

**BRITISH PHARMACOPOEIA COMMISSION  
EXPERT ADVISORY GROUP (EAG): MEDICINAL CHEMICALS 1 (MC1)**

**SUMMARY MINUTES**

A meeting of Expert Advisory Group (EAG): Medicinal Chemicals 1 (MC1) was held at 151 Buckingham Palace Road, London SW1W 9SZ on Tuesday, 15<sup>th</sup> December 2015.

**Present:** Professor A G Davidson (*Chairman*), Professor D Cairns (*Vice-chairman*), Dr. M Ahmed, Dr. J C Berridge, Mr. M Broughton, Mr. A J Caws, Mr. P Fleming, Dr. J Lough and Mr. D Malpas.

**Apologies:** Mr. A James

**In attendance:** Mrs. M Barrett, Ms. H Corns, Mr. N Vadukul and Ms. K. Busuttil

**359 Welcome**

The Chairman welcomed everyone to the meeting.

**I GENERAL MATTERS**

**360 Minutes**

The minutes and summary minutes of the meeting held on 8<sup>th</sup> June 2015 were confirmed.

**361 Emergency evacuation procedure** MC1 (15) 31

The emergency evacuation procedure for Buckingham Palace Road was noted.

**362 Declaration of interests** MC1 (15) 32

Mr. A Caws, Professor D Cairns, and Dr. J Lough declared interests in one or more agenda items and appropriate action was taken.

**363 Issues arising from the BP Commission** MC1 (15) 33

Members were provided with an update on matters recently discussed by the BP Commission.

**Summary minutes** In future a brief statement on members' interests would be included at the beginning of summary minutes of meetings of the BP Commission, the Expert Advisory Groups and Panels of Experts.

**Triennial Review** The review had recommended publication of draft monographs, for public consultation on the BP website, at agreed times and with a set date for comments.

**Assay limits** The standard assay limits for BP formulated preparation monographs were "95.0 to 105.0% of the stated amount", unless wider limits were justified. Some older monographs had wider limits and it was suggested that the Secretariat should introduce a formal revision programme with a view to updating monographs that contained out of date specifications. It was noted that other aspects needed to be taken into consideration, for example the process capability and the accuracy/precision of a method. It was noted that there were no ICH guidelines on limits.

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2015

**European Pharmacopoeia Commission (EPC) Issues** A summary of the EAG: MC1 related decisions, taken at EPC Sessions, were provided for information.

**364 BP website MC1 (15) 34**

The Secretariat informed members that the new BP website went live in August 2015 and a demonstration of the new site was given. The Secretariat also informed members that draft new and revised monographs would be posted to the BP website at regular intervals for comment beginning in 2016. The four intervals would be 1 January to 31 March, 1 April to 30 June, 1 July to 30 September and 1 October to 31 December.

## II MATTERS ARISING FROM THE MINUTES

**365 Matters arising MC1 (15) 35**

A list of 'Matters Arising' from the minutes of the meeting of EAG: MC1, held in June 2015, and those outstanding from previous meetings has been appended (Annex 1).

**366 MC1 status update MC1 (15) 36**

A document outlining the EAG: MC1 work schedule was presented for information.

## III NEW MONOGRAPHS

**367 Chewable Mebendazole Tablets MC1 (15) 37**

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

**368 Metformin and Sitagliptin Tablets MC1 (15) 38**

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

**369 Sitagliptin and Prolonged-release Metformin Tablets MC1 (15) 39, Annexes 1-7**

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

**370 Prolonged-release Carbamazepine Tablets MC1 (15) 40**

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

**371 Ritonavir Oral solution MC1 (15) 41**

Members agreed to defer this item to the next meeting due to time constraints.

**372 Ritonavir Tablets MC1 (15) 42**

Members agreed to defer this item to the next meeting due to time constraints.

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2015

### IV MONOGRAPHS IN PROGRESS

**373 Loperamide Tablets MC1 (15) 43**

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

**374 Loperamide Oral Solution MC1 (15) 44**

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

**375 Orodispersible Loperamide Tablets MC1 (15) 45**

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

**376 Carbamazepine Oral Suspension MC1 (15) 46**

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

**377 Chewable Carbamazepine Tablets MC1 (15) 47**

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

**378 Prolonged-release Metformin Tablets MC1 (15) 48**

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

**379 Leflunomide Tablets MC1 (15) 49**

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

**380 Moxonidine Tablets MC1 (15) 50**

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

**381 Valaciclovir Tablets MC1 (15) 51**

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

**382 Pantoprazole Preparations: MC1 (15) 52  
Pantoprazole For Injection  
Gastro-resistant Pantoprazole Tablets**

Members were informed that the BPC had agreed that when methods were assessed by the Secretariat to evaluate whether BP laboratory assessment was required, a standard documentation of the risk-based assessment should be recorded. This would ensure a consistent approach across all the Expert Groups. As a worked example, the Secretariat

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2015

had compared the formal approach to Pantoprazole preparations which had previously been discussed by members at the June 2014 meeting.

### V REVISION OF MONOGRAPHS

#### 383 Loperamide Capsules MC1 (15) 53

The monograph for Loperamide Capsules in BP 2015 tests only for impurity F (Loperamide *N*-oxide). The BP Laboratory assessed a draft Related substances test for the Capsules and the results were presented to members.

**Related substances** The BP Laboratory carried out testing on hard and soft shell capsules. Members agreed that the test as drafted was suitable for both types of capsule. An instruction to freshly prepare the solutions was included on the advice of the laboratory.

**Publication** The revised monograph would be published in BP 2017.

#### 384 Paracetamol Capsules, Soft Gel MC1 (15) 54

Members would seek advice on whether a new monograph should be developed and discuss this item at the next meeting.

#### 385 Warfarin Tablets MC1 (15) 55

The BP Laboratory had assessed the draft revised Related substances test for Warfarin Tablets using HPLC and found it suitable for all the samples tested.

385.1 **System suitability solution** A solution containing 0.002% w/v each impurity B and impurity C was proposed by the laboratory for system suitability as per the Ph. Eur. monograph. A resolution of not less than 2.0 had been drafted. Members agreed that this solution should be included in the test.

385.2 **Warfarin Sodium Clathrate Tablets** The monograph for Warfarin Tablets applied to products containing Warfarin Sodium and Warfarin Sodium Clathrate. The Laboratory was unable to source any samples of the Clathrate form for testing. The Secretariat would circulate the draft to manufacturers of the Clathrate for comment.

385.3 **Publication** The revised monograph would be published in BP 2017 subject to comment from manufacturers.

#### 386 Ranitidine Preparations: MC1 (15) 56 Ranitidine Injection Ranitidine Oral Solution Ranitidine Tablets

**Related substances** A review of limits in the BP monograph for Ranitidine Tablets had been requested as the current limits were not aligned with ICH guidelines. The Related substances tests in Ranitidine Injection, Ranitidine Oral Solution and Ranitidine Tablets monographs had been updated from TLC to LC methods in the BP 2008; however the original limits had been retained with a view to future review. Revised limits in line with the Ph. Eur. monograph for Ranitidine Hydrochloride were agreed with a view to encouraging manufacturers to comment and provide information to ensure that appropriate limits were set.

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2015

- 387 Pyrimethamine Tablets MC1 (15) 57**
- Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.
- 388 Piperonyl Butoxide MC1 (15) 58**
- A revised monograph for Piperonyl Butoxide has been published in BP 2016. Following publication a manufacturer had asked that the Related substances gradient table was amended to include the term *isothermal*. Members agreed that this amendment would be made for BP 2017.
- Total limit for impurities** Members agreed that a request to widen total impurities to 2.5%, from the published 2.0%, would be supported and the revised monograph would be published in BP 2017.
- 389 Alverine Capsules MC1 (15) 59**
- Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.
- 390 Cetirizine Tablets MC1 (15) 60**
- A manufacturer had requested that the limit of disregard in the Related substances test for Cetirizine tablets was amended to 0.1% from 0.05% - the ICH guideline limit for tablets with a maximum daily dose of less than 1g. Members agreed that the limit would be amended for BP 2017.
- 391 Baclofen Tablets MC1 (15) 61**
- Assay** The BP Laboratory had been asked to assess a system suitability requirement for the Assay of Baclofen Tablets when retesting Baclofen assay standard. After reviewing the laboratory report members agreed that a system suitability solution containing 0.2% w/v of baclofen and 0.004% of impurity A would be suitable and a requirement of resolution of at least 7 would be included in the monograph.
- Baclofen Injection** The Secretariat had identified a number of MAH for baclofen injection/infusion products and proposed that a monograph for these products should be developed, as family monographs can be automatically initiated when identified. Members endorsed the proposal to add Baclofen Injection to the MC1 work programme.
- VI **REPORTS AND CORRESPONDENCE**
- 392 Meloxicam Injection (BP Vet.) MC1 (15) 62**
- Members agreed to progress this item by correspondence in the week following the meeting.
- POST MEETING NOTE:** Following the meeting members reviewed a request from a manufacturer to revise the pH limits and Related substances test in the monograph for Meloxicam Injection
- Alkalinity** A manufacturer had stated that pH limits at shelf-life of 7.5 to 9.1 were registered in their UK licence. The current BP limits were pH 8.0 to 9.0. Members reviewed the data provided and agreed that the pH limits would be widened to 7.5 to 9.1 for BP 2017.

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2015

*Related substances* The manufacturer also requested that the limits in the monograph were revised to follow VICH guidelines. Members agreed that each unspecified impurity would be limited at NMT 1.0% and impurities A and B would also be limited at NMT 1.0%.

*Related substances Impurity B* Members agreed that the limit for impurity B would be widened to NMT 2.0% after reviewing the submitted data.

*Limit of disregard A* A limit of disregard of 0.3% was agreed.

*Circulation to stakeholders* The draft revised monograph would be circulated to stakeholders and, if no adverse comments were received, the revised text would be published in BP 2017

**393 Papaveretum MC1 (15) 63**

Members agreed to progress this item by correspondence in advance of the next meeting, due to time constraints.

**394 Cyclizine Injection MC1 (15) 64**

Members agreed to progress this item by correspondence in the week following the meeting.

**POST MEETING NOTE: *Related substances limits*** Following the June 2015 meeting the manufacturer had been asked to provide further data to support their request to widen the limits for each of impurity A and impurity B to not more than 2.0%. Members reviewed the submitted data and agreed that the limits would be widened for BP 2017.

**395 Halquinol MC1 (15) 65**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

**396 Metformin Tablets MC1 (15) 66**

***Circulation to stakeholders*** Following the June 2015 meeting the draft revised monograph was circulated to manufacturers for comment. The manufacturer who supplied the data for Prolonged-release Metformin Tablets stated that their product complied with the current BP monograph and they would prefer that the current Related substances test and Assay remained in the publication. Members agreed to put the revision on hold until further feedback was received from manufacturers.

**397 Caffeine Citrate Injection MC1 (15) 67**

Members agreed to progress this item by correspondence in the week following the meeting.

**POST MEETING NOTE: *Acidity limits*** The acidity limits for Caffeine Citrate Injection in BP 2015 were 4.2 to 5.2. These limits had been based on the licensed product available in the UK when the monograph was developed. Another manufacturer had obtained a Marketing Authorisation with a pH specification of 2.0 to 3.0. This manufacturer had explained that their product was prepared with caffeine and citric acid whereas the other licensed product was prepared with caffeine, citric acid and sodium citrate. Members agreed by correspondence that the acidity range would be widened to pH, 2.0 to 5.2 for BP 2017.

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2015

- 398 Cisplatin Injection MC1 (15) 68**
- Members agreed to progress this item by correspondence in advance of the next meeting, due to time constraints.
- 399 Dipyridamole Oral Suspension MC1 (15) 69**
- Members agreed to progress this item by correspondence in the week following the meeting.
- POST MEETING NOTE: Acidity** Following a review of pH data for the UK licensed products for Dipyridamole Oral Suspension members agreed by correspondence that the acidity limits would be widened to pH 5.4 to 6.4. The change would be published in BP 2017.
- 400 Degree of Hydration MC1 (15) 70**
- This item was presented for information, members were asked to note that changes to MC1 monographs may be required in light of Ph. Eur. proposing hydrate naming changes. The amendments would be carried out and checked within the Secretariat.
- 401 Heavy Metals Test MC1 (15) 71**
- This item was presented for information. Members noted that the BP would be harmonising with the Ph. Eur. approach for the implementation of ICH Q3D. Heavy metals tests would be deleted from specific human medicines' monographs and the Secretariat would be taking this opportunity to identify candidates for revision or omission.
- 402 Any Other Business MC1 (15) 72**
- Meloxicam preparations**
- Members agreed to progress this item by correspondence in advance of the next meeting, due to time constraints.
- Speaking to papers**
- Members agreed to progress this item by correspondence in advance of the next meeting, due to time constraints.
- Propofol Injection**
- Members agreed to progress this item by correspondence in advance of the next meeting, due to time constraints.
- Reports and Correspondence vs Revision of monographs**
- Members agreed to progress this item by correspondence in advance of the next meeting, due to time constraints.
- Prolonged-release Diltiazem Tablets**
- Members agreed to progress this item by correspondence in advance of the next meeting, due to time constraints.

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2015

**403**     **Dates of next meetings**  
**2016:**  
Monday 6<sup>th</sup> June  
Tuesday 13<sup>th</sup> December

**MC1 (15) 73**

**Annex 1. Matters arising from previous meetings other than those mentioned on the agenda**

<b>Itraconazole Capsules</b>	A requisition had been submitted to the BP Laboratory and the draft new monograph had been posted on the BP website for initial comments.
<b>Cinnarizine Tablets</b>	A requisition had been submitted to the BP Laboratory.
<b>Phenytoin Preparations</b>	The MHRA Laboratory was in the process of carrying out a product survey and had been asked by the Secretariat to assess the Ph. Eur. method for Related substances for use in the BP monographs to control Related substances and Assay in all formulations. Dissolution tests will also be included in the Capsules and Tablets monographs following the completion of the lab work.
<b>Amlodipine Tablets</b>	The BP Laboratory to start the assessment at the earliest opportunity.
<b>Aspirin Tablets</b>	The BP Laboratory to continue the assessment at the earliest opportunity.