

BRITISH PHARMACOPOEIA COMMISSION

Committee B: Medicinal Chemicals

MINUTES: 28th October 2003

IV NEW MONOGRAPHS

504 (Ramipril Preparations (tablets) ^{pink} B(03)12, Annexes 1 to 4

504 1 **General** Draft monographs for Ramipril Capsules and Ramipril Tablets were presented based on information received from [REDACTED] and taking note of the Ph Eur monograph for Ramipril. Members noted that a monograph for Ramipril Capsules had been included on the BP work programme for some time [REDACTED]

The BP Commission had recommended that monographs for both formulations should be developed but that, in accordance with current policy, publication of the tablets monograph should be deferred until a marketing authorisation had been granted [REDACTED]

[REDACTED] However, members were reminded that products had to meet a set of agreed criteria before elaboration of a monograph was approved and that monographs could not set tighter than the registered limits

[SECRETARIAT NOTES
[REDACTED]

(2) A marketing authorisation for the tablets formulation has now been granted]

504 5 **Related substances** [REDACTED] had proposed an isocratic HPLC method which was similar to that proposed for assay determination. The method was accepted, subject to confirmation from [REDACTED] that the necessary reference materials were available and to minor editorial corrections. The company would also be asked why the proposed limits were "slightly tighter than the currently approved Product Licences" and to clarify the need for two pH adjustments during preparation of the mobile phase.

Limits It was noted that there were currently four strengths available of each formulation (containing 1.25, 2.5, 5 and 10 mg of ramipril). Limits of 5% for the diketopiperazine impurity (main degradation impurity), 0.5% for one impurity, 0.2% for any other impurity and 6% for the sum of total impurities had been proposed for the tablets formulation and for the three higher strength capsule formulations. The 1.25 mg capsules were less stable and limits of 8% for the diketopiperazine impurity and 9% for the sum of total impurities had been proposed for this formulation. Stability data had been provided to support the need for different limits and this was also reflected in the shorter shelf-life for the 1.25 mg capsules.

Members were reluctant to include the more relaxed limits in a single monograph intended to cover all strengths of the capsules formulation. It was suggested that the tighter limits should be specified

and that [REDACTED] should be encouraged to amend the shelf-life of the 1.25 mg capsules in order to bring them within the specification. However, it was pointed out that the different sets of limits had been accepted by the Licensing Secretariat and so this approach was not possible. It was suggested that separate sets of limits for impurities should be included within a single monograph. Alternatively, the feasibility of including a separate monograph for the lowest strength formulation was proposed. It was agreed that advice on this aspect should be sought from the BP Commission.

Committee B: Medicinal Chemicals

MINUTES: 25th October 2004.

V MONOGRAPHS IN PROGRESS

538 **Ramipril Capsules**
539 **Ramipril Tablets**

B(04)13; Annexes 1& 2
B(04)14; Annex 1

538.2 **Related substances** The Chairman had referred the issue on impurity limits from the last meeting (minute 504 referred) to the Commission which decided that there should be a single monograph for all strengths of capsules. However, in the test for related substances there should be separate limits for the lowest strength formulation (which was reported to be less stable [REDACTED]). Members noted the significant differences in limits for related substances between [REDACTED] products, where the principal degradation products were given as the Ramipril-Diketopiperazine and Ramipril-Diacid (also known as 'ramilprilat', the

principal metabolite) respectively. [REDACTED] confirmed that both of the impurity profiles were registered and were satisfactory from a regulatory perspective, since they were both qualified. Members recalled that the Ph Eur monograph for the parent compound limits the Ramipril-Diketopiperazine as a specified impurity, whereas the Ramipril-Diacid is listed as 'other detectable', and agreed that the limits must cover the ranges of both impurity profiles.

The committee advised that a comparison of different samples using both methodologies, with aged samples if possible, would be useful for the Laboratory to perform.

ACTIONS

(b) The Laboratory to check related substances using samples and methods from both manufacturers.

Committee B: Medicinal Chemicals

MINUTES: 28th November 2005.

V MONOGRAPHS IN PROGRESS

594 **Ramipril Capsules**
Ramipril Tablets

B(05)34; Annexes 1 & 2
LR 5260, LR 5259

594.2 **Related substances** The Secretariat agreed to amend the test taking into account differences in the limits applied by each manufacturer.

ACTIONS (a) The Secretariat to amend the monograph as agreed and circulate to manufacturers.
(b) The Laboratory to establish a BPCRS for Ramipril.

Expert Advisory Group MC2: Medicinal Chemicals

MINUTES: 31st October 2006.

III REPORTS AND CORRESPONDENCE

647 **Ramipril Tablets**

MC2(06)6; Annexes 1 to 3

647.1 Correspondence had been received requesting that the test for Related Substances set different limits dependent on the quantity of Ramipril in the tablets and that the limits set for named impurities were revised in line with the degradation pathways. Ramipril degraded to ramipril diacid under acidic conditions and ramipril diketopiperazine under basic conditions. It was noted that the published monograph for Ramipril Capsules set different limits dependent on the quantity of Ramipril in the product; however, the limits for impurities D and E in this monograph appeared to be reversed in comparison with those for the tablet formulation.

- 647.2 An innovative form of words would be required in drafting a test to allow for both degradation pathways. [REDACTED] agreed to prepare a draft test that provided limits for a combination of impurities D and E of not more than 6% for tablets containing 2.5 mg or more of Ramipril and 8% for tablets containing 1.25 mg of Ramipril. The total for all impurities would remain the same. It was suggested that for consistency, these changes should also be applied to the monograph for Ramipril Capsules.

ACTIONS: The Secretariat to amend the monograph as agreed.

Expert Advisory Group MC2: Medicinal Chemicals

MINUTES: 27th March 2007.

III REPORTS AND CORRESPONDENCE

713 Ramipril Tablets and Capsules MC2(07)8; Annexes 1 to 3

- 713.2 At the previous meeting of Expert Advisory Group MC2, held on 31st October 2006, it was agreed that the Related substances test for Ramipril Capsules and Tablets should be redrafted to allow for both acidic and basic degradation pathways (minute 647 refers). Further correspondence had been received from a manufacturer regarding the limits for impurities in these monographs and highlighting that, in certain circumstances, the BP monograph for the formulated products set a higher standard than that required by the Ph. Eur. monograph for Ramipril parent material.
- 713.3 The Secretariat had revised the Related substances test limits in the monographs for Ramipril Capsules and Tablets taking into consideration the points above. Members considered that the revised text was suitable; however, it was agreed that limits of not more than 0.2% should also be included for unknown impurities and that the impurities should be listed as in the Ph Eur monograph for the parent substance.

ACTIONS: The Secretariat to amend the monograph as agreed