to reduce stress to the cat.

- Ideally, repeat serum biochemistry and haematology two weeks and one month after stopping treatment (to detect any changes that could suggest early relapse);
- Note that relapse can occur with clinical signs but without any significant biochemical/haematological abnormalities.

In the event of relapse

e.g. recurrence of effusion, pyrexia, development of ocular or neurological signs, or return of hyperglobulinaemia:

- Ensure that you are still confident that the cat has FIP – review diagnosis, look for additional pathology, consider repeat sampling (e.g. external laboratory analysis of any fluid; cytology or biopsy of lymph nodes), AGP;
- If relapse occurs during treatment – increase dosage of GS-441524 or remdesivir by 3-5 mg/kg per day and monitor as above, ensuring treatment is not stopped before the cat has been normal for at least 2 weeks. The increased dosage used will depend on the dosage the cat is on at the time of the relapse, the nature of the relapse and finances but can be up to that recommended for neurological FIP (see earlier);
- If relapse occurs after completion of treatment – restart treatment with GS-441524 or remdesivir at a higher dosage (3-5 mg/kg per day higher than used previously) and treat for another 12 weeks. The increased dosage used will depend on the dosage the cat is on at the time of the relapse and the nature of the relapse, but can be up to that recommended for neurological FIP (see Table 1);
- If it is not possible to increase the dosage of GS-441524 or remdesivir (e.g. the highest neurological dosage is already in use), consider adding in mefloquine as an adjunct treatment (see above).

Adjunctive treatments

- If the cat is on prednisolone treatment, this should be stopped whilst giving GS-441524 or remdesivir, unless it is required for short term management of specific immune-mediated disease arising as a result of FIP e.g. haemolytic anaemia;
- Supportive therapies such as antiemetics, appetite stimulants, fluid therapy and analgesics can be given with GS-441524 or remdesivir as required.

Trial treatment with GS-441524 or remdesivir?

Now that effective antivirals are available for the treatment of FIP, they can be used as trial treatments in cases in which FIP is highly suspected rather than confirmed. Although confirmation of a diagnosis of FIP is always preferable, the costs and invasive nature of some diagnostics (e.g. to collect biopsies) mean that trial treatment is being increasingly used in the field, especially as treatment should be started as soon as possible.

Potential future updates

We are constantly learning about treatment with these drugs and advice may change in time. Other agents, e.g. protease inhibitors (e.g. GC374) and other nucleoside analogues (e.g. Molnupiravir or the related EIDD-1931) have also been trialled in cats, but are not commercially available at this time. How these agents and other immunomodulatory agents (e.g. polyphenyl immunostimulant, interferon omega) will fit into a future protocols is unknown at this time.

Further reading

Tasker, S.; Addie, D.; Egberink, H.; Hartmann, K.; Hofmann-Lehmann, R.; Hosie, M. J.; Truyen, U.; Belak, S.; Boucraut-Baralon, C.; Frymus, T.; Lloret, A.; Marsilio, F.; Pennisi, M. G.; Thiry, E.; Mostl, K., ABCD Guidelines Feline Infectious Peritonitis – factsheets & diagnostic tools. 2022, accessed 16th January 2023. <https://www.abcdcatsvets.org/portfolio-item/factsheets-tools-for-feline-infectious-peritonitis-fip/>
Thayer, V.; Gogolski, S.; Felten, S.; Hartmann, K.; Kennedy, M.; Olah, G. A., 2022 AAEP/EveryCat Feline Infectious Peritonitis Diagnosis Guidelines. Journal of Feline Medicine and Surgery 2022, 24, (9), 905-933. <https://journals.sagepub.com/doi/full/10.1177/1098612X221118761>

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Thank you to Richard Malik & Sally Coggins for their advice and assistance in producing this document.

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graduated with first-class honours from The University of Sydney in 2007. Sally is currently investigating novel antiviral therapeutics for Feline Infectious Peritonitis and is currently conducting clinical trials open for national recruitment.



International Society of Feline Medicine

ISFM supports the creation of evidence-based documents to support vets with their clinical decision making and encourages the collaboration of experts to help cats. For further information on ISFM's work and becoming a member visit

<https://icatcare.org/veterinary/isfm/vet-membership/>.

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