BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC2: Medicinal Chemicals

SUMMARY MINUTES

A meeting of this Expert Advisory Group was held at 151 Buckingham Palace Road, London SW1W 9SZ on Tuesday 9th May 2017.

Present: Dr G Cook (*Chairman)*, Mr C Goddard (*Vice-Chairman*), Prof J Miller, Mr N Wynne, Mr J Cowie, Dr D Edwards, Dr J Lim and Dr A Ruggiero. Mr S Jones was present for item MC2(17)07.

In attendance: Ms H Corns, Mr L Elanganathan, Ms S Gomersal, Dr K Radi, Mrs M-L Wall (MHRA), Ms F Lee (BP Lab), Mrs C Galdino (BP Lab) and Ms N Ionescu (BP Lab).

Apologies: Mrs M Turgoose and Mr P Murray

325 Introductory Remarks

Welcome The Chairman welcomed Fiona Lee, Carolina Galdino and Nicoleta Ionescu from the BP Lab.

The Chairman welcomed May-Louise Wall, Kristina Radi, and Laxsaan Elanganathan as the new additions to the BP Secretariat.

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.

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

326 Emergency evacuation procedure

The emergency evacuation procedure for the building was provided.

I MINUTES

327 The minutes and summary minutes of the meeting held on 1st November 2016 were confirmed with no amendments.

II MATTERS ARISING FROM THE MINUTES

328 The following matters arising and correspondence items from the meeting held on 1st November 2016 were noted.

Liothyronine Preparations, Levothyroxine Preparations (Minute 281)

The Secretariat was awaiting further information before progressing the revision of these monographs.

Salmeterol Inhaled Preparations (Minutes 290, 291) The draft monographs would be included in a future BP publication, subject to comments.

Cyclophosphamide Preparations (Minute 294) The Secretariat was awaiting further information before progressing the revision of these monographs.

Pimobendan Preparations The draft monographs would be included in a future BP publication, subject to comments.

329 Comments Received on Draft Monographs

Comments were discussed via the forum and actions confirmed with the Chair.

Enalapril Tablets The below amendments were agreed by the Chair following a request from a manufacturer that correction factors and agreed specifications were amended, published in the BP 2018.

- impurity C - 1.5%
- impurity D - 1.0%
- impurity 1 - 0.3%
- any other secondary peak – 0.2%
- sum of any other secondary peaks, excluding impurities C, D and 1 – 1.5%
- disregard any peaks due to maleic acid and L-alanyl-L-proline and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) - 0.1%

Ketoprofen Gel An MAH requested a revision of limits for impurities A-E, total impurities, and an increase to the any secondary peak and disregard limits. Members and Licensing agreed to the changes, and the below amendments were published in BP 2018.

- Impurity A – 0.5%
- Impurity C – 0.5%
- Impurities B, D, and E – 0.5%
- Any other impurity – 0.2%
- Sum of impurities, excluding A and C – 2.5%
- Disregard – 0.1%

Ketoprofen Injection The draft monograph would be included in a future BP publication.

Ketoprofen Tablets The draft monograph would be included in a future BP publication.

Carprofen Tablets The draft monograph would be included in a future BP publication.

330 BPCRS Updates

Fluvastatin Impurity F BPCRS Report Following establishment of Fluvastatin Impurity F BPCRS, a single peak for impurity F was seen instead of multiple peaks that had been expected. The Fluvastatin monographs would be amended in a future publication to reflect this finding.

331 BPC Update

An update from the March 2016 BPC meeting was presented to members for information.

332 PCY Update

An update of EAG PCY activities was presented to members for information.

III MONOGRAPHS

333 Naproxen Preparations:
Naproxen Oral Suspension (revised)
Naproxen Tablets (revised)
Gastro-resistant Naproxen Tablets (revised)
Effervescent Naproxen Tablets (new)
Naproxen Suppositories

Naproxen Oral Suspension - Content It was agreed that the content limits in the monograph should be revised from 90.0 to 110.0% to 95.0 to 105.0% subject to comments from MAHs.

Naproxen Oral Suspension – Identification Members agreed that Identification B could be deleted from the monograph and that chloroform in the IR test should be replaced with dichloromethane.

Naproxen Oral Suspension – Dissolution Members agreed that a dissolution test should be investigated for the monograph, as naproxen is not readily soluble.

Naproxen Oral Suspension – Related substances It was agreed to assess whether the Ph Eur LC related substances method could replace the current TLC method.

Naproxen Oral Suspension – Assay An LC assay, harmonised with the Related substances test, had been included in the draft revised monograph. This test was intended to replace the UV assay for which reports of variable results had been received.

Naproxen Oral Suspension – laboratory assessment Members confirmed that the draft revised Related substances and assay tests should be assessed in the laboratory.

Naproxen Tablets – Identification Members agreed that Identification B could be deleted from the monograph and the proposal to harmonise the sample preparation with the Gastro-resistant Naproxen Tablets was agreed.

Naproxen Tablets and Gastro-resistant Tablets – Related substances A preliminary investigation had shown that the Ph Eur related substances method looked promising as a replacement for the current TLC procedure. It was agreed that further lab investigation was required before the test could be adopted in the monographs.

Naproxen Tablets and Gastro-resistant Tablets – Assay A preliminary investigation indicated that the Ph Eur Related substances method would be suitable for the assay procedure. Members agreed that further lab investigation was required to confirm suitability of the method.

Effervescent Naproxen Tablets – The draft monograph would be included in a future BP publication, subject to comments.

Naproxen Suppositories It was agreed that this monograph should be proposed for omission from a future edition of the BP as no UK MAH for naproxen suppositories had been found.

334 Tetracaine Hydrochloride Eye Drops

Content The Secretariat agreed to review the content limit and confirm with the MAH that draft limits of 92.5 – 105% would be suitable.

Identification A UV test had been drafted and a peak comparison in the Assay was accepted by members as the second Identification test.

Acidity and alkalinity The Secretariat agreed to investigate whether a pH range was required for the monograph.

Related substances An HPLC procedure had been drafted to replace the TLC test.

Assay An HPLC method, harmonised with the Related substances test, had been drafted to replace the titration.

335 Adrenaline Preparations:
Adrenaline Injection/ Epinephrine Injection (revised)
Dilute Adrenaline Injection 1 in 10,000/ Dilute Epinephrine Injection 1 in 10,000 (revised)

Content The content would be amended to: '0.0900 to 0.1100% w/v, and not less than 0.0850% w/v is L-adrenaline' for Adrenaline Injection and '0.0090 to 0.0110% w/v, and not less than 0.0085% w/v is L-adrenaline' for Dilute Adrenaline Injection.
More detailed means of calculating the L-adrenaline calculation would be produced to assist users.

Related substances – impurity F Inadequate separation of impurity F had been reported when following the proposed test. Future improvement of the method would be investigated.

Other adrenaline-related monographs Stakeholders would be asked to participate in the revision of the BP monographs for Lidocaine and Adrenaline Injection, Bupivacaine and Adrenaline Injection and Noradrenaline Injection.

336 Galantamine Preparations:
Galantamine Oral Solution (new)
Galantamine Tablets (new)

The draft monographs would be included in a future BP publication, subject to comments.

337 Anastrozole Tablets (new)
The draft monograph would be included in a future BP publication, subject to comments.

338 Carbocisteine Preparations:
Carbocisteine Capsules (new)
Carbocisteine Oral Solution (new)

The draft monographs would be included in a future BP publication, subject to comments.

339 Clenbuterol Preparations
Clenbuterol Granules (new)
Clenbuterol Injection (new)

The draft monographs would be included in a future BP publication, subject to comments.

340 Phenindione (revised) **(**

340.1 **Identification** It was agreed that Identification tests B and C would be deleted as the IR test in Identification test A was sufficient as a standalone test.

340.2 **Related substances** A draft LC procedure had been included based on that from the updated Tablets monograph. A proposal for suitable limits would be investigated an brought to a future meeting for review.

341 Methylphenidate Preparations:
Methylphenidate Capsules, Prolonged-Release (new)

The draft monographs would be included in a future BP publication, subject to comments.

342 Salbutamol preparation monographs BPCRS issue:
Salbutamol Oral Solution (revision)
Salbutamol Tablets (revision)
Salbutamol Injection (revision)

The lab had informed the Secretariat that *2-tert-Butylamino-1-(4-hydroxy-3-methylphenyl)ethanol sulfate BPCRS* was no longer available to be sourced as the salt form but only as the base. It was agreed that where this BPCRS was used in monographs, the BPCRS could be changed to the base form.

Prolonged-release Salbutamol Tablets It was agreed that this monograph should be proposed for omission from a future edition of the BP, as no UK MAH for Prolonged-release Salbutamol Tablets had been found..

***Salbutamol BPCRS* and *Salbutamol sulfate BPCRS* usage** All salbutamol monographs would be updated to replace *salbutamol BPCRS* with the sulfate form as both BPCRS had an assigned content of salbutamol and could be used in the same tests within monographs. Members also accepted the proposal that *salbutamol BPCRS* would no longer be renewed once the current batch has been exhausted – a note for users would be included in the leaflet.

343 Salbutamol Inhaled preparation monographs:
Salbutamol Pressurised Inhalation (revised)
Salbutamol Nebuliser Solution (revised)
Salbutamol Powder (revised)
Salbutamol Inhalation Powder, pre-dispensed (revised)
Production – Salbutamol Pressurised Inhalation The changes required from the updated Inhaled products policy had been made.

Identification B – Salbutamol Pressurised Inhalation It was agreed that the peak comparison in Identification test B could be removed.

Uniformity of Delivered Dose - Salbutamol Pressurised Inhalation The Secretariat had drafted an LC method for this new test.

Related substances - Salbutamol Pressurised Inhalation It was agreed that the Secretariat should look into updating this test with a method that had been submitted with a shorter run time.

Uniformity of Dosage Units – Salbutamol Nebuliser Solution Stakeholders would be contacted for methods developed specifically for nebuliser solution products.

Title - Salbutamol Powder, Salbutamol Inhalation Powder, pre-dispensed The monograph title was updated to pre-metered in line with the inhaled products policy.

Identification - Salbutamol Powder, Salbutamol Inhalation Powder, pre-dispensed The Secretariat agreed to look into updating the Identification tests with IR methods.

344 Ipratropium Preparations:
Ipratropium Pressurised Inhalation (revision)
Ipratropium Nebuliser Solution (revision)

Identification - Ipratropium Pressurised Inhalation It was agreed that MAHs should be contacted for methods and UV was suggested an alternative to IR if necessary.

Related substances - Ipratropium Pressurised Inhalation A draft HPLC method was presented and the required changes to the limits section would be made.

A separate test for impurity A was agreed and MAHs would be contacted for methods. The Secretariat would also investigate an alternative test if no methods were received..

Uniformity of Delivered Dose – Ipratropium Pressurised Inhalation A Uniformity of Delivered Dose test (UoDD) had been drafted and the Secretariat agreed to review the solutions as actuations of the preparation into a small volume of solvent could be problematic.

Identification - Ipratropium Nebuliser Solution It was agreed that test B could be deleted from the monograph.

Related substances - Ipratropium Nebuliser Solution The Secretariat agreed to look into including a System suitability requirement and a disregard solution in the published method.

Uniformity of Dosage Units - Ipratropium Nebuliser Solution The Secretariat agreed to contact MAHs for data to ensure methods would be suitable for current nebuliser products.

345 Propranolol preparation monographs:
Prolonged-release Propranolol Capsules (revised)
Propranolol Tablets (revised)

Propranolol Injection (revised)

Content - Prolonged-release Propranolol Capsules, Propranolol Injection BPC requested that the wide content limits were reviewed but members agreed the current content limits should be retained.

Identification - Prolonged-release Propranolol Capsules The draft IR procedure was accepted and it was agreed lab investigation would be carried out.

Related substances - Prolonged-release Propranolol Capsules, Propranolol Injection, Propranolol Tablets Complete harmonisation with the Ph. Eur. parent monograph had been requested but it was agreed to retain the current method.

Assay - Prolonged-release Propranolol Capsules, Propranolol Injection, Propranolol Tablets An LC method also used in the Related substances test had been drafted and lab investigation was agreed.

Identification - Propranolol Injection Members accepted the proposal to remove ID test B as ID test A (an IR method) was sufficient.

Identification - Propranolol Tablets It was agreed to omit tests B and C.

346 Chlorhexidine Preparations:
Chlorhexidine Gluconate Gel (revised)
Chlorhexidine Irrigation Solution (revised)
Chlorhexidine Mouthwash (revised)
Lidocaine and Chlorhexidine Gel (revised)

4-chloroaniline A replacement for the packed column GC method for 4-chloroaniline had been investigated, and a draft method was presented. Laboratory assessment was agreed and the Secretariat agreed to review the 20 ppm limit.

Chlorhexidine Gluconate Gel As oral and topical products are available, the need to develop two separate monographs would be reviewed by EAG PCY.

347 Indapamide Preparations:
Indapamide Tablets (revised)
Indapamide Tablets, Prolonged-Release (revised)

Declared content – Tablets A review of available products was ongoing to harmonise the monographs. EAG PCY would be requested to provide guidance following the review.

Dissolution – Tablets It was noted that the old BP criteria of not less than 75% in 45 minutes (SC I E. 3.4) was included as the monograph was first published before 2007.

Related substances – Tablets, Prolonged-release Tablets A UHPLC procedure had been drafted and additional guidance on UHPLC was proposed to be added in the monograph to aid users. The Secretariat agreed to look into the required changes.

IV FOR INFORMATION

348 Flexible Collodion

A revision had been requested due to more up to date methods being used in practice. Members suggested that the monograph should be referred to PCY and Panel CX.

349 MC2 Work status and updates

The MC2 work programme was presented to members for information.

VI ANY OTHER BUSINESS

None raised at the meeting.

VII DATE OF NEXT MEETING

The date of the next meeting is 24th October 2017.