*EP Attorney Letter Head*

***Via Facsimile and Registered Mail***

Xx January 2019

European Patent Office (Munich)
80298 Munich
Germany

Our Reference

European Patent Application No: 16767831.7
Applicant: UNICHEM LABORATORIES LIMITED

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We are writing in response to the communication pursuant to Rules 70(2) and 70a(2) EPC, dated 07.08.18.

At the outset it is confirmed that it is desired to proceed further with the subject European patent application.

In view of the objections raised in the opinion accompanying the European Search Report, we submit amended claims 1-9 as a basis for further examination. The amended claims are enclosed as a highlighted version of the claims previously on file and as a clean copy. We respectfully ask to at this point defer any amendments to the description.

## I. Amendments to the Claims

Claim1 has been amended solely to address formal issues.

Claims 2 to 6 remain unchanged.

Claim 7 has been amended. The term “comprises” has been cancelled and replaced by the term “is”.

Claim 8 remains unchanged.

Claims 9 to 24 have been cancelled without prejudice or disclaimer.

New claim 9 has been added to recite that the potassium salt of azilsartan medoxomil obtained in claim 1D) is crystalline. Basis for this claim can be found in paragraphs [0064] and [0071] of the application as originally filed.

As none of the above amendments comprise subject matter extending beyond the application as originally filed, they should be allowable within the meaning of Article 123(2) EPC.

## II. Comments Regarding the Objections Raised in the European Search Opinion

### Article 123(2) EPC:

The Examiner deems that the claim set filed with entry into the EPO-phase does not satisfy the requirements of Article 123(2) EPC because previous claim 7 has been broadened in an unallowable way by replacing the term “is” by the term “comprises”. Applicant has now amended claim 7. As suggested by the Examiner, the term “is” has been reinstated in claim 7. Thus, this objection is rendered moot and should be withdrawn.

### Unity:

The Examiner deems that the present application lacks unity within the meaning of Article 82 EPC. The Examiner listed the following groups of claims, each held to relate to a different invention:

Group 1: Claims 1-9 and 16-24

A process for the preparation of any form of azilsartan medoxomil potassium

Group 2: Claims 10-15

Applicant respectfully disagrees. However, solely in an effort to expedite prosecution of the present application, the Applicant herewith submits an amended claim set *inter alia* comprising the (amended) original process claims 1 to 8 (Examiner's "group 1"). The subject matter directed towards crystalline form of azilsartan medoxomil potassium in claims 10-15 has been removed. It has to be understood that the amendments made herein should not be construed as an admission or an abandonment of any subject-matter of the original application. The applicant reserves the right to pursue any originally disclosed subject-matter later in these proceedings or in subsequent divisional applications pursuant to Article 76 EPC.

**Novelty:**

The Applicant is pleased to note that the Examiner has acknowledged that the subject-matter of previous claims 1 to 24 is novel over the prior art of record.

**Inventive Step:**

The Examiner stated that the subject-matter of the previous claims 1-9 and 16-24 is not inventive over the combination of D1 and D2. The Examiner also stated that previous claims 10-15 lack inventive step over D1 or D2 in view of the common general knowledge in the art. Applicant respectfully disagrees.

With this response, previous claims 9 to 24 have been cancelled and thus the inventive step objection raised against these claims no longer applies.

The present set of claims contains claims 1 to 9, which are directed to a process for preparation of potassium salt of azilsartan medoxomil. Claim 1, the sole independent claim, reads as follows:

> "*A process for the preparation of Azilsartan Medoxomil Potassium, which comprises:*
>
> *A) Dissolving Azilsartan Medoxomil in a mixture of Chlorinated solvent and an Alcohol to obtain a clear solution of Azilsartan Medoxomil;*

B) *Dissolving organic or inorganic Potassium source in a mixture of Chlorinated solvent and an Alcohol to obtain a second solution;*

C) *Adding second solution obtained in step B), drop wise to the solution of Azilsartan Medoxomil prepared in step A), to precipitate out Azilsartan Medoxomil potassium; and*

D) *Isolating Azilsartan medoxomil potassium*."

D1 discloses crystalline forms A, B, C, D, E, F, G, H, I, J, K and L of azilsartan medoxomil potassium. D1 also discloses process for preparing the disclosed crystalline forms of azilsartan medoxomil potassium, the process comprising dissolving azilsartan medoxomil in a solvent to form a solution, adding potassium salt to the solution, then forming crystals at a suitable temperature. According to the invention of D1, the solvent used for producing the particular crystalline forms of azilsartan medoxomil potassium is selected from dimethyl formamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, water, ether solvents, ketone solvents, ester solvents, aromatic hydrocarbon solvents, alkane solvents, nitrile solvents and combinations thereof (see, D1, paragraph [0043]). In the embodiments of D1, the alkane solvents are selected from dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride, nitroethane, n-hexane, cyclohexane or n-pentane or n-heptane; the aromatic hydrocarbon solvents are selected from benzene, toluene or xylene; and the nitrile solvents are selected from acetonitrile or malononitrile (see, D1, paragraph [0045]).

D1 does not disclose any alcohol solvent, let alone a mixture of a chlorinated solvent with an alcohol solvent for preparation of azilsartan medoxomil potassium starting from azilsartan medoxomil, as recited in the present independent claim 1.

Further, the cited reference D1 discloses very detailed procedures and solvent combinations for preparing the particular crystalline forms of azilsartan medoxomil potassium. The preparation procedures of D1 which make use of chlorinated solvent are depicted below:

| Procedure | Solvent combination | Product |
|---|---|---|
| Example 8 | Dichloromethane(DCM) - acetone | Crystalline form C of Azilsartan medoxomil potassium |
| Example 13 | 1,2-dichloroethane - acetone | Crystalline form C of Azilsartan medoxomil potassium |
| Example 16 | 1,2-dichloroethane - tetrahydrofuran (THF) | Crystalline form C of Azilsartan medoxomil potassium |
| Example 18 | 1,2-dichloroethane - acetone | Crystalline form C of Azilsartan |

| | | |
|---|---|---|
| | | medoxomil potassium |
| Example 29 | Chloroform - acetone | Crystalline form E of Azilsartan medoxomil potassium |
| Example 32 | Tetrachloromethane - tetrahydrofuran (THF) | Crystalline form G of Azilsartan medoxomil potassium |
| Example 40 | Dichloromethane(DCM) - dimethylsulfoxide (DMSO) | Crystalline form J of Azilsartan medoxomil potassium |

Applicant respectfully submits that the processes disclosed in D1 are very specific and detailed with respect to solvent combination. D1 does not suggest or provide motivation for a skilled person to modify those detailed processes disclosed by D1, which were specifically designed to produce particular crystalline forms C, E, G and J of azilsartan medoxomil potassium. The production of such crystalline forms disclosed by D1 was taught as requiring the disclosed detailed preparation procedures.

D2 discloses a process for preparing potassium salt of azilsartan medoxomil, the process comprising the steps of: (a) dissolving azilsartan medoxomil methylene dichloride solvate in one or more of suitable organic solvents to obtain solution; (b) adding potassium source to the solution to obtain azilsartan medoxomil potassium in reaction mixture; and (c) obtaining azilsartan medoxomil potassium by removal of solvent (see, D2, claim 46). According to D2, the suitable organic solvent comprises one or more of methanol, ethanol, isopropanol, n-butanol, acetone, methyl ethyl ketone, methyl isobutyl, ketone, acetonitrile, dimethyl formamide, dimethyl acetamide, dimethylsulfoxide, N-methyl pyrrolidone, acetic acid, ethyl acetate, isopropyl acetate, isobutyl acetate, and butyl acetate (see, D2, claim 49).

D2 does not disclose any chlorinated solvent, let alone a mixture of a chlorinated solvent with an alcohol solvent for preparation of azilsartan medoxomil potassium starting from azilsartan medoxomil, as recited in the present independent claim 1.

Furthermore, the process disclosed in D2 for the preparation of azilsartan medoxomil potassium is completely different than the process employed in the present application. The processes taught in D2 for making azilsartan medoxomil potassium is highly detailed, requiring “methylene dichloride solvate of azilsartan medoxomil” as starting material, single solvent for reacting azilsartan medoxomil with potassium source (acetone in Example-6 of D2, methanol in Example-7 of D2), and an anti-solvent (water in Example-7 of D2) to precipitate azilsartan medoxomil potassium from the reaction mixture. D2 does not disclose or suggest any process wherein a potassium salt of azilsartan medoxomil is prepared by

making a solution of azilsartan medoxomil in a mixture of chlorinated solvent with an alcohol and then mixing therewith a potassium source dissolved in a mixture of chlorinated solvent and an alcohol to precipitate out azilsartan medoxomil potassium. It is therefore evident that the processes for preparing potassium salt of azilsartan medoxomil disclosed in D2 are completely different from the process of the present application.

Furthermore, as explained in paragraphs [0063] and [0064] of the present application, when azilsartan medoxomil is dissolved in single chlorinated solvent or single alcohol solvent to make a solution thereof, the azilsartan medoxomil does not remain in solution for longer period of time, and the end product of the process is not obtained in high crystalline quality. Surprisingly, use of a mixture of a chlorinated solvent with an alcohol results in a solution of azilsartan medoxomil which remains clear for longer period of time and results in a highly crystalline end product, i.e. azilsartan medoxomil potassium. Therefore, the use of a mixture of a chlorinated solvent with an alcohol for the preparation of azilsartan medoxomil potassium starting from azilsartan medoxomil cannot be said to be obvious, on the basis of a combination of documents D1 and D2.

For the reasons set forth above, it is therefore respectfully submitted that it is not obvious to combine the teachings of the individual references and that the skilled person would have no incentives and no valid reasons for combining the cited references D1 and D2. Applicant respectfully submits that the process of independent claim 1 is very different, requiring different solvents and different process steps. The cited references D1 and D2, alone or in combination, would not have provided the skilled person with the motivation or with a reasonable expectation of success in undertaking the significantly different process of independent claim 1, nor would such different process be perceived by the skilled person to have a predictable result.

In view of the foregoing, Applicant respectfully submits that independent claim 1 is inventive and as such, independent claim 1 is patentable over the prior art of record. Further, dependent claims 2-9 are similarly patentable not only by virtue of their dependency from patentable independent claim, but also by virtue of the additional features of the invention they define.

In light of the arguments presented above, Applicant kindly requests that the inventive step objection be withdrawn.

**Clarity:**

The Examiner remarks that the present application does not comply with Rule 43(2) as it contains two independent process claims 1 and 16 and two independent product claims 10 and 13 in the same category. It is believed that said objection is overcome by the present claim amendments wherein previous independent claims 10, 13 and 16 have been deleted. The present application now comprises only one independent claim, i.e. claim 1.

Previous claims 9-13, 15 and 16 have been cancelled and thus the clarity objections raised against these claims no longer apply.

**III. REQUEST:**

Based on the above submissions and enclosed amended claims, Applicant respectfully requests allowance of the claims and a speedy grant of the patent.

Nonetheless, should the Examiner have further issues, a Communication under Art 94(3) is requested. In order to avoid direct rejection of the present application, oral proceedings under Art 116 EPC are requested.

Sincerely yours,

Enclosures:
Marked up copy of Amended claims
Clean copy of amended claims