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 24 April 2018.

Present: Dr G Cook (*Chairman)*, Mr C Goddard (*Vice-Chairman*), Prof J Miller, Mr P Murray, Mr N Wynne, Mr J Cowie, Dr A Ruggiero, Dr J Lim and Dr K Bracht.

In attendance: Ms H Corns, Mr L Elanganathan, Ms S Gomersal, Dr C Lenihan (MHRA) and Ms N Ionescu (BP Lab).

Apologies: Mrs M Turgoose.

372 Introductory Remarks

Welcome The Chairman welcomed Dr K Bracht who was attending her first meeting as a new Licensing representative on the group and Dr A Ruggiero who had recently been approved as an external member by BPC.

The Chairman also welcomed Nicoleta Ionescu who attended from the BP Lab.

BP Update Members were provided with an update on BP staff changes.

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

Declaration of Interests Dr Cook, Dr Murray, Mr Wynne, Dr Ruggiero and Mr Cowie declared interests in one or more agenda items and appropriate action was taken.

Emergency evacuation procedure

373 The emergency evacuation procedure for the building was provided.

I MINUTES

374 The minutes and summary minutes of the meeting held on 24th October 2017 were confirmed with no amendments.

II MATTERS ARISING FROM THE MINUTES

375 Matters arising from the 24 October 2017 meeting were noted.

III MONOGRAPHS

376 Ibuprofen Preparations
Ibuprofen Capsules (revised)
Ibuprofen Gel (revised)
Ibuprofen Granules (new)
Ibuprofen Oral Suspension (revised)
Ibuprofen Orodispersible Tablets (new)
Ibuprofen Prolonged-release Capsules (revised)
Ibuprofen Prolonged-release Tablets (revised)
Ibuprofen Tablets (revised)

Ibuprofen Granules
The draft monograph would be included in a future BP publication, subject to comments.

Ibuprofen Oral Suspension – Dissolution A dissolution test was included in the monograph based on the USP test procedure, with a limit of 75% (Q) in 30 minutes. The monograph would be circulated to manufacturers for comment.

Ibuprofen Capsules – Related substances The unknown peak observed during lab investigation had been confirmed as the ibuprofen PEG ester. A suitable limit for this impurity would be decided at a future meeting subject to further information from manufacturers.

Ibuprofen Orodispersible Tablets
The draft monograph would be included in a future BP publication, subject to comments.

Ibuprofen Tablets, Ibuprofen Prolonged-release Capsules, and Ibuprofen Prolonged-release Tablets – Assay The concentrations for solution (1) in the Tablets, Prolonged-release Tablets and Prolonged-release Capsules monographs would be aligned with laboratory recommendations in a future publication at 0.01% w/v, as the monographs included the same chromatographic conditions as the lab investigation.

The instruction to centrifuge the sample at 2500 g for 5 minutes was considered to be unnecessarily prescriptive in the preparation of solution (1) and would be removed in a future publication.

377 Bisoprolol Tablets (revised)
Content A request had been received with supporting data to widen the Content requirement to 90.0 – 105.0% from 95.0 – 105.0%. Members agreed that a lower content threshold of 92.0% should be included in the draft monograph made available for public consultation. If further justification was received to support a wider content limit of 90.0 – 105.0%, this would be considered at a future meeting.

Identification A A saturation time of 1 hour for the mobile phase had been to added so that the test could be accurately reproduced.

Related substances A request for revision and supporting data had been received to amend the limits in the test. Members recommended that, on the basis of the information provided, the following limits should be consulted on:

- Impurity A: 0.3%
- Impurity G: impurity 1(Bisoprolol N-aldehyde): 0.5%
- Impurity L: 1.0%
- Impurity K: 3.0%
- Impurity M: 0.6%
- Any other secondary peak: 0.2%
- Sum of any other secondary peaks: 3.0% (excluding impurities K and L)

378 Temozolomide Preparations:
Temozolomide Capsules (new)
Temozolomide Injection (new)

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

379 Furosemide Preparations:
Furosemide Injection (revised)
Furosemide Tablets (revised)
Furosemide Oral Solution (new)

Dissolution – Tablets In line with product specifications, the limit was amended to Q = 75% in 45 minutes. The draft monograph would be made available for public consultation.

Related substances column – Injection; Tablets It was noted that the column suggested

in the test was no longer available and members agreed that an alternative suggestion would be included.

Related substances limits – Injection; Tablets The limits for unspecified impurities and the limit of disregard were updated in line with ICH guidelines:

- a limit for any secondary peaks at 0.2% for the Injection monograph
- the disregard limit at 0.1% for the Injection and Tablets monographs.

The draft monograph would be made available for public consultation.

Assay – Injection The test had been updated with a HPLC assay procedure provided by a manufacturer and the draft revised monograph will be posted for public consultation.

Assay – Tablets It was agreed that the Related substances test could be harmonised with the Assay procedure as a university lab project had confirmed this as suitable. The draft monograph would be made available for public consultation.

Oral Solution
The draft monograph would be included in a future BP publication, subject to comments.

380 Chlorhexidine Preparations
Chlorhexidine Gluconate Gel (revised)

Chlorhexidine Mouthwash (revised)
Chlorhexidine Irrigation Solution (revised)
Lidocaine And Chlorhexidine Gel (revised)

Chlorhexidine Gluconate Gel – Monograph Title Following agreement that separate monographs for cutaneous and oral gel products were required, further guidance from EAG PCY and EAG Nomenclature (NOM) would be sought to advise on the suitable monograph titles, which will be discussed at a future meeting.

Chlorhexidine preparations – Review of 4-chloroaniline Limit The limits applied across the preparation monographs and the approach to the limit calculation were under review. Support from a toxicological assessor would be sought to ensure an appropriate limit can be included in a future revision.

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

382 Nicorandil Tablets (revised)

Polymeric impurities/Related substances An additional method had been provided by a manufacturer for the control of both non-polymeric and polymeric impurities and would be investigated by the lab for potential inclusion in the monograph.

Assay An additional method had been provided by a manufacturer which would be investigated by the lab for potential inclusion the monograph.

383 Salbutamol Pressurised Inhalation, Suspension (revised)

Content Clarification had been requested as to whether the updated requirement of 85.0 – 115.0% of the stated delivered dose (ex-actuator) was specific for each formulation. It was confirmed that the content would be specific for labelling requirements of products.

Identification Concerns had been raised that ethanol may interfere with the IR method if used as a co-solvent. As this had already been investigated by the BP Labs when the method was first developed, no change would be required as the test had been written to account for such interference, with wavenumbers between 1650 to 400 cm^{-1}.

Uniformity of delivered dose A system suitability test would be included in the monograph

applying a tailing factor as agreed by members.

Related substances – Limits Requests had been received to amend the limits. Based on product specifications and supporting information the sum of all secondary peaks would be widened to 1.5%.

384 Salmeterol preparations:
Salmeterol Inhalation Powder, pre-metered (new)
Salmeterol Pressurised Inhalation, Suspension (new)

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

385 Ipratropium Pressurised Inhalation, Solution (revised)

Definition; Title The current published monograph (Ipratropium Pressurised Inhalation) states in the Definition that the preparation "is a solution or suspension". The Secretariat agreed to seek guidance from EAG PCY on whether the revised monograph should include this definition or whether only Solutions would be applicable. No change to the monograph was proposed at this time.

Production The requirement for water was questioned as the product was an aqueous solution. The Secretariat agreed to ask PCY to explain the purpose of the water test.

Impurity A Solution concentrations were amended in order to correctly visualise the spots on the TLC plate, as requested by a manufacturer.

Related substances The concentration of the test solution had been amended to 0.04% w/v based on a request received. The retention times had also been questioned by a manufacturer and further information would be sought to understand whether an amendment to the test would be necessary.

Related substances – Limits A request had been received to widen the limits for impurities. Based on ICH guidance and the evidence provided, the limits were been widened to:

- 0.5% for unspecified impurities
- 1.5% for total impurities.

Uniformity of delivered dose As for the Related substances test, the preparation of the test solution was updated based on a request received, to 0.0002% w/v.

386 Pimobendan Preparations (VET)
Pimobendan Capsules (new)
Chewable Pimobendan Tablets (new)

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

387 Adrenaline preparations:
Adrenaline Injection/Epinephrine Injection (revised)
Dilute Adrenaline Injection 1 in 10,000/Dilute Epinephrine Injection 1 in 10,000 (revised)

Related substances A lab investigation would be carried out to optimise separation of impurity F. The results of the investigation would be presented at a future meeting.

Assay A lab investigation would be carried out to evaluate the suitability of two tests for L-adrenaline content determination. The results of the investigation would be presented at a future meeting.

388 Telmisartan and Hydrochlorothiazide Tablets (new)

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

389 MC2 Work status and updates

The MC2 work programme was presented to members for information.

390 Ph. Eur. Updates

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

VI ANY OTHER BUSINESS

None raised at the meeting.

VII DATE OF NEXT MEETING

Wednesday 24 October 2018.