IVERMECTIN

At 07/05/2021

1. Event: Initial submission

Action

Due diligence request ivermectin entry into CTAP database on 17th November 2020.

Sources

NICE inform due diligence: In w/c 09/11/20 the RAPID-C19 oversight group discussed Ivermectin and during those discussions it was suggested that this topic maybe one of interest for the CTAP team to look at and consider if it was suitable for entry into a UK trial. A summary of the discussion is below.

- A phase 3 double blinded randomised controlled trial shows statistically significant benefit in clinical improvement and viral clearance. There is also a claim of benefit in mortality, but statistical significance of the result is not reported. The Oversight Group have agreed to wait for publication and future trials to report before progressing this topic.

The briefing [3.2 RAPID C-19 RAP_Briefing Ivermectin v1.4] was attached.

Comment

N/A

Outcome

CTAP0113 Ivermectin is created in the database on 17th November 2020.

2. Event: Antivirals 10/12/2020

Action

CTAP due diligence team presented a brief on Ivermectin [Briefing Ivermectin 041120] to the antiviral sub-group.

Sources

The studies used to build this brief were:

1. Caly, L. (2020). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Research, 178, 104787. https://doi.org/10.1016/j.antiviral.2020.104787
2. Campbell, W. C., Burg, R. W., Fisher, M. H., & Dybas, R. A. (1984). The discovery of ivermectin and other avermectins. In P. S. Magee, G. K. Kohn, & J. J. Menn (Eds.), Pesticide Synthesis Through Rational Approaches (Vol. 255, pp. 5–20). American Chemical Society. https://doi.org/10.1021/bk-1984-0255.ch001
3. Campbell, William C. (2016). Lessons from the history of ivermectin and other antiparasitic agents. Annual Review of Animal Biosciences, 4(1), 1–14. https://doi.org/10.1146/annurev-animal-021815-111209
4. Camprubí, D., Almuedo-Riera, A., Martí-Soler, H., Soriano, A., Hurtado, J. C., Subirà, C., Grau-Pujol, B., Krolewiecki, A., & Muñoz, J. (2020). Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients. PLOS ONE, 15(11), e0242184. https://doi.org/10.1371/journal.pone.0242184
5. Chaccour, C., Abizanda, G., Irigoyen-Barrio, Á., Casellas, A., Aldaz, A., Martínez-Galán, F., Hammann, F., & Gil, A. G. (2020). Nebulized ivermectin for COVID-19 and other respiratory diseases, a proof of concept, dose-ranging study in rats. Scientific Reports, 10(1), 17073. https://doi.org/10.1038/s41598-020-74084-y

6. Chaccour, C., Hammann, F., Ramón-García, S., & Rabinovich, N. R. (2020). Ivermectin and covid-19: Keeping rigor in times of urgency. The American Journal of Tropical Medicine and Hygiene, 102(6), 1156–1157. https://doi.org/10.4269/ajtmh.20-0271
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8. de Castro Jr., C. G., Gregianin, L. J., & Burger, J. A. (2020). Continuous high-dose ivermectin appears to be safe in patients with acute myelogenous leukemia and could inform clinical repurposing for COVID-19 infection. Leukemia & Lymphoma, 61(10), 2536–2537. https://doi.org/10.1080/10428194.2020.1786559
9. DiNicolantonio, J. J., Barroso, J., & McCarty, M. (2020). Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19. Open Heart, 7(2). https://doi.org/10.1136/openhrt-2020-001350
10. Gorial, F. I., Mashhadani, S., Sayaly, H. M., Dakhil, B. D., AlMashhadani, M. M., Aljabory, A. M., Hassan M Abbas, Ghanim, M., & Rasheed, J. I. (2020). Effectiveness of ivermectin as add-on therapy in covid-19 management(Pilot trial). MedRxiv, 2020.07.07.20145979. https://doi.org/10.1101/2020.07.07.20145979
11. Guzzo, C. A., Furtek, C. I., Porras, A. G., Chen, C., Tipping, R., Clineschmidt, C. M., Sciberras, D. G., Hsieh, J. Y.-K., & Lasseter, K. C. (2002). Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. Journal of Clinical Pharmacology, 42(10), 1122–1133. https://doi.org/10.1177/009127002401382731
12. Jermain, B., Hanafin, P. O., Cao, Y., Lifschitz, A., Lanusse, C., & Rao, G. G. (2020). Development of a minimal physiologically-based pharmacokinetic model to simulate lung exposure in humans following oral administration of ivermectin for covid-19 drug repurposing. Journal of Pharmaceutical Sciences, 109(12), 3574–3578. https://doi.org/10.1016/j.xphs.2020.08.024
13. Padhy, B. M., Mohanty, R. R., Das, S., & Meher, B. R. (2020). Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis: Ivermectin in COVID-19: A meta-analysis. Journal of Pharmacy & Pharmaceutical Sciences, 23, 462–469. https://doi.org/10.18433/jpps31457
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16. Sia, D. K., Mensah, K. B., Opoku-Agyemang, T., Folitse, R. D., & Darko, D. O. (2020). Mechanisms of ivermectin-induced wound healing. BMC Veterinary Research, 16(1), 397. https://doi.org/10.1186/s12917-020-02612-z
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19. SmPC UK Ivermectin cream. (n.d.). https://www.medicines.org.uk/emc/product/6819
20. Specialist Pharmacy Service Ivermectin. (n.d.). https://www.sps.nhs.uk/medicines/ivermectin/
21. Szente Fonseca, S. N. (2020). Risk of hospitalization for Covid-19 outpatients treated with various drug regimens in Brazil: Comparative analysis. Travel Medicine and Infectious Disease, 38, 101906. https://doi.org/10.1016/j.tmaid.2020.101906
22. US FDA label Ivermectin. (n.d.). https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf
23. Ventre, E., Rozières, A., Lenief, V., Albert, F., Rossio, P., Laoubi, L., Dombrowicz, D., Staels, B., Ulmann, L., Julia, V., Vial, E., Jomard, A., Hacini-Rachinel, F., Nicolas, J.-F., & Vocanson, M. (2017). Topical ivermectin improves allergic skin inflammation. Allergy, 72(8), 1212–1221. https://doi.org/10.1111/all.13118
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25. WHO. (2019). WHO Model List of Essential Medicines - 21st List, 2019. https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06
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29. https://zbib.org/c5db298230034d3fa9b55be16a4c9d82

Comment

As noted in the record of decisions, the antiviral sub-group commented:

Ivermectin	• From a virological point of view the panel questioned claims that the major mechanism of antiviral action was via inhibition of shuttling of viral nuclear capsid protein into the nucleus because in contrast to the influenza virus SARS-CoV-2 doesn't replicate in the host cell nucleus. The evidence presented appeared to be an extrapolation from influenza data. • Additionally, the panel considered that the ability of ivermectin to inhibit syncytial formation may only	It was felt that further pre-clinical data was required on Ivermectin's antiviral properties before it could be reconsidered in that space. It was agreed that Ivermectin could still be considered for a Phase 2 or 3 trial as a potential immunomodulatory compound if the meta-analysis of the studies on-going show a mortality benefit and the subpanel recommended these

	be an in vitro phenomenon and as such it was difficult to identify a specific antiviral mechanism of action. • Even at the highest doses achievable in humans, plasma levels would likely be an order of magnitude lower than that required for an antiviral effect. However, it was noted that the compound did accumulate in the lung. • Although widely studied worldwide, the studied doses may be insufficient for antiviral activity in SARS-CoV-2. • On the positive side, ivermectin's safety profile would make it suitable for Phase 2 or 3 trials. • Data from an in vivo study of ivermectin in Syrian hamster[1] suggest no antiviral activity of ivermectin but support an anti-inflammatory activity in the lung of the hamster. • It was noted that there are ongoing unpublished meta-analyses [2], which track the clinical ivermectin trials in COVID-19. Some early analyses indicate mortality benefit across the COVID disease pathway. The antiviral data seems less clear. • The group considered that the currently available evidence support an anti-inflammatory effect, while the potential antiviral efficacy in COVID-19 was doubtful. Therefore, the compound should be referred to the immunomodulatory subgroup for their assessment. • It was noted that there was a potential interaction between ivermectin and dexamethasone through Cyp3A4. If it were to be used in later stages of the disease in a hospital context this would need to be managed via the dosing regimen and measuring	data be shared with the immunomodulatory subgroup. It was also suggested that the immunomodulatory subgroup may wish to consider if there was a role for selective serotonin reuptake inhibitors with sigma-1 receptor agonist activity (e.g. fluvoxamine), acting as anti-inflammatory agents in the community setting.

	concentrations. Other DDIs may also need to be carefully managed in earlier disease, particularly given polypharmacy in older patients.	

[1] https://www.biorxiv.org/content/10.1101/2020.11.21.392639v1

[2] https://ivmmeta.com

Outcome

The antiviral sub-group asked the due diligence team to update the Ivermectin briefing with the Syrian hamster study and meta-analysis prior to the Immune meeting.

Ivermectin was sent to the 16/12/2020 Immune meeting.

3. Event: Immune 16/12/2020

Action

CTAP due diligence team presented an updated brief on Ivermectin [Briefing Ivermectin update 141220] to the immune and anti-inflammatory sub-group.

Sources

The studies used to build this brief were those in the original brief, plus:

30. Ahmed, S., Karim, M. M., Ross, A. G., Hossain, M. S., Clemens, J. D., Sumiya, M. K., Phru, C. S., Rahman, M., Zaman, K., Somani, J., Yasmin, R., Hasnat, M. A., Kabir, A., Aziz, A. B., & Khan, W. A. (2020). A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. International Journal of Infectious Diseases, 0(0). https://doi.org/10.1016/j.ijid.2020.11.191
31. Andersson, U., Ottestad, W., & Tracey, K. J. (2020). Extracellular HMGB1: A therapeutic target in severe pulmonary inflammation including COVID-19? Molecular Medicine, 26(1), 42. https://doi.org/10.1186/s10020-020-00172-4
32. Kiki-Mvouaka, S., Ménez, C., Borin, C., Lyazrhi, F., Foucaud-Vignault, M., Dupuy, J., Collet, X., Alvinerie, M., & Lespine, A. (2010). Role of P-glycoprotein in the disposition of macrocyclic lactones: A comparison between ivermectin, eprinomectin, and moxidectin in mice. Drug Metabolism and Disposition: The Biological Fate of Chemicals, 38(4), 573–580. https://doi.org/10.1124/dmd.109.030700
33. McElvaney, O. J., McEvoy, N. L., McElvaney, O. F., Carroll, T. P., Murphy, M. P., Dunlea, D. M., Ní Choileáin, O., Clarke, J., O'Connor, E., Hogan, G., Ryan, D., Sulaiman, I., Gunaratnam, C., Branagan, P., O'Brien, M. E., Morgan, R. K., Costello, R. W., Hurley, K., Walsh, S., … McElvaney, N. G. (2020). Characterization of the inflammatory response to severe covid-19 illness. American Journal of Respiratory and Critical Care Medicine, 202(6), 812–821. https://doi.org/10.1164/rccm.202005-1583OC
34. Melo, G. D. de, Lazarini, F., Larrous, F., Feige, L., Kergoat, L., Marchio, A., Pineau, P., Lecuit, M., Lledo, P.-M., Changeux, J.-P., & Bourhy, H. (2020). Anti-COVID-19 efficacy of ivermectin in the golden hamster. BioRxiv, 2020.11.21.392639. https://doi.org/10.1101/2020.11.21.392639

35. https://zbib.org/01366e86332a4460ae6eca29482d8977

Comment

As noted in the record of decisions, the immune sub-group commented:

Ivermectin	This submission was referred from the antiviral sub-group. The group also questioned the biological rationale. Anti-inflammatory effects have so far been observed in a hamster model but have not yet been confirmed clinically. Current clinical evidence and meta-analyses are not considered sufficiently robust to recommend ivermectin.	Not currently recommended for any trials. UK-CTAP secretariat to monitor clinical trial landscape in case more robust evidence becomes available.

Outcome

The immune sub-group advised CTAP that it was not recommended but asked the UK-CTAP secretariat to monitor clinical trial landscape of ivermectin in case more robust evidence became available.

4. Event: CTAP 11/01/2021

Action

CTAP discussed the last antiviral and immune meetings.

Sources

N/A

Comment

As noted in the record of decisions, CTAP raised an observation on the immune 16/12 immune record of decisions. CTAP specifically requested that Ivermectin be revisited subsequent to meta-analysis of WHO data.

Outcome

CTAP awaited the WHO analysis.

5. Event: Prophylaxis 13/01/2021

Action

Both the original [Briefing Ivermectin 041120] and updated ivermectin brief [Briefing Ivermectin update 141220] and a supply and manufacturing document [ivermectin_Candidate_mfg] were presented to the first prophylaxis sub-group meeting.

Sources

See sources for Antiviral 10/12 and Immune 16/12 above.

Comment

As noted in the record of decisions, the prophylaxis sub-group commented:

Ivermectin	Concerns about the proposed antiviral efficacy: • Concern that mechanism of action is not relevant for SARS-CoV-2 infection: SARS-CoV-2 replication takes place in cytoplasm, not in the nucleus where ivermectin is expected to inhibit viral replications • In vivo data from a hamster model does not support antiviral efficacy • Highly unlikely that it can be a potent antiviral against SARS-CoV-2 in the current dosing considerations Proposed anti-inflammatory mechanisms are of lesser relevance in the prophylaxis setting. Current clinical evidence base for treatment in COVID-19 is limited and of very low quality. Evidence generation and meta-analyses are still ongoing.	The group agreed to deprioritize ivermectin for the prophylaxis setting due to concerns on mechanism of action, pharmacology and efficacy. UK-CTAP secretariat to continue monitoring the evidence base for future re-consideration.

Outcome

The prophylaxis sub-group advised CTAP and the Prophylaxis Oversight Group that ivermectin was not currently prioritised for prophylaxis trials but would stay under review.

6. Event: Additional information 19/01/2021

Action

TTF forwarded additional information.

Sources

36. [NL_H_3952_001_FinalSPC]
37. [HCV_ivermectin_info_draft1]:
38. Anon SUMMARY OF PRODUCT CHARACTERISTICS IVERMECTIN SUBSTIPHARM 3 mg, tablets https://mri.cts-mrp.eu/Human/Downloads/NL_H_3952_001_FinalSPC.pdf
39. Caly L., Druce J.D., Catton M.G., Jans D.A., Wagstaff K.M. (June 2020) The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antivir Res. 2020;178:104787.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7129059/
40. Cepelowicz Rajter, J. et al (October 2020) Use of Ivermectin Is Associated With Lower Mortality in Hospitalized PatientsWith Coronavirus Disease 2019The Ivermectin in COVID Nineteen Study https://www.sciencedirect.com/science/article/pii/S0012369220348984
41. Fink, D and A.G.Porras Pharmacokinetics of Ivermectin in Animals and Humans pp113-130 in Ivermectin & Abamectin William C. Campbell (ed) Springer Verlag 0-387-96944-6

42. Greene, B.M. K.R.Brown and H.R.Taylor Use of Ivermectin in Humans pp311.323 in Ivermectin & Abamectin William C. Campbell (ed) Springer Verlag 0-387-96944-6
43. Pandey S., et al (2020) Diabetes Metab Syndr. 2020 November-December; 14(6): 1921–1922. Published online 2020 Sep 28. Ivermectin in COVID-19: What do we know? https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7521351/
44. Sparavigno, A.C. (September 2020) Researchgate Ivermectin for Covid-19 https://www.researchgate.net/publication/342170742_Ivermectin_for_Covid-19

Comment

N/A

Outcome

The due diligence team are notified.

7. Event: Second submission

Action

A proposer submits ivermectin on 22nd January 2021.

Sources

N/A

Comment

N/A

Outcome

CTAP0212 ivermectin is created.

8. Event: CTAP 10/02/2021

Action

[Briefing Ivermectin update 141220], [Ivermectin update Feb21] and [Ivermectin meta-analysis Jan 9 DRAFT FOR REVIEW] were sent to the 10/02/2021 CTAP meeting.

Sources

N/A, see meta-analysis doc for their sources

Comment

As noted in the record of decisions, UK-CTAP commented:

Ivermectin	• The chair introduced the item highlighting the meta-analysis provided in the papers and asked the panel whether this analysis would cause them to review their recommendation not to prioritize Ivermectin. • The group noted the Merck statement on Ivermectin[i]. • The panel agreed that the meta-analysis supported the panels	• CONFIRMATION of the recommendation that Ivermectin is not currently prioritized for inclusion in UK Publicly Funded Trials

	original recommendation not to prioritise Ivermectin. • The panel expressed discomfort at any potential inclusion of Ivermectin into a UK publicly funded trial, reconfirming its view there was no plausible rationale for inclusion and noting there was an opportunity cost in terms of patient numbers that could be recruited into a trial with a more plausible expectation of efficacy. • The panel noted that if a drug taken were into trial to specifically to provide a definitive outcome of "no efficacy" it had ethical implications.	

[i] https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/#:~:text=Merck%20Statement%20on%20Ivermectin%20use%20During%20the%20COVID%2D19%20Pandemic,-Save&text=KENILWORTH%2C%20N.J.%2C%20Feb.%204,during%20the%20COVID%2D19%20pandemic.

Outcome

CTAP confirmed ivermectin was not recommended for publicly funded trials.

Active on-going monitoring tags from specific sub-groups was ended as CTAP confirmed ivermectin was not currently prioritised.

CTAP0212 ivermectin's proposer was sent an 'already considered' email.

9. Event: CTAP email 23/02/2021

Action

CTAP chair circulated [DD_HMG_Population_Mapping_0121] which references ivermectin.

Sources

Airfinity

Comment

N/A

Outcome

N/A - reference only.

10. Event: Additional information 02/03/2021

Action

TTF forwarded additional information.

Sources

45. https://covid19criticalcare.com/videos-and-press/flccc-lecture-for-ypo-gold-on-ivermectin/
46. https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Ivermectin-in-the-prophylaxis-and-treatment-of-COVID-19.pdf

Comment

Outcome

The due diligence team confirm that there is no information in this email that has not been considered by the team and panels already.

11. Event: Additional information 03/03/2021

Action

TTF forwarded additional information.

Sources

47. https://academic.oup.com/qjmed/advance-article/doi/10.1093/qjmed/hcab035/6143037
48. https://www.frontiersin.org/articles/10.3389/fphar.2021.643369/abstract

Comment

Outcome

The due diligence team confirm that there is no information in this email that has not been considered by the team and panels already.

12. Event: Internal Horizon Scanning 05/03/2021

Action

The due diligence team circulated a study amongst themselves.

Sources

49. https://jamanetwork.com/journals/jama/fullarticle/2777389

Comment

Question What is the effect of ivermectin on duration of symptoms in adults with mild COVID-19?

Findings In this randomized clinical trial that included 476 patients, the duration of symptoms was not significantly different for patients who received a 5-day course of ivermectin compared with placebo (median time to resolution of symptoms, 10 vs 12 days; hazard ratio for resolution of symptoms, 1.07).

Meaning The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand effects on other clinically relevant outcomes.

Outcome

The due diligence team confirm that there is no information in this email that has not been considered by the team and panels already.

13. Event: POG Meeting 27/04/2021

Action

The Prophylaxis Oversight Board met in April.

Sources

POG minutes

Comment

The minutes from the meeting state: [It was] raised that an updated ivermectin meta-analysis has been shared with RAPID C-19 with a signal of efficacy for treatment and prophylaxis. However, the meta-analysis is not convincing, and the external validity is still questionable. [It was] stated that there is no prior plausibility for ivermectin and no plausible mechanism of action. The WHO ivermectin meta-analysis clearly stated that ivermectin should not be used outside of trials as the data is very weak.