BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC2: Medicinal Chemicals

SUMMARY MINUTES

A meeting of this Expert Advisory Group (EAG): Medicinal Chemicals 2 (MC2) was held via videoconference on the 3rd and 4th November 2021.

Present: Dr G Cook (*Chairman)*, Mr C Goddard (*Vice-Chairman*), Prof J Birchall, Ms K Boon, Mr J Cowie, Dr K Foster, Mr E Hook, Dr J Lim, Prof J Miller, Dr A Ruggiero and Mr N Wynne.

In attendance: Ms H Corns, Ms A Thomson, Dr H Bowden (for item MC2(21)19 only), Ms K Busuttil and Mr C Thompson.

Apologies: Dr K Foster (for 4th November session only).

511 Introductory Remarks

Welcome The Chairman welcomed members to the meeting and also welcomed Ms K Busuttil and Mr C Thompson who attended from the BP Laboratory.

Confidentiality Members were reminded that all papers and minutes were confidential and should not be disclosed outside the BP Commission.

Declaration of Interests Members were reminded that they are required to inform the Secretariat of any changes to their interests throughout the year.

512 BP Update **MC2(21)17**

Members were provided with an update on recent BP activities and personnel changes.

513 MINUTES

The minutes and summary minutes from the meeting held on the 5th and 7th May 2021 were confirmed without amendment.

514 MATTERS ARISING FROM THE MINUTES **MC2(21)18**

Matters arising and correspondence items from the meeting held on the 5th and 7th May 2021 were noted. Members had no additional comments.

MONOGRAPHS

Dr G Cook, Mr J Cowie and Mr N Wynne declared interests in one or more agenda items and appropriate action was taken.

515 Trimethoprim preparations: **MC2(21)19**
Trimethoprim Oral Suspension (Revised)
Trimethoprim Tablets (Revised)

Content (Oral Suspension) Licensing colleagues indicated that all products should be able to meet a tighter content limit therefore it was agreed that 95.0-105.0% would be included in the draft monograph subject to public consultation.

Identification (Oral Suspension) Members agreed to replace TLC with UV-DAD subject to laboratory investigation of characteristic UV absorbance. Concordance of retention time in the HPLC assay would be retained as a secondary requirement.

Identification (Tablets) Members advised that the laboratory investigate an alternative extraction solvent to replace chloroform in the infrared procedure.

Dissolution (Oral Suspension) The current monograph did not contain a dissolution test. It was recommended by licensing colleagues that the monograph should be revised to include one, on account of Trimethoprim's BCS class 2 nature.

It was agreed that a dissolution test should be investigated as part of the laboratory evaluation and that HPLC would be the preferred quantification method, over UV absorbance due to potential excipient interference.

Dissolution (Tablets) As per BP policy it was proposed that the Trimethoprim Tablets monograph be updated to include a dissolution test. It was agreed that the dissolution test from the USP monograph would be included within the draft monograph and tested in the laboratory.

The draft monograph proposed harmonising the dissolution quantification with the HPLC assay, however the group agreed that given the UV was the original quantification method, that this should be utilised in the laboratory investigation.

The limits were agreed at 75%Q at 45 minutes and would be subject to lab work and public consultation.

Related substances (Oral Suspension) The related substances method from the collaborating manufacturer's data package had been included in the draft revised monograph. The manufacturer's method for related substances was harmonised with the current BP assay method. It was agreed that this would be tested in the laboratory for all products on the market.

It was noted that the current monograph did not specify a disregard limit. It is proposed to align with ICH and the product specifications at 0.1% disregard, 0.2% unspecified impurities and 0.4% total impurities. Comments from licensing colleagues suggested there was low risk to degradation products and that these limits should be sufficient control for the oral suspension monograph.

These limits would be subject to lab work and public consultation.

The manufacturers method included only a standard verification as a system suitability. It was proposed that a resolution requirement be investigated as part of the laboratory investigation. Alternatives to the resolution requirement agreed by the group included peak tailing or symmetry.

Related substances and Assay (Tablets) The related substances method in the current monograph was written in the old style and it was proposed to editorially restyle the test. The current Assay method in the monograph was a UV absorbance quantification method. It was proposed to harmonise the assay method with the related substances, subject to laboratory investigation.

The limits were agreed by the group to be aligned with ICH with a disregard limit at 0.1%. unspecified impurity at 0.2% and total impurities at 0.4%. This would widen the

limits for the impurities from the current monograph however it was agreed, with support from licensing colleagues that there is low risk of degradation products. Based on the licensed product specifications the products on the market should be able to meet these limits but they would be subject to the lab testing and the public consultation.

The current system suitability method utilised the number of theoretical plates. It is proposed that a resolution requirement be investigated as part of the laboratory investigation. Alternatives to the resolution requirement agreed by the group included peak tailing or symmetry.

Method evaluation assessment The group agreed to the following lab work outlined in the method evaluation assessment. For the Oral suspension monograph the Identification, dissolution, related substances methods would be tested. For the Tablets monograph the Identification, dissolution and assay method would be tested.

516 Fenofibrate preparations: MC2(21)20
Fenofibrate Tablets (New)
Fenofibrate Capsules (New)

The draft new monographs would be included in a future BP publication, subject to amendments and comments from manufacturers.

517 Atorvastatin Tablets (New) MC2(21)21

The draft new monograph would be included in a future BP publication, subject to amendments and comments from manufacturers.

518 Latanoprost Eye Drops (New) MC2(21)22

The draft new monograph would be included in a future BP publication, subject to amendments and comments from manufacturers.

519 Ciprofibrate Tablets (Revised) MC2(21)23

Identification Laboratory assessment of the IR test had found chloroform to be the only suitable extraction solvent of the four solvents tested. As it was BP policy to avoid the use of chloroform in monographs, where possible, members agreed that a HPLC/UV-DAD identification test should be included in the monograph. Members agreed that the UV spectrum of ciprofibrate was sufficiently characteristic for the alternative test to be accepted.

Related substances Members were reminded an unspecified impurity limit of 0.1%, aligned with product specifications rather than ICH guidelines (0.2%), had previously been agreed. Licensing representatives noted that this may have been due to an older approach of tightening in-line with batch data and that no patient safety concerns had been identified that required limits tighter than ICH.. Members agreed that the unspecified impurity limit should be harmonised with ICH guideline in the absence of safety concerns. The other related substances limits were retained as agreed at the previous review of the draft monograph.

520 Dorzolamide preparations: MC2(21)24

Dorzolamide Eye Drops (Revised)
Dorzolamide and Timolol Eye Drops (Revised)

Related substances The Secretariat received correspondence from a manufacturer requesting widening of the limit for Dorzolamide Impurity B in two drug product monographs, qualified by (Q)SAR data and in line with the USP. Members did not feel there was sufficient justification to widen the limit for Dorzolamide Impurity B from 1.3% in Dorzolamide Eye Drops and 1.1% in Dorzolamide and Timolol Eye Drops, to 2% in both. Licensing colleagues revealed that all of the UK licensed specifications were in line with the current BP requirements as published, with none limiting Dorzolamide Impurity B at 2.0% as per the request. Members wished to remind the manufacturer that, should they be unable to meet specification, they would need to file a variation request with Licensing.

Minor technical and editorial comments were made by members via the DRT and would be taken into account.

521 Tranylcypromine Sulfate (Revised) MC2(21)25

Identification B A member recalled that Tranylcypromine Sulfate might not be able to comply with Identification test B (characteristics of sulfates). The Secretariat was not aware of reported issues and agreed to investigate further.

POST-MEETING NOTE: The Secretariat identified that this issue was reported on the Phenelzine Sulfate monograph.

Hydrazine A manufacturer had provided a method for hydrazine which had been included in the draft revised monograph. Members questioned whether the test was capable of the level of precision needed for a 195 ppm limit and agreed that introducing greater precision within the test solutions, an approach that EDQM take in similar situations, was appropriate. Greater precision was preferred over rounding to 200 ppm as 195 ppm was the calculated specification based on the maximum daily dose and threshold of toxicological concern.

Related substances Members noted that solution (3) in the draft was 12.5 times more concentrated than the limit for impurities C and D and recommended that a 10 times more dilute solution with a signal to noise ratio requirement of 10 was added to the test. The Secretariat agreed to amend the monograph accordingly.

522 Sertraline Tablets (Revised) MC2(21)26

Dissolution A BP user query led to the discovery that the dissolution medium described in the Sertraline Tablets monograph did not match that of the donor method. As the user did not report problems with using the medium as linked in the BP monograph, and given the similarity (both sodium acetate buffer solutions of pH 4.5), members agreed to retain the existing wording until the monograph was next revised.

523 Bupivacaine Injection preparations: MC2(21)27
Bupivacaine Heavy Injection (Revised)
Bupivacaine Injection (Revised)

Content (Heavy Injection only) Expression of the heavy injection strength content in terms bupivacaine hydrochloride monohydrate had been questioned, compared to the other bupivacaine containing BP monographs expressed the strength as anhydrous bupivacaine hydrochloride. Licensing colleagues confirmed that the strength of all current licensed Bupivacaine Heavy Injection was expressed in terms of anhydrous bupivacaine hydrochloride and members agreed the monograph should be amended to align with licensed products.

Content (Injection only) A proposal to tighten the content limits from 92.5% - 107.5% to 95.0% - 105.0% was accepted, subject to stakeholder comments.

Identification The identification tests had been rationalised in the draft revised monographs with IR retained as a standalone identification test for bupivacaine. For the Heavy Injection, the 2 identification tests for glucose were retained as neither test was sufficiently discriminatory to be used individually.

Related substances Members endorsed the inclusion of an isocratic LC method with UV detection which had been found to be suitable for controlling a number of Ph Eur impurities, including impurity F (2,6-dimethylaniline) which the subject of a separate test in both monographs. Limits of 0.5% for impurity B, 0.2% for unspecified impurities and 1% for total impurities with a disregard limit of 0.1% were agreed by members.

The limit for impurity F in the Heavy Injection was 800 ppm compared to 400 ppm in the standard Injection monograph. Licensing representatives reported that recent applicants had been asked to reduce their proposed specification to 10 ppm, as data had not supported a higher limit, and agreed to investigate further and provide advice on an appropriate limit for the revised monographs.

Assay Members endorsed harmonisation of the assay procedure with the revised related substances test, subject to stakeholder comments.

Impurities Members accepted the transparency statement informing monograph users that impurities B, E and F could be determined using the related substances test.

524 Solifenacin Tablets (New) MC2(21)28

Comments were received from one manufacturer during the public consultation window and presented to the group for consideration. The draft new monograph would be included in a future BP publication subject to amendments.

FOR INFORMATION

525 Out of Stock BPCRS MC2(21)29

The Secretariat reviewed the out-of-stock BPCRS for monographs relevant to EAG MC2 and presented these to the group. Members approved proposals for in situ generation of Captopril Disulfide given its longstanding unavailability.

526 MC2 Work status and updates MC2(21)30

The MC2 work programme was presented to members for information.

527 Ph. Eur. Updates MC2(21)31

The Secretariat thanked members for their contributions to the ongoing Pharmeuropa review, with the 33.4 public deadline end of December.

528 ANY OTHER BUSINESS

Nitroxinil Injection (Vet) The sole UK MAH had informed the Secretariat that they were withdrawing the product from the market and were unable support the revision of the monograph. Members agreed that the monograph should be put forward for omission from the BP, subject to confirmation of the recommendation from Panel Vet.

529 NEXT MEETING

Tuesday 10th May 2022 (and Thursday 12th May if held virtually).