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 1 November 2016.

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

In attendance: Ms H Corns, Mr P Crowley, Ms S Gomersal, Mr A Twitchell (MHRA), Ms F Lee (BP Lab), Ms C Galdino (BP Lab) and Ms M Rueda (BP Lab).

Apologies: None

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

301 Introductory Remarks

Welcome The Chairman welcomed Fiona Lee, Carolina Galdino and Marta Rueda from the BP Lab.

The Chairman made members aware of the BP team restructure and staff changes. The Chairman also thanked Peter Crowley as this was his last MC2 meeting, and his support for the group was commended.

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.

302 Emergency evacuation procedure

The emergency evacuation procedure for the building was provided.

I MINUTES

303 The minutes and summary minutes of the meeting held on 2 March 2016 were confirmed with no amendments.

II MATTERS ARISING FROM THE MINUTES

304 The matters arising and correspondence items from the meeting held on 2 March 2016 were noted.

Chewable Montelukast Tablets, Montelukast Tablets A manufacturer had requested an increase to the limits of total impurities, following the increase in the limit for impurity G. Further justification to an increase to the total impurity limits was requested before any further amendments would be considered.

III MONOGRAPHS

306 Methylphenidate Preparations:
Methylphenidate Tablets (new)
Prolonged-release Methylphenidate Capsules (new)
Prolonged-release Methylphenidate Tablets (new)
The draft monographs would be included in a future BP publication, subject to comments.

307 Ketoprofen Preparations:
Ketoprofen Tablets (new)
Ketoprofen Injection (new)
Ketoprofen Gel (revised)
Ketoprofen Oral Solution (new)
The draft monographs would be included in a future BP publication, subject to comments.

Ketoprofen Gel - Related substances The draft revised test for Related substances was found suitable for the control of impurities with the exception of ketoprofen ethyl ester. A separate test for ketoprofen ethyl ester, using the assay chromatographic conditions, was included in the draft monograph.

Ketoprofen Gel - Assay A solution containing ketoprofen ethyl ester BPCRS was included in the test to allow the analyst to determine the amount of ketoprofen ethyl ester present.

308 Carprofen Preparations:
Carprofen Injection (new)
Carprofen Tablets (new)
The draft monographs would be included in a future BP publication, subject to comments.

309 Phenylephrine Preparations:
Phenylephrine Eye Drops (revised)
Phenylephrine Injection (revised)

Content – Eye Drops The content limits were amended to 95.0 – 105.0%, harmonised with the content limit with the Phenylephrine Injection monograph.

Identification A The TLC identification tests had been replaced with the TLC test used for Identification in both the USP Phenylephrine Hydrochloride Injection and Phenylephrine Hydrochloride Ophthalmic Solution monographs, to remove the use of chloroform.

Identification B – Eye Drops It was agreed that the colour change Identification test would be replaced with a peak comparison in the Assay.

Identification B – Injection It was agreed that the colour change Identification test would be replaced with a peak comparison in the Related substances test. An additional solution containing phenylephrine hydrochloride BPCRS would be included in the Related substances test for this purpose.

Identification C – Injection The proposal to delete the test for chlorides, due to the presence of chloride salt excipients in some products, was accepted.

Acidity or alkalinity – Eye Drops The Secretariat agreed to review pH range.

Related substances The gradient LC procedure, based on the Ph. Eur. Phenylephrine Hydrochloride test, had been found suitable for the products tested. No comments had been received from manufacturers when the revised Related substances test for Phenylephrine Eye Drops was posted for stakeholders on comment.

310 Enalapril Tablets (revised)
The draft monograph would be included in a future BP publication, subject to comments.

311 Adrenaline Injection Preparations:
Adrenaline Injection (revised)
Dilute Adrenaline Injection (revised)

Content Comments had been received requesting that the limits in the draft revised monograph were widened, however members agreed that widened limits were not justified..

The content limit as written in the draft revised monograph potentially permitted 75% of the active L-adrenaline to be present whilst still meeting the requirements of the monograph. It was agreed that an additional content limit for not less than 85% L-adrenaline would be included.

Acidity Members agreed that a range of pH 2.8 to 4.0 would be included, based on product specifications and lab findings.

D-adrenaline To accommodate different formulations and manufacturing processes, a D-adrenaline level of NMT 15% was agreed when coupled with a combined total impurity limit at a similar amount.

Related substances As for D-adrenaline, to accommodate different formulations and manufacturing processes, a D-adrenaline level of NMT 15% was agreed when coupled with a combined total impurity limit at a similar amount. A total impurities limit excluding impurity F in the Related substances test was agreed to control against high levels of other impurities. A sum of impurities including impurity F and D-adrenaline at NMT 16% was considered acceptable. It was agreed that the draft revised monographs should be circulated to stakeholders again prior to publication.

Storage It was agreed that a temperature of 25°C would be included, as temperature had been shown to affect the stability of adrenaline in solution.

312 Phenindione Tablets (revised)

Content Data had been received which indicated that it was necessary to retain a lower limit of 92.5% in the monograph. Members agreed that there was not sufficient justification to retain the upper limit of 107.5%.

Identification A Replacement of chloroform with an alternative solvent would be investigated for a future revision.

Identification B Members agreed that this test could be omitted as the IR was sufficiently discriminatory to be a standalone test.

Dissolution The Secretariat had revised the test based on validated methods and agreed to seek further guidance from Licensing on the suitability of the dissolution medium.

Related substances Comments had been received on the draft method and the Secretariat agreed that the chromatographic conditions would be amended accordingly to incorporate a wider impurity limit for impurity 1 at 1.5%.

Assay Comments received regarding the use of a chilled autosampler and a correction to the extraction solvent were accepted by members.

Phenindione Members requested that the TLC related substances procedure in the Phenindione monograph should be updated with the LC method provided by the manufacturer. Members considered that the titration Assay in the Phenindione monograph should be retained.

313 Indapamide Preparations:
Indapamide Tablets (revised)
Prolonged-release Indapamide Tablets (revised)

Uniformity of content – Prolonged-release Tablets It was noted that there was no Uniformity of content test in the Prolonged-release Tablets monograph, and a test based on the Assay had been included.

Assay It was noted that the mean of the uniformity of content test should be included under Assay. The Secretariat agreed to revise the monograph accordingly.

314 Phenelzine Tablets (revised)

Identification A Replacement of chloroform with an alternative solvent would be investigated

Identification B Members agreed that the colour change test for Identification B should be replaced with a peak comparison to the Assay.

Identification C Members agreed that Identification test C should be deleted as the Identification tests A and B were sufficient to confirm identification.

Dissolution A new test, using an LC procedure was accepted.

Hydrazine A test to control hydrazine would be investigated.

Assay An alternative system suitability requirement to replace peak symmetry would be investigated.

315 Aminophylline Injection (revised)

Content The content of Ethylenediamine would be stated in terms of percentage of the stated amount instead of in grams.

Related substances The following changes to the method were agreed, based on optimisation data provided:

- flow rate changed from 2 mL/min to 1.5 mL/min
- concentration of the test solution changed from 0.25% w/v to 0.01% w/v

Assay of theophylline The Secretariat had drafted a harmonised test with the Related substances in the revised monograph, which was accepted.

316 Co-Beneldopa Preparations:
Dispersible Co-Beneldopa Tablets (revised)
Co-Beneldopa Capsules (revised)

Related substances A request to widen the Related substances in the Co-beneldopa Capsules and Dispersible Tablets monographs had been submitted. As there was sufficient justification on widening the limits, members agreed that the Co-beneldopa Capsules limits could be revised to: Benserazide Impurity A NMT 0.5%, Benserazide Impurity B NMT 0.5% with a total of NMT 1.5%. It was also agreed that the Dispersible Co-beneldopa Tablets limits should be revised to: Benserazide Impurity A NMT 0.5%, Benserazide Impurity B NMT 1.0% with a total of NMT 2.0%. For both monographs, it was agreed that the disregard limit should be increased to 0.1% in-line with ICH.

317 Telmisartan Tablets (new)
The draft monographs would be included in a future BP publication, subject to comments.

318 Temozolomide Preparations:
Temozolomide Capsules (new)
Temozolomide Injection (new)
The draft monographs would be included in a future BP publication, subject to comments.

319 Methylthioninium Injection (revised)
Characteristics It was agreed that a Characteristics section should be included, describing the colour of the injection.

Related substances limits Members agreed that the limit for unspecified impurities in the BP monograph should be aligned with ICH and the Ph. Int. draft, at 0.2%.

320 Omissions
Members were presented with a list of proposed monographs for omission from the BP 2018. It was agreed that omission should be proposed to BPC.

IV FOR INFORMATION

321 Olmesartan Tablets (revised)
It had been brought to the attention of the Secretariat that an incorrect mobile phase had been published in the Related substances test. The method should have matched the Ph. Eur. Related substances method. This would be rectified by means of the BP 2018 and a letter of intent had been posted on the BP website to inform users of the error.

322 Chlorhexidine Gluconate Gel (revised)
It had been brought to the attention of the Secretariat that there was an error in the test solution concentrations in the Assay, which would be rectified by means of the BP 2018, along with a minor correction to the equivalence figure for the determination of content. A letter of intent had been posted on the BP website to inform users of the error.

323 Anastrozole Tablets (new)
Members were informed that Lab investigation was being carried out at the time and that the monograph should be presented at a future meeting.

MC2 Work status and updates
The MC2 work programme was presented to members for information.

V ANY OTHER BUSINESS

VI DATE OF NEXT MEETING

The date of the next meeting is 13 April 2017.