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 5th and 7th May 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, Dr H Bowden, Ms A Thomson, Ms K Busuttil and Ms M Nanasi.

Apologies: None

491 Introductory Remarks

Welcome The Chairman welcomed members to the meeting and also welcomed Ms K Busuttil and Ms M Nanasi 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.

492 BP Update **MC2(21)01**

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

493 MINUTES

The minutes and summary minutes from the meeting held on the 6th & 9th October 2020 were confirmed without amendment.

494 MATTERS ARISING FROM THE MINUTES **MC2(21)02**

Matters arising and correspondence items from the meeting held on the 6th & 9th October 2020 were noted. Members had no additional comments.

MONOGRAPHS

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

495 Levothyroxine preparations: MC2(21)03
Levothyroxine Tablets (Revised)
Levothyroxine Oral Solution (Revised)

Identification Members agreed to introduce HPLC/UV-DAD identification tests into the monographs.

Related substances (Oral Solution) It appeared from previous lab work that the method was capable of detecting additional impurities to impurity A, which was the only impurity listed in the transparency statement. The Secretariat agreed to further investigate in order to add greater clarity to the Impurities section of the monograph.

Related substances (Tablets) One stakeholder had requested that that a total impurity limit of 10% was included in the monograph, to clarify that the content limits of 90.0 – 105.0% needed to be met whilst the impurity limits allowed up to 13% of total impurities. The impurity limits had been written to accommodate a range of product specifications. Members agreed that a total impurity limit would be beneficial and the Secretariat agreed to confirm suitability of the limits with MHRA License Assessors prior to publication of the revised monograph.

Uniformity of content/Assay (Tablets) One stakeholder reported poor reproducibility when analysing 25 µg tablet samples. The methods had not been changed in the draft revised monographs and the Secretariat would seek further information from the stakeholder.

Another stakeholder requested that a separate assay procedure was retained within the monograph. The BP practice was to use the average result of uniformity of content testing for assay, to reduce the number of tests required to demonstrate compliance. Discussion highlighted that for release testing the BP approach was more convenient as both tests were required; however, this was not the case for stability testing. Members concurred that there was insufficient justification to recommend the proposed change to BP policy, as this would shift the inconvenience to release testing rather than resolve an issue.

496 Liothyronine preparations: MC2(21)04
Liothyronine Tablets (Revised)
Liothyronine for Injection (New)

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

Identification (Tablets) No comments were made on the proposals to introduce HPLC/UV-DAD identification tests into the monographs. Members confirmed that this test should be included.

Dissolution (Tablets) No comments received on the proposed dissolution medium of water, agreed at the previous meeting. Members confirmed that this test should be included.

The MHRA lab reported that poor recovery had been obtained, during pre-approval testing, when using the PVDF filter specified in the draft revised monograph. GMF filters, found suitable in other assessments gave approximately 80% recovery. The lab opted for centrifugation which was found not to affect recovery. Members noted that each test in the monograph contained a different filtration or centrifugation step and recommended that, based on advice from the lab, a consistent approach was taken across all tests.

Related substances (Tablets) Comments received from stakeholders indicated that the drafted method was suitable for compendial use with corrections applied. It was noted that the correction factor in the draft monograph was the reciprocal of the true value, which had been amended and would be brought to the attention of MAH. It was also noted that solution A had been incorrectly transcribed, which was the likely cause of the peak splitting reported in one set of comments.

A reference solution closer in concentration to the limit for impurity 1 was advised, to avoid a combination of multiplication factors.

497 Duloxetine Gastro-resistant Capsules (New) **MC2(21)05**

The draft monograph would be included in a future BP publication, subject to laboratory evaluation and stakeholder comment.

498 Mebeverine preparations: **MC2(21)06**
Mebeverine Tablets (Revised)
Mebeverine Prolonged-release Capsules (New)

The draft new monograph for Mebeverine Prolonged-release Capsules would be included in a future BP publication, subject to amendments and comments from manufacturers.

Identification (Tablets) The laboratory investigated the use of dichloromethane as a replacement for chloroform in the IR extraction and found this to be a suitable alternative. The revised extraction had been drafted into the monograph and was accepted by the group.

Dissolution (Tablets) Introduction of a dissolution test to the monograph proved to be difficult as the test needed to provide suitable control of film-coated and sugar-coated tablets. It was agreed that further investigation was needed before a test could be included in the monograph.

Related substances (Tablets) A related substances test had been found to be suitable the tablets. All samples tested were able to pass the drafted impurity limits.

It was agreed that the quantification of impurity C should utilise an external BPCRS standard, as a correction factor greater than 5 was determined in the laboratory assessment.

Assay (Tablets) The Assay method had been based upon manufacturer's data and was found to be suitable. All samples tested were able to pass the drafted limits of 95.0-105.0%.

499 Adrenaline Injection preparations: MC2(21)07

Adrenaline Injection/Epinephrine Injection (Revised)
Dilute Adrenaline Injection 1 in 10,000 /Dilute Epinephrine Injection 1 in 10,000 (Omission)

Medication error data and BP Labelling requirements Data had been received from NHS Improvement's National Reporting and Learning System (NRLS) and discussed with MHRA colleagues. There was general consensus that moving away from the 1 in 1000 and 1 in 10,000 strength labelling would be beneficial for healthcare providers and could reduce medication errors. Once new labelling had been agreed, along with timelines for the change implementation, the BP labelling requirements would be revised.

Adrenaline Injection/Epinephrine Injection MHRA colleagues had recommended that a single, open strength BP monograph covering all Adrenaline Injection/Epinephrine Injection products would be beneficial, as this would also cover the 0.05% w/v licensed product. Members agreed the recommendation and noted that correction of the draft was required which the Secretariat agreed to address prior to the stakeholder consultation process.

Dilute Adrenaline Injection 1 in 10,000 /Dilute Epinephrine Injection 1 in 10,000 As a consequence of the revision to create an open strength Adrenaline Injection/Epinephrine Injection monograph, a separate monograph for the dilute injection was no longer required. Members agreed the monograph should be taken to BPC for omission.

500 Solifenacin preparations: MC2(21)08

Solifenacin Oral Suspension (New)
Solifenacin Tablets (New)

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

501 Tranylcypromine Sulfate (Revised) MC2(21)09

Nitrosamine formation risk assessment The outcome of a risk assessment provided by a manufacturer showed that there was no requirement for a test or production statement in the monograph.

Elemental impurities Justification provided by a manufacturer demonstrated that tests for elemental impurities were not required in the monograph.

Hydrazine A manufacturer reported that hydrazine was monitored as a process-related impurity and members agreed that a test should be included in the monograph.

Related substances Members agreed that an improved method should be adopted with limits more aligned to regulatory expectations.

Assay Members agreed that the titration method for assay should be retained in the drug substance monograph as it offered greater precision than an HPLC method.

502 Mitoxantrone Sterile Concentrate (Revised) MC2(21)10

Title Members approved proposals to revise the monograph title from Mitoxantrone Infusion to Mitoxantrone Sterile Concentrate. The infusion requirements under Definition, Bacterial endotoxins and Labelling were deleted from the monograph.

Acidity Members approved a revised pH requirement of 2.5 – 4.5 requested by manufacturer and supported by the data which demonstrated stability in the lower pH range.

Related Substances The test would be revised to introduce means to identify the peak due to impurity D.

503 Phenoxybenzamine Capsules (Revised) MC2(21)11

Content A request to retain the lower content limit of 92.5% was received during the consultation window. Members required further information before the request could be agreed.

Dissolution Members questioned whether a reduced dissolution medium volume of 500 mL was necessary and if the standard 900 mL volume could be applied.

Assay Members agreed that the assay sample preparation should be scaled up from 5 capsules to 10 capsules, ensuring that 20 dosage units were used for the test.

504 Diclofenac Diethylamine (Revised) MC2(21)12
Diclofenac Gel (Revised)

Monograph note (Gel) The Secretariat had revised the BP monograph to cover both salt forms used to formulate diclofenac gels within the UK market. An additional note had been added to the top of the monograph that stated: *"Diclofenac Gel prepared from Diclofenac Diethylamine is not necessarily interchangeable with Diclofenac Gel prepared from Diclofenac Sodium."* A lack of data was available to assess the bioequivalence of the different gel formulations.

Definition (Gel) The Secretariat had revised the definition to cover both diethylamine and sodium salt forms, taking into account BNF and SPC data. The approach received approval from members.

Content (Gel) The Secretariat had revised the content statement to incorporate the different salt forms, retaining limits of 95.0% to 105.0% for both. Members confirmed that the limits remained suitable.

Identification (Gel) A TLC method that used the same mobile phase composition and spray derivatisation for spot visualisation, without the use of chloroformwas approved for inclusion in the Diclofenac Gel monograph.

Related substances (Diethylamine, Gel) Confirmation of the requirement for correction factors for impurities A and F (0.7 and 0.3 respectively) was received and included in the monographs. The test had been revised to direct users to prepare the sample solution based on an amount equivalent to the diclofenac base.

Assay (Gel) The test had been revised to account for the quantification of the content via the diclofenac base. Salt corrections had been added to allow conversion to the sodium and the diethylamine forms.

FOR INFORMATION

505 LC/UV-DAD for Identification MC2(21)13

Guidance for EAG members was provided to support adoption of LC/UV-DAD for Identification tests, following approval by BPC in November 2020.

506 Out of Stock BPCRS MC2(21)14

A review of out of stock BPCRS for monographs relevant to EAG MC2 was presented to the group.

507 MC2 Work status and updates MC2(21)15

The MC2 work programme was presented to members for information.

508 Ph. Eur. Updates **MC2(21)16**

The Secretariat thanked members for their contributions to the ongoing Pharmeuropa review.

509 ANY OTHER BUSINESS

510 NEXT MEETING

Wednesday 3rd November 2021