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 6th and 9th October 2020.

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 K Busuttil (BP Lab) and Ms M Nanasi (BP Lab). Mr S Maddocks and Mr M Whaley were in attendance for the Gliclazide preparations, the AQbD Update and the Atorvastatin Tablets agenda items.

Apologies: None

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

471 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.

472 BP Update

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

473 MINUTES

The minutes and summary minutes on the meeting held on the 13th May 2020 were confirmed without amendment.

474 MATTERS ARISING FROM THE MINUTES

Matters arising and correspondence items from the meeting held of the 13th May 2020 were noted. Members had no additional comments.

III MONOGRAPHS

475 Gliclazide preparations:
Gliclazide Tablets (Revised)
Gliclazide Prolonged-release Tablets (New)

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

Gliclazide Tablets - Dissolution A limit of 75% (Q) in 45 minutes had been introduced to the test. Members agreed to the proposed limit, subject to stakeholder comments, and requested that application of the HPLC assay method was investigated for the determination of content.

476 Atorvastatin Tablets (New)

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

477 Salbutamol preparations (Revised):

Salbutamol Inhalation Powder
Salbutamol Inhalation Powder, pre-metered
Salbutamol Injection
Salbutamol Oral Solution
Salbutamol Nebuliser Solution
Salbutamol Pressurised Inhalation, suspension
Salbutamol Tablets
Salbutamol Prolonged-release Tablets

Identification HPLC-UV/DAD was proposed for identification in all monographs, excluding the pressurised inhalation suspension monograph which contained an IR test. The group agreed that the test should be applied to all monographs in the family in place of TLC, colour change and retention time tests, subject to stakeholder comments.

The inclusion of the test for sulfates within the salbutamol finished product monographs was reviewed. It was agreed that the sulfate test would be retained the Oral Solution, Prolonged-release Capsules and Tablets monographs only, as the use of sulfuric acid in Injection and Nebuliser Solution product formulations could result in false positives.

Dissolution (Salbutamol Tablets) A test had been included in the draft revised monograph which was accepted, subject to stakeholder consultation.

Related substances - limits The unspecified impurity limit across the published Salbutamol preparation monographs were not aligned with ICH guidelines. A secondary peaks limit of 0.2% and a disregard limit of 0.1% had been drafted into the

monographs. Members accepted the change, subject to comments from manufacturers.

2-*tert*-Butylamino-1-(4-hydroxy-3-methylphenyl)ethanol and Related substances (Oral Solution) The published monograph contained a single impurity procedure for 2-*tert*-Butylamino-1-(4-hydroxy-3-methylphenyl)ethanol (Ph Eur impurity C). The Secretariat had replaced the single impurity test with a related substances method based upon MAH data, which was accepted by members subject to laboratory assessment and stakeholder comments.

Salbutamol Ketone and Related substances (Injection, Nebuliser Solution, Oral Solution) The published monographs contained two impurity control methods; Salbutamol Ketone and Related substances. The related substances method drafted in the revised Oral Solution monograph was able to detect all impurities limited within these monographs with a single procedure. The Secretariat had included this method in the draft revised Salbutamol Injection, Oral Solution and Nebuliser Solution monographs and was agreed by MC2 members, subject to stakeholder comments.

Related substances (Tablets) The Tablets monograph contained a TLC related substances method. The Secretariat had drafted a revised test, based on the Salbutamol Inhalation Powder monograph as there were similarities in formulation excipients used in the products. Members accepted the revised method, subject to stakeholder comments.

Assay (Nebuliser Solution) The UV method was had been replaced with HPLC test, based on the method in the Salbutamol Injection monograph. Members accepted that the revised method, subject to public consultation.

Assay (Oral Solution) The experts agreed that the chromatographic conditions used for the assay should be harmonised with the revised related substances test conditions, subject to stakeholder comments.

478 Adrenaline preparations (Revised):

Adrenaline Injection/Epinephrine Injection
Dilute Adrenaline Injection 1 in 10,000/ Dilute Epinephrine Injection 1 in 10,000

Monograph titles/Labelling It had been reported by the CHM expert working group on adrenaline auto-injectors (EWG AAI) that the BP labelling requirement for adrenaline injections was a potential cause of medication dosing errors. Data was being obtained to identify the causes of such errors requirements, which would be presented to experts for discussion at a future meeting.

Characteristics An apparent inconsistency was noted between the characteristics in the monographs ‘a colourless or almost colourless solution‘ and an MAH labelling instruction of ‘replace if the solution is discoloured’. Members agreed that this should be investigated and presented at a future meeting for discussion.

Related substances – calculation of impurities During review of the revised monographs published in the BP 2021, it was noted that in Related substances test B, impurities were limited against a combined peak area of L- and D- adrenaline as the method was achiral. The permissible limit of 15% for D-adrenaline had the potential to affect the calculated result of other impurities present. Members agreed that adjustment of peak areas in solutions (2) and (3), to correct for the D-adrenaline present, should be included in Related substances B.

As the peak area adjustment was to correct a calculation error, not to change the impurity limits, it was agreed that the Secretariat would request information from manufacturers to determine what the adjusted limits should be for their products to remain in compliance with the monographs.

479 Dapsone Tablets (Revised)

Identification Members agreed that as the IR spectrum for dapsone was sufficiently discriminatory, that test B (TLC) should be deleted.

Dissolution The test limit had been updated to 75% (Q) in 45 minutes and the analytical procedure revised to align with the revised assay method. Members accepted the changes subject to laboratory assessment and stakeholder comments.

Related substances A revised procedure based on the drafted Ph. Eur. Dapsone related substances gradient LC method had been included in the draft revised monograph, which replaced the TLC test. Limits of NMT 0.4% each for 4-amino-4-hydroxy-diphenyl sulfone and 4-amino-diphenyl sulfone, 0.3% for the O-dimer, 0.2% for secondary peaks and 2.0% for total impurities with a disregard limit of 0.1% were agreed, subject to laboratory assessment and manufacturers comments.

Assay An isocratic LC method, based on a MAH method had been drafted to replace the published titration procedure. Members accepted the changes subject to laboratory assessment and stakeholder comments.

480 Niclosamide (Chewable) Tablets (Revised)

Title The title ‘Niclosamide Tablets’ had been reviewed in light of the requirement for patients to chew or crush the tablets before ingestion. A revised title of ‘Niclosamide Chewable Tablets’ was favoured by members of EAG: PCY experts. MC2 members agreed to the change and requested that the Secretariat confirm that the general monograph for Chewable Tablets covers formulations that were crushed.

Identification Members agreed to the deletion of identification tests B and C as the IR identification test was discriminatory.

Disintegration As a result of the change in title proposed the disintegration statement within the current monograph was redundant. Members agreed to the deletion of the disintegration statement.

5-chlorosalicylic acid A query from a user had highlighted that the limit for 5-chlorosalicylic acid within the Ph Eur Niclosamide monograph was 60 ppm, whereas the BP monograph implied that the impurity should not be present. The Secretariat had revised the test to include a limit of 60 ppm for the 5-chlorosalycilic acid measured in comparison to a reference solution. Members agreed to the change proposed.

481 Levothyroxine preparations (Revised):
Levothyroxine Oral Solution
Levothyroxine Tablets

Identification Members agreed the proposals to replace tests A (retention time comparison in the assay) and B (colour change, wet chemistry) by a single LC/UV-DAD identification test, subject to stakeholder comments.

Related substances (Oral Solution) A request to increase the limit for impurity A (liothyronine) from 2% to 3% had been received from an MA applicant. The request was supported by MHRA licence assessors who had accepted the applicant's justification. Members agreed the requested change.

Members noted that the impurity control in the monograph was not as comprehensive as the method drafted for the Tablets monograph. The Secretariat agreed to investigate improvement of the method.

Related substances (Tablets) The Secretariat reported that a toxicological study had been completed and an 8% shelf-life limit for the levothyroxine maillard impurity (impurity 1) and a total impurity limit of 10% at shelf-life, based on the data, was potentially acceptable to MHRA Licensing assessors, subject to outcomes of the assessment process. Members agreed the proposed impurity 1 limit, subject to stakeholder consultation and a positive assessment outcome; however, recommended that the drafted total impurity limit of 5%, excluding impurity 1, was retained based on licensed specifications.

Assay (Tablets) Members requested investigation of the assay to determine whether the method separated impurity 1 from levothyroxine, which the Secretariat agreed to take forward.

482 Liothyronine preparations:
Liothyronine Injection (New)
Liothyronine Tablets (Revised)

Identification Members agreed the proposals to adopt a single LC/UV-DAD identification test, subject to endorsement by BPC and stakeholder comments.

Related substances (Injection) The sole MAH for this product had been asked whether the method drafted for Liothyronine Tablets was applicable to Liothyronine Injection so that the monographs would have a harmonised procedure. No response had been received to date.

Related substances (Tablets) The Secretariat reported that the outcomes of the MAH toxicological study had been completed. At a recent scientific advice meeting, the MAH presented those outcomes and MHRA colleagues were largely satisfied with a proposal of a 6% shelf-life limit for the liothyronine maillard impurity (impurity 1) and a total impurity limit of 8% at shelf-life, based on the data, subject to outcomes of the assessment process. Members agreed the proposed impurity 1 limit, subject to stakeholder consultation.

Members also recommended that consideration was given to separation of the impurity 1 limit into a 'for tablets containing lactose' subsection and use of a more concentrated solution of liothyronine for solution (2). The Secretariat agreed to investigate both recommendations.

Assay (Tablets) Members requested investigation of the assay to determine whether the method separated impurity 1 from liothyronine, which the Secretariat agreed to take forward.

483 Rivastigmine Transdermal Patches (New)

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

484 Melphalan for Injection (Revised)

Related substances B Investigation of a user query had highlighted that the melphalan methyl ester impurity had been incorrectly labelled as Ph Eur impurity I in the BP monograph. The Ph Eur impurity list names the methyl ester as impurity H.

Impurity I was limited at 0.5% in the BP monograph. Correction of the impurity name from impurity I to impurity H tightened the limit of impurity I from 0.5% to 0.3%, under the secondary peak limit. No comments were received from during public consultation on the draft revised monograph and members agreed that the revised monograph should be published.

FOR INFORMATION

485 AQbD Update

Members were provided with an update on AQbD activities.

486 Out of Stock BPCRS

Long term out of stock BPCRS materials brought to the attention of the group for comment and advice regarding the sourcing of the materials.

487 MC2 Work status and updates

The MC2 work programme was presented to members for information.

488 Ph. Eur. Updates

An update on changes to Ph. Eur. monographs that affected MC2 monographs was presented to members.

489 ANY OTHER BUSINESS

490 NEXT MEETING

Meeting split into 2 sessions as expected to be held remotely:

09.30 – 12.00 Wednesday 5th May 2021
09.30 – 12.00 Friday 7th May 2021