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European Patent Office
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By epoline

20 September 2019

Our Ref: ADAR-901/01EP 325049-3194

Dear European Patent Office,

Re: European Patent No. 2482822
Orally Administered Corticosteroid Compositions
Adare Development I, L.P.

1. General

1.1 The Patentee, Adare Development I, L.P., herein provides its response to the Grounds of Opposition filed by Dr. Falk Pharma GmbH pursuant to Article 99 EPC.

1.2 The Patentee will refer to the numbering of documents utilised by the Opponent.

2. Requests

2.1 The Patentee requests the maintenance of European Patent No. 2482822 (hereinafter "the Patent") as granted.

2.2 Oral Proceedings under the provisions of Article 116 EPC are requested in the event that the Opposition Division is minded to decide otherwise.

2.3 Although the Patentee does not consider any claim amendments to be warranted by the Opponent's Grounds of Opposition, the right to file one or more Auxiliary Requests in response to issues raised, and in order to meet the requirements of the European Patent Convention, is expressly reserved.

3. Documents

3.1 The Opponent has relied upon D1 and D4-D6 in its statement, all of which were published prior to the priority date of the Patent (1 October 2009) and, therefore, are available for the assessment of novelty and inventive step for the subject matter claimed in the Patent.

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3.2 The Opponent has also relied upon D2, which is an International (PCT) patent application that has validly entered its European regional phase of processing. D2 was filed before, but published after, the date of filing of the Patent (30 September 2010). As the priority claim for the Patent is valid, D2 can only form part of the state of the art for the Patent if its own priority claim is valid. The Opponent has asserted that this is the case. If true, D2 is citeable under Article 54(3) EPC only, i.e. available for the assessment of novelty, but not inventive step, for the subject matter claimed in the Patent.

3.3 The Opponent has also relied upon D3, which is a US patent application that was published after the date of filing of the Patent (by virtue of it being the priority document for D2). Consequently, D3 is not part of the state of the art for the subject matter claimed in the Patent.

3.4 The Patentee files herewith the following documents in support of its submissions.

D7 Jorveza® summary of product characteristics, first published 18 January 2018 (downloaded from the European Medicines Agency at www.ema.europa.eu/en/medicines/human/EPAR/jorveza#product-information-section);

D8 Jorveza® 1 mg tablets package leaflet (PIL) for United Kingdom-Ireland, dated 15 March 2018;

D9 Breuer *et al., Pure Appl. Chem.*, 2009; 81(5): 971-999;

D10 PubChem extract, information available as of 15 October 2015 (downloaded from https://pubchem.ncbi.nlm.nih.gov/compound/Budesonide#section=Solubility&fullscreen=true);

D11 Bonnet *et al., Pharm Technol Hosp Pharm* 2018; 3(2): 91-99; and

D12 Miehlke *et al., Gut* 2016; 65: 390-399.

4. Subject Matter of the Patent

4.1 The Patent generally relates to orally administered corticosteroid compositions that are useful for treating conditions associated with inflammation of the gastrointestinal (GI) tract. The Patent highlights one condition in particular, namely eosinophilic oesophagitis (EE). EE is an inflammatory disease of the oesophagus that is painful, leads to difficulties in swallowing and predisposes patients to complications such as food impaction (see paragraphs [0002] *et seq.* of the Patent).

4.2 The Patent explains that, at the time of the invention, there were no approved topically applied anti-inflammatory drugs for treatment of conditions associated with inflammation of the (upper part of) the GI tract (see paragraph [0002] of the Patent). The experimental and "off-label" treatments previously known in the prior art, however, had a number of problems and unwanted side effects. The systemic administration of corticosteroids in

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particular was viewed as negative. In contrast to this, topical administration offers a local effect.

4.3 The experimental and "off-label" treatments for EE known in the prior art were steroid drugs formulated and approved for inhalation. The medications were directed at the back of the throat. As a result, these drugs were not appreciably administered. The patients were instructed to rinse out the mouth directly after the administration and take no food or water for two hours. The subsequent rinsing was recommended because otherwise residues of the drug in the mouth and throat could cause so-called candidiasis (infectious fungal disease). Swallowing (the rinsing), by contrast, was contraindicated because the active ingredient could be flushed out of the oesophagus. Aqueous corticosteroid preparations, intended for oral inhalation by nebulisation, were also mixed with sugar to produce a thickened and sweetened liquid for the administration (see paragraph [0003] of the Patent).

4.4 Off-label treatments for EE by an administration of corticosteroid tablets containing, for example, prednisolone (a steroid) were also known. The systemic administration of corresponding steroids performed in this case, however, is associated with a number of known and unwanted side effects. These include, for example, general weakening of the immune system and, in children with long-term systemic administration, the particularly troubling side effect of growth retardation, which can lead to a reduction in body size in adulthood (see paragraph [0004] of the Patent).

4.5 This resulted in the need for an orally administered corticosteroid formulation allowing a topical (and not systemic) treatment of inflammation of the GI tract, in particular EE (see paragraph [0005] of the Patent).

4.6 Against this background, the invention claimed in the Patent solves the problems known from the prior art by providing an orally dispersing corticosteroid composition.

4.7 In this regard, the Patent in its independent claim 1 relates to the following composition, presented as a breakdown of features:

1.1 An orally dispersing tablet comprising

1.1.1 less than or equal to 20 mg of budesonide or a solvate or ester thereof,

1.1.2 and at least one pharmaceutically acceptable ingredient which facilitates the dispersal of the tablet in the oral cavity,

1.2 wherein the tablet is suitable for topical administration of budesonide in the upper gastrointestinal tract.

4.8 This breakdown of features differs from the Opponent's breakdown of features (in section II of its Statement) in that the feature "orally dispersing tablet" is explicitly listed as feature 1.1. In addition, in our breakdown, the structural features 1.1.1 and 1.1.2, as well as the functional feature 1.2, are separated from each other more clearly than in the Opponent's breakdown of features.

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4.9 The term "orally dispersing" refers to a solid dosage form that disintegrates rapidly in the oral cavity of a patient after administration, without chewing. The rate of oral disintegration can vary, but is significantly faster than the rate of oral disintegration of conventional solid dosage forms or chewable solid dosage forms (i.e. tablets or capsules) intended to be swallowed immediately after administration (see paragraph [0009] of the Patent).

4.10 "Budesonide" is an anti-inflammatory corticosteroid that can be administered topically and has a very low systemic effect.

4.11 A "pharmaceutically acceptable ingredient which facilitates the dispersal of the tablet in the oral cavity" is a substance in addition to the active ingredient, which can swell, dissolve or otherwise facilitate the disintegration or dissolution of the orally dispersing tablet. Such ingredients can include a disintegrant, sugar alcohol, saccharide etc. (see paragraphs [0009] and [0031] of the Patent).

4.12 The Opponent has cast aspersion on the claims of the Patent that relate to such ingredients and other excipients, alleging that they are unclear. As the Opponent has correctly stated, however, clarity under Article 84 EPC is not a ground for opposition. The Opponent's allegations are therefore wholly irrelevant.

5. Added Matter (Articles 100(c) and 123(2) EPC)

5.1 The Patent is derived from International Patent Application No. PCT/US2010/050860 ("the original application"). The claims as originally filed have been amended during prosecution of the application (in its European regional phase), to result in those granted in the Patent.

5.2 In section III of its Statement, the Opponent has alleged that claim 1 in the Patent includes subject matter that was not present in the original application. In particular, the Opponent has alleged that the claimed subject matter represents an undisclosed "*selection of different characteristics from different lists*". The Opponent has specifically referred to the omitted disintegration time and the selection of budesonide in claim 1 of the Patent in this regard. The Patentee entirely disagrees with the assessment by the Opponent.

5.3 In accordance with established Board of Appeal case law, the relevant question to be decided in assessing whether an amendment adds subject matter extending beyond the content of the application as filed is whether the amendments are directly and unambiguously derivable from the application as filed.

5.4 Furthermore, as set out in Board of Appeal decision T296/96, "*when assessing whether a feature has been disclosed in a document, the relevant question is whether a skilled person would seriously contemplate combining the different features cited in that document*".

5.5 The combination of features claimed in claim 1 of the Patent is entirely consistent with the disclosure in the original application. Below follows an explanation of why the subject matter claimed in the Patent contains no inadmissible extension relative to the disclosure of the original application, and especially not with respect to (i) the omitted disintegration time, and (ii) the selection of budesonide.

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5.6 The subject matter claimed in claim 1 of the Patent is disclosed in the original application, for example, by the following text passages:

- The embodiment on page 2, lines 9-14 in combination with page 15, lines 3-6 of the original application discloses, for example, an orally dispersing solid pharmaceutical composition with less than or equal to 20 mg of a corticosteroid (feature 1.1 and feature 1.1.1 (both partially));

- That the orally dispersing solid pharmaceutical compositions can be tablets (feature 1.1) and include a pharmaceutically acceptable ingredient which facilitates the dispersal of the tablet in the oral cavity (feature 1.1.2) is disclosed on page 3, lines 14-22;

- Budesonide, or a solvate or ester thereof, is named as the preferred active ingredient, for example, on page 10, lines 10-15 (feature 1.1.1); and

- The suitability of the solid composition for topical administration to the upper GI tract is described, for example, on page 5, lines 12-14 (feature 1.2).

(i) Disintegration within 60 seconds is not an essential feature

5.7 The Opponent has alleged that a key aspect of the solid pharmaceutical compositions disclosed in the original application was that these compositions "*should rapidly disintegrate in simulated saliva within 60 seconds when tested according to a specific US procedure*". According to the Opponent, "*This characteristic runs through the entire application and affects most forms of execution*". This, however, is not correct.

5.8 Page 15, lines 3-9 of the original application explicitly discloses that the solid pharmaceutical compositions of the invention can have "*any rate of disintegration or dissolution in the oral cavity*", as long as it "*provides a therapeutically effective amount of corticosteroid to the inflamed tissues of the gastrointestinal tract*". This is evidently a more accurate requirement of the invention than that alleged by Opponent. The passage also shows that a restriction of disintegration to within 60 seconds precisely need not necessarily be present in the definition of an "*orally dispersing tablet*".

5.9 It is similarly disclosed on page 3, lines 16-19 of the original application with respect to orally dispersing tablets that: "*The rate of oral disintegration can vary, but is significantly faster than the rate of oral disintegration of conventional solid dosage forms or chewable solid dosage forms (i.e. tablets or capsules) which are intended to be swallowed immediately after administration.*" Consequently, in this general definition, no particular disintegration rate, for example, of about 60 seconds or less, is stipulated.

5.10 Page 14, line 28 – page 15, line 2 of the original application also teaches, quite simply, that the rate of disintegration of the solid pharmaceutical compositions of the invention "*can be measured*" using various *in vitro* test methods, such as the USP <701> Disintegration Test and that, if so measured, the disintegration rate is "*typically about 60 s or less*". Consequently, the words "*can*" and "*typically*" clearly teach that the corresponding

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measurement result in the USP <701> Disintegration Test is not an essential feature of the solid pharmaceutical compositions of the invention.

5.11 The Opponent has alleged that the passage on page 15, lines 3-9 of the original application concerns "*another embodiment*" to the alleged requirement for a 60-second disintegration time in the USP <701> Disintegration Test, i.e. claim 1 effectively combines separate features that were not originally taught to be combined. This is not correct either.

5.12 Firstly, when read in context, the passage on page 15, lines 3-9 actually concerns "*other embodiments*" to those disclosed on page 14, lines 24-27, i.e. an earlier passage that similarly concerns disintegration time in the oral cavity and specifies particular rates of disintegration.

5.13 Secondly, the passage on page 14, line 28 – page 15, line 2 and that on page 15, lines 3-9 are not mutually exclusive and the skilled person would immediately realise that overlap is possible (but not essential).

5.14 Thirdly, the language used in page 15, lines 3-9 where it concerns "*other embodiments*" is mere drafting style. As a further illustration of this, the passage on page 7, lines 9-12 of the original application presents "*still other embodiments*" (in which solid pharmaceutical compositions of the invention disintegrate within 30 seconds in the oral cavity) that are not alternatives to, but rather encompassed by, the referred embodiment presented on page 7, lines 3-9 (in which solid pharmaceutical compositions of the invention disintegrate within 60 seconds in the oral cavity).

5.15 The Opponent has also alleged that the passage on page 15, lines 3-9 of the original application "*refers to an isolated version, without mentioning the other ingredients and/or properties of these pharmaceutical compositions*".

5.16 However, this passage forms part of the general description of invention and, as such, its disclosure applies to each and every embodiment of the described "*solid pharmaceutical compositions of the present invention*".

5.17 The passage is also consistent with the definition of an "*orally dispersing tablet*" provided on page 3, lines 16-19 of the original application. As such, the skilled person would understand the disclosure on page 15, lines 3-9 to apply to <u>all</u> orally dispersing tablets of the invention.

5.18 The Opponent has also objected to the omission of a minimum amount of budesonide from claim 1 vis-à-vis the passage on page 15, lines 3-9 (which teaches that, in some embodiments, solid pharmaceutical compositions according to the present invention provide about 0.5 mg to about 20 mg of the corticosteroid to the inflamed tissues of the GI tract after oral administration).

5.19 However, the amount of budesonide recited in claim 1 of the Patent is explicitly disclosed in claim 1 of the original application, upon which it is based.

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5.20 The claimed amount of budesonide is also explicitly disclosed on page 10, lines 22-24 of the original application, which forms part of general description and hence its teaching applies to each and every embodiment of "*solid pharmaceutical compositions of the present invention*".

5.21 The passage on page 15, lines 6-9 of the original application also only teaches the range of about 0.5 mg to about 20 mg corticosteroid as an example, and not an essential feature, of the solid pharmaceutical compositions having the disintegration rate disclosed on page 15, lines 3-6.

5.22 The Opponent has also alleged that the original application intends that different embodiments cannot be combined (referring, for example, to page 15, lines 11 and 23 of the original application, which recite "*in one embodiment*" and "*in certain embodiments*", respectively).

5.23 However, it is entirely untrue that the subject matter disclosed in broader statements of the invention can only be defined by a further feature for a single "embodiment" in isolation. Taking the passages referred to by the Opponent as an example, it is simply not true that, if the solid pharmaceutical compositions of the invention include one of the suitable adhesive agents disclosed on page 15, lines 11-22, the adhesive agent cannot also be intimately associated with the corticosteroid, as disclosed on page 15, lines 23-30.

5.24 The Opponent's interpretation is also illogical – the features of "separate" embodiments (i.e. where an embodiment relates to one specific feature as being preferred while the other features of the embodiment are not further described) are not mutually exclusive and the skilled person would never consider them to be so. In fact, the opposite is true; taking the passages referred to by the Opponent, for example, the skilled person would immediately learn from page 15, lines 10-30 that, if an adhesive agent is included in the composition, it can be intimately associated with the corticosteroid, and indeed in any of the arrangements described on page 15, lines 25-30.

5.25 The Opponent has also disproportionally focused on the structure of the description as originally filed, to the detriment of subject matter that the skilled person would have directly and unambiguously derived from the application as a whole.

5.26 Indeed, as was held in Board of Appeal decision T 99/13, the assessment of the requirements of Article 123(2) EPC should be made from the standpoint of the skilled person on a technical and reasonable basis, avoiding artificial and semantic constructions. As was held in Board of Appeal decision T 190/99, a patent must also be construed by a mind willing to understand, not a mind desirous of misunderstanding.

5.27 The Opponent has queried how page 15, lines 3-14 should in fact be understood.

5.28 Evidently, the addressee of a patent specification is the skilled person. Focus should hence be placed on what is really disclosed to the skilled person by the specification as originally filed, as directed to a technical audience.

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5.29 The skilled person is taught by page 2, lines 3-6 of the original application, for example, that the invention relates to compositions that provide corticosteroids topically in the upper GI tract. The skilled person is also taught by page 7, lines 3-15 of the original application, for example, that disintegration time matters only insofar as a therapeutic amount of corticosteroid must be delivered topically to inflamed tissues, and that disintegration times such as 60 seconds, or even 30 seconds, are not essential. The definition of an "orally dispersing tablet", on page 3, lines 16-19 of the original application, also addresses the disintegration rate as: "*significantly faster than the rate of oral disintegration of conventional solid dosage forms or chewable solid dosage forms (i.e. tablets or capsules) which are intended to be swallowed immediately after administration.*"

5.30 The skilled person hence would not understand the passage on page 15, lines 3-14 of the original application to disclose an "arbitrarily long" disintegration time as the Opponent has suggested because this is not in accordance with the rest of the disclosure. In fact, the entire disclosure should be read within the context of "orally dispersing tablets/solids" as defined on page 3, lines 16-19, i.e. given the disclosed disintegration rate, which directly contradicts the "arbitrarily long" disintegration time proposed by the Opponent.

5.31 Furthermore, the term, "*rapidly*", on page 3, line 15 of the original application, which the Opponent has relied upon as allegedly limiting the disclosed composition, is modified in the very next sentence (page 3, lines 16-17), as mentioned immediately above, to mean that the rate of oral disintegration is "*significantly faster than the rate of oral disintegration of a convention solid dosage form or chewable solid dosage form*", i.e. "*rapid*" is not limited to "*less than 60 seconds*" as the Opponent has alleged. This understanding is also consistent with the passage on page 15, lines 3-14.

5.32 The Opponent's allegation that the omission of disintegration time from claim 1 of the Patent has extended the teaching of the original application therefore entirely lacks foundation.

(ii) Budesonide is not an inadmissible selection

5.33 Turning to the Opponent's allegation that claim 1 of the Patent includes an undisclosed selection of budesonide from "various lists", this is also not true.

5.34 The selection of budesonide can only be a selection from one list (of active ingredients), in which budesonide is explicitly preferred (individualised), in any case. Reference is made to page 10, lines 10-15 of the original application in this regard.

5.35 Furthermore, page 2, lines 3-6 of the original application teaches that the invention is actually about the formulation for delivering a corticosteroid topically to the GI tract, rather than the identity of the specific corticosteroid. The original application hence makes clear that each of the disclosed formulations can be used with any of the disclosed active ingredients, including budesonide as claimed. Reference is also made to page 4, lines 18-21 of the original application, which recites budesonide first in the list of exemplary corticosteroids.

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5.36 The list of corticosteroids disclosed on page 10, lines 10-13 and individualisation of budesonide at page 10, lines 14-15 of the original application also forms part of the general description and hence it is clear that any "*pharmaceutical composition of the present invention*" can include any of the listed corticosteroids and, indeed, budesonide in particular.

5.37 Even if the claimed subject matter were considered by the Opposition Division to represent a "*selection of different characteristics from different lists*" as the Opponent has alleged, the specific 'choices' are explicitly disclosed in the original application, in any case. In this regard:

- "Orally dispersing tablet" is listed first in the general description (see page 7, lines 16-19) and is individualised (see page 3, lines 14-25, Example 1 and claim 15);

- "Less than or equal to 20 mg" applies to all solid pharmaceutical compositions (see page 10, lines 22-24);

- "Budesonide" is listed first in the general description (see page 10, lines 10-13), first in the claims (see original claim 3) and is individualised (see page 10, lines 14-15);

- "Pharmaceutically acceptable ingredient..." is disclosed in specific combination with "orally dispersing tablet" (see page 3, lines 19-22); and

- "Suitable for topical administration..." applies to all solid pharmaceutical compositions (see page 5, lines 12-14).

5.38 Therefore, the Opponent's assertion that claim 1 encompasses new matter is entirely unfounded.

5.39 Claim 1 is compliant with the provisions of Article 123(2) EPC.

6. Sufficiency of Disclosure (Articles 100(b) and 83 EPC)

6.1 The Opponent has alleged that the claimed invention is not disclosed in the Patent sufficiently clearly and completely for a person skilled in the art to repeat it. In particular, the Opponent has alleged that (i) solvates and esters of budesonide cannot be made, (ii) claim 1 is defined by "results to be achieved", and (iii) the claims of the Patent do not encompass the examples.

6.2 Below follows an explanation of why the subject matter claimed in the Patent is sufficiently disclosed in the original application, particularly with respect to the above embodiments selected by the Opponent.

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(i) Solvates and esters of budesonide can be made

6.3 The Opponent has alleged that budesonide solvates and esters for pharmaceutical use are not known in art or disclosed in specification, i.e. the skilled person is not able to make the claimed tablets comprising a solvate or ester of budesonide.

6.4 However, the Opponent is reminded that the burden of proof for establishing insufficiency rests on the Opponent (T 182/89).

6.5 The Opponent has not provided any evidence whatsoever to the effect that there are no solvates or esters of budesonide. As such, the Opponent's allegations regarding claim 1 should be summarily dismissed as lacking any proper credible basis.

(ii) Claim 1 is not defined by "results to be achieved"

6.6 The Opponent has alleged that claim 1 of the Patent is defined by results to be achieved, namely, (i) dispersal of the tablet in the oral cavity, and (ii) topical administration of the budesonide in the upper GI tract, and that the skilled person would not know which ingredient(s) to select to achieve these. This, however, is not true.

6.7 Regarding dispersal of the tablet in the oral cavity, page 3, lines 22-23 of the original application lists disintegrants, sugar alcohols, saccharides etc. explicitly for the purpose of dispersing the tablet in the oral cavity (see page 3, lines 19-22). Page 12, lines 13-17 of the original application also discloses pharmaceutically acceptable ingredients that are typically used in disintegrating tablet formulations, which again expressly includes mannitol (a sugar alcohol), crospovidone (a disintegrant) and such like.

6.8 Example 1 in the original application even exemplifies mannitol and crospovidone and their ability to disintegrate orally dispersing tablets (in about 60 seconds or less, using the USP <701> Disintegration Test). As the Opposition Division will appreciate, it is not unusual to measure *in vivo* parameters such as oral dispersion without chewing by using appropriate *in vitro* assays (e.g. disintegration in saliva-like fluids). There is clearly no undue burden for the skilled person to perform such simple tests showing a dispersal, at least *in vitro*.

6.9 As such, the skilled person is taught by the specification which pharmaceutically acceptable ingredients may be chosen to facilitate the dispersal of the tablet in the oral cavity and, even if there were any doubt in this regard, how to easily test for the desired result.

6.10 Regarding the topical administration of budesonide in the upper GI tract, prior to the priority date of the Patent it was not known if an orally dispersing tablet would topically deliver a corticosteroid to the upper GI tract. However, the Patentee has found that this can indeed be achieved.

6.11 The Patentee has described in detail and exemplified at least one formulation for achieving dispersal of an orally dispersing tablet in the oral cavity (see the example in the Patent), even though there is no requirement for any examples in a patent specification in this regard (Board of Appeal decision T 1437/07). The Patentee has also described alternative

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embodiments or variations extending over the area protected by the claims (see, for example, pages 10-15 of the original application).

6.12 As such, the Patent provides sufficient information to allow a person skilled in the art, using his/her common general knowledge, to perform the invention over the whole area claimed without undue burden and without needing inventive skill. The onus of establishing that the invention cannot be performed and repeated over substantially the whole of the claimed range, should the Opponent persist in this view, therefore lies with the Opponent.

(iii) The claims of the Patent do not encompass the examples

6.13 As the Opponent has noted, the example in the Patent relates to fluticasone propionate as the active ingredient, not budesonide. Example 2 in the original application, which is not retained in the Patent, related to a liquid composition, not an orally dispersing tablet. The examples therefore do not fall within the scope of the claims.

6.14 However, there is no requirement under Article 83 EPC for any examples, only that the application discloses the claimed invention in a manner sufficiently clear and complete for it to be carried out by the skilled person. No absolute proof of the invention is thus necessary here, only plausibility (i.e. the nature of the invention is such that it relies on a technical effect which is either self-evident or predictable or based on a conclusive theoretical concept).

6.15 As described in the original application, the invention is a formulation (i.e., orally dispersing tablet) that is suitable to topically deliver a corticosteroid to the upper GI tract. The application teaches that the formulation can topically deliver any corticosteroid, including budesonide. In the present case, the Patentee has carried out experiments on a formulation as claimed in claim 1 (albeit with a different active ingredient) and as detailed in the description and considers that the indicated results are obtainable using budesonide as the active ingredient instead. There is no reason whatsoever to doubt the veracity of the claimed results and the Opponent has provided no arguments or evidence to the effect that any doubt about the achievability of results with budesonide in fact exists.

6.16 The burden of proof is therefore discharged to the Opponent, which has to substantiate its allegation that orally dispersing tablets according to the claims in the Patent cannot be provided without undue burden.

6.17 It is anticipated that the Opponent will not be able to substantiate its allegation in this regard, as its own approved drug on the market falls within the scope of the claims and proves that tablets as claimed in the Patent can be readily reproduced.

6.18 Filed herewith as D7 and D8, respectively, are the Summary of Product Characteristics and Package Leaflet for the Opponent's so-called "Jorveza® 1 mg orodispersible tablet". It is quite clear from these documents that Jorveza® is an orally dispersing tablet as claimed in claim 1 of the Patent.

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6.19 Jorveza® thus demonstrates that tablets as claimed in claim 1 of the Patent can be readily reproduced by the skilled person and used for the therapeutic indications recited in claims 16 and 17 of the Patent. The Patent must therefore provide a sufficient disclosure of the subject matter claimed.

6.20 The Patent is therefore compliant with the provisions of Article 83 EPC.

7. Novelty (Articles 100(a) and 54 EPC)

7.1 The Opponent has alleged that the subject matter claimed in the Patent lacks novelty over that disclosed in each of D1, D2 and D4. This is not correct, for at least the following reasons.

D1

7.2 The Opponent has alleged that paragraph [0032] of D1 discloses tablets containing budesonide that dissolve rapidly in the mouth, such that the budesonide is released in the mouth and oesophagus, and a solution is formed to coat the oesophagus. This, however, is not true.

7.3 Paragraph [0032] of D1 actually teaches a choice of different dosage forms, and a separate choice of formulation for each one. With respect to rapidly dissolving formulations in particular, paragraph [0032] states: "*The lozenge or other **similar** **tablet**, capsule, or other solid, wo[u]ld dissolve rapidly in the **mouth** **or** **esophagus** to produce a solution that can then coat the esophagus…*" (emphasis added).

7.4 There is no teaching in D1 to select a 'similar' tablet that dissolves rapidly in the mouth, as opposed to one that dissolves rapidly in the oesophagus, at all, i.e. this represents an undisclosed selection of individual elements from multiple lists. A budesonide tablet that dissolves rapidly in the mouth is consequently a novel selection over that disclosed in paragraph [0032] of D1 (under the "two-lists principle").

7.5 Even if a budesonide tablet that dissolves rapidly in the mouth were to be considered disclosed in paragraph [0032] of D1, it would not be an "orally dispersing tablet" as claimed in claim 1 of the Patent in any case.

7.6 In this regard, and as shown by its title, D1 primarily concerns viscous, i.e. liquid, budesonide compositions for the treatment of inflammatory diseases in the GI tract. Alternative (solid) pharmaceutical compositions are mentioned in D1 merely as a secondary aspect. None of the experimental examples in D1 use such a solid composition.

7.7 In the sparsely detailed statements on solid formulations provided in D1, e.g. in its paragraph [0032], it is not expressly described that the solid dosage forms mentioned there dissolve without chewing. However, paragraph [0009] of the Patent states that this is the case with the orally dispersing tablets of the present invention. Indeed, D1 discloses solid dosage forms that cannot disperse or dissolve in the mouth without chewing. For example, many capsules (as mentioned in paragraph [0032]) are digested in the stomach or colon and,

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therefore, are swallowed as a whole. Tablets that are dissolved in a liquid prior to oral administration (also as mentioned in paragraph [0032]) were also very common at the publication date of D1. Paragraph [0032] of D1 hence relates to a different "dissolving tablet" that is not an "orally dispersing tablet" according to the Patent. This is also affirmed by claims 19-22 of D1, which leave it entirely open whether the claimed solid dosage forms, including a "dissolving tablet", dissolve rapidly or slowly, or whether they dissolve in the mouth, in the oesophagus or in a liquid vehicle prior to administration.

7.8 Nor is it mentioned in paragraph [0032] of D1 that the "rapid" dissolution described there has the same speed as the "rapid" dispersion according to the definition in paragraph [0009] of the Patent, namely a disintegration "*significantly faster than the rate of oral disintegration of conventional solid dosage forms or chewable solid dosage forms… which are intended to be swallowed immediately after administration*." Instead, the "rapid dissolution" of the compositions disclosed in paragraph [0032] of D1 is merely compared with a dosage form for "slow release" to the oesophagus.

7.9 However, a person skilled in the art would equate the comparison with (also not further defined) "slow" release dosage forms to so-called "sustained" release mechanisms, thereby understanding the dosage forms described in D1 to disintegrate in the mouth particularly slowly and thus more slowly than conventional tablets, which is contrary to paragraph [0009] of the Patent.

7.10 "Slow release" is described, for example, in D9, as a synonym for "sustained release" or "extended release", i.e. release slowly over an extended period of time (see page 997 under "sustained release"). Overall, the active ingredient is released more slowly (compared to conventional solid dosage forms).

7.11 Moreover, paragraph [0032] of D1 explicitly states that the rapidly dissolving tablet is "similar" to a lozenge. D9 provides the IUPAC definition of a lozenge on its page 990; it states: "*Tablet, which <u>does not contain a disintegrant</u> and which is <u>sucked to dissolve</u> in the mouth to produce either a local (e.g. antiseptic) or systemic (e.g. vitamins) effect. Note: Lozenges must be palatable and <u>slowly soluble</u>*" (emphasis added). Even if the skilled person had understood the 'similar' tablet disclosed in paragraph [0032] of D1 to dissolve in the mouth without chewing, therefore, s/he would necessarily have also understood that it would do this <u>particularly slowly</u>. This is made even more clear by the fact that, as evidenced by D9, a lozenge does not contain a disintegrant. By contrast, a disintegrant is one example of a pharmaceutically acceptable ingredient that is used in the tablets claimed in the Patent (see claim 7) because it facilitates dispersal in the oral cavity such that the tablet is suitable for topical administration of budesonide in the upper GI tract.

7.12 It follows from this that, in paragraph [0032], D1 does not directly and unambiguously disclose an orally dispersing tablet (feature 1.1) in the sense of the Patent.

7.13 The Opponent has alleged that Example 2 and paragraph [0053] of D1 disclose a dosage unit of 500 µg Pulmicort® (which is an aerosolised composition formulated for budesonide to topically contact inflamed lung tissue in the treatment of asthma), and that paragraph [0058]

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of D1 discloses a dosage amount of from 0-1 mg/day up to 5-6 mg/day per patient. Whilst this may be true, however, the following must also be taken into account.

7.14 Example 2 of D1 does not teach an "orally dispersing tablet"; it merely teaches a mixture of Pulmicort® with Splenda® (sucralose, an artificial sweetener made by chlorination of sucrose) for "*topical oesophageal therapy*". As disclosed in paragraph [0046] of D1, the Pulmicort® used in D1 is already a liquid composition: "*He was placed on a regimen of twice daily oral budesonide suspension (Pulmicort®) 500 micrograms (4 ml) mixed with about 10 packets (1 gram each) sucralose, (Splenda®), a non-absorbed sugar in order to increase fluid viscosity to be swallowed twice daily.*" (emphasis added). The 500 µg Pulmicort® preparation is therefore a (liquid) suspension containing 4 ml volume, the viscosity of which is increased by Splenda®. It is not a solid composition.

7.15 Paragraphs [0053] and [0058] of D1 do not teach an "orally dispersing tablet" either; they merely teach oral viscous budesonide (OVB; see paragraph [0048] of D1 for its definition), which is made from a mixture of liquid budesonide with Splenda®. In this regard, a viscous budesonide composition like OVB is necessarily a liquid because only liquids have a viscosity. Furthermore, in paragraph [0053] of D1, a volume of 8-12 ml is expressly indicated; but a volume indication is customary only with liquids and not with solid pharmaceutical dosage forms.

7.16 There is no teaching in D1 that the dosages disclosed in Example 2, paragraph [0053] and paragraph [0058] of D1 should be formulated in an orally dispersing tablet instead. As discussed above, D1 only exemplifies a dosage of budesonide in connection with the liquid dosage form. Such an orally dispersing tablet is thus not disclosed in combination with an active ingredient amount of less than or equal to 20 mg budesonide.

7.17 In fact, paragraph [0031] of D1 explicitly teaches that the exact dosage depends on the route of administration, the form in which the composition is administered, the subject to be treated, their age and body weight/height, and the preference and experience of the attending physician. This passage therefore expressly describes that the active ingredient amounts to be used, if disclosed in connection with liquid dosage forms, need not necessarily also apply for other (e.g. solid) dosage forms, and instead the dosages depend on many mutually independent parameters.

7.18 As emerges unmistakably from paragraph [0031] of D1, therefore, the amount of budesonide in the sense of the disclosure in Example 2 of D1 cannot be simply transferred to another dosage form such as an orally dispersing tablet in the sense of the Patent. The same applies for the indicated amounts of budesonide in paragraphs [0053] and [0058] of D1.

7.19 Therefore, no orally dispersing tablet with an amount of less than or equal to 20 mg budesonide (feature 1.1.1) is directly and unambiguously disclosed in D1.

7.20 A direct and unambiguous disclosure of an orally dispersing tablet with an amount of less than or equal to 20 mg budesonide, i.e. a composition with a defined amount of budesonide, cannot be derived from a disclosure of a possible daily dosage either. For one thing, in paragraph [0015] of D1, the disclosed daily dose of 1-2 mg or 2-3 mg is not disclosed in

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connection with budesonide or an orally dispersing tablet, but only generally in connection with a corticosteroid. It is also explicitly taught only for "certain embodiments". As already noted, it is expressly mentioned in paragraph [0031] of D1 that the exact dose depends on various parameters, which also include the dosage form, i.e. the form in which the composition is administered. Furthermore, it is expressly mentioned that this also depends on the corticosteroid used: "*The optimal concentration of the corticosteroid in the composition will necessarily depend upon the specific corticosteroid to be used…*"

7.21 A person skilled in the art immediately realises that the 1-2 mg or 2-3 mg daily dosage instruction for corticosteroid should apply only for liquid dosage forms because, in all experimental examples of D1, a corresponding daily dosage (in multiple individual dosages) is used (1 mg daily in Examples 1 and 2, and 1 mg or 2 mg daily in Example 3, where one patient inadvertently received only 0.5 mg daily).

7.22 Furthermore, the claims of D1 also teach that the daily dose of 1-2 mg or 2-3 mg from paragraph [0015] relates only to liquid formulations. Claims 27 and 28, which disclose these daily doses, do not depend on claims 15-26, which also comprise solid formulations (see, for example, claims 19-21). Instead, claims 27 and 28 depend only on independent claim 1 of D1. This states: "*A method of preventing or alleviating esophageal inflammation in an individual comprising orally administering to said individual a corticosteroid in association with at least one excipient to increase the viscosity of the composition*." (emphasis added). Dependent claims 2 and 3 make it even more clear that claim 1 must relate only to liquids because they define a required fluid viscosity that only a liquid composition could have (see also paragraph [0021] of D1).

7.23 In addition, a direct and unambiguous disclosure of an absolute amount of up to 20 mg budesonide cannot be derived from a dosage instruction as presented in paragraph [0031] of D1 such as "*10 to 400 µg/kg body weight per day*." The indications, "*µg/kg body weight per day*", are so generic as to cover practically a very high number of absolute active ingredient amounts, e.g. according to body weight, and D1 does not even indicate a preferred body weight. A simple "inference" of individual, more precise active ingredient amounts cannot be assumed.

7.24 Furthermore, it must be noted that D1 does not disclose that, with solid compositions, a mere once daily administration of the dosage form would be particularly preferred. A once per day administration is indeed mentioned in the last sentence of paragraph [0031] of D1, but in connection with a liquid dosage form, the volume of which can also be divided up over the day.

7.25 The fact that this disclosure relates only to liquid dosage forms is also made clear by the corresponding passage in paragraph [0031] of D1 being introduced with the words: "*In general, in a liquid dose,…*"

7.26 Following this introduction, the subsequent sentences speak throughout of a sufficient volume (in the sense of volume of a liquid) of the dosage, and then the (optional) distribution of the liquid volume over the day is added.

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7.27 Overall, by describing the daily dose to be administered (whether in mg/day or in µg/kg body weight/per day), no absolute amount of 20 mg budesonide or less in an orally dispersing tablet is directly and unambiguously disclosed.

7.28 The Opponent has also alleged that paragraph [0041] of D1 teaches that budesonide should remain mainly in the GI tract, especially the oesophagus.

7.29 However, this is only true for corticosteroids in general, and not budesonide in particular.

7.30 It is also only true "*in one illustrative embodiment*", which embodiment is not taught in specific combination with all elements of the tablets claimed in the Patent.

7.31 The Opponent has also alleged that paragraph [0037] of D1 teaches a pharmaceutically acceptable ingredient, for example, polyvinylpyrrolidone (PVP), sodium carboxymethylcellulose (CMC) or methylcellulose (vis-à-vis claim 4 of the Patent), and mannitol or sorbitol (vis-à-vis claims 7 and 8 of the Patent). Whilst this may be true, however, the following must also be taken into account.

7.32 The ingredients are clearly presented as individual elements in multiple lists. There is no teaching for the skilled person to select PVP, CMC or methylcellulose over the other listed cellulose preparations, or mannitol or sorbitol over the other listed sugars.

7.33 Such ingredients are also not taught in specific combination with any of the other elements of the tablets claimed in the Patent.

7.34 In summary, therefore, the subject matter claimed in claim 1 of the Patent is novel over that disclosed in D1. Naturally, the same also applies for claims 2-19, which are dependent from claim 1.

D2

7.35 Even if the priority claim of D2 is valid, such that D2 forms part of the state of the art for the Patent under Article 54(3) EPC, the subject matter claimed in the Patent is novel over that disclosed in the same in any case, for at least the following reasons.

7.36 The Opponent has alleged that paragraph [0022] of D2 discloses budesonide as an active ingredient. Whilst this may be true, however, D2 discloses long lists of active ingredients other than corticosteroids, too (see paragraphs [0021], [0022] and [0025]-[0043] of D2). Whilst budesonide (and fluticasone) may be individualised as corticosteroids, equally preferred active agents are individualised too, for example, in paragraphs [0027] and [0028].

7.37 The Opponent has alleged that paragraph [0023] of D2 discloses a preferred unit dose of 0.25-5 mg corticosteroid. Whilst this may also be true, however, the disclosure is rather generic, both in terms of relating to corticosteroids in general and the disclosed amounts largely being "*administered daily or in a unit dose*" (emphasis added). A clearly truly preferred amount of budesonide in particular, therefore, is not directly and unambiguously derivable from this paragraph.

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7.38 The Opponent has also alleged that paragraphs [00159] and [00161] of D2 disclose orally disintegrating tablets. Whilst this may be true, they are not disclosed in specific combination with budesonide as the active agent and a dosage unit of 20 mg or less. Paragraphs [0006] and [0008] of D2 also disclose long lists of other dosage forms.

7.39 Even if an orally disintegrating tablet were selected out of the dosage forms disclosed in D2, paragraphs [00103]-[00185], [00210]-[00218], [00308] and [00309] of D2 teach many different formulations in this regard. At least some of these formulations would not be suitable for topical administration of budesonide in the upper GI tract (for example, those with enteric coatings and sustained-release agents, which prevent release of the active ingredient until the tablet reaches the lower GI tract; see, for example, paragraphs [00119], [00127], [00131], [00175] and [00183] of D2 in this regard). Although D2 describes such tablets as "orally disintegrating", therefore, the presence of enteric coatings and sustained-release agents necessarily means that they are not "*orally dispersing tablets*" that are "*suitable for topical administration of budesonide in the upper gastrointestinal tract*" as claimed in the Patent.

7.40 Thus, there is no direct and unambiguous disclosure in D2 to select, in specific combination, (i) a corticosteroid as the active ingredient, (ii) budesonide as the corticosteroid, (iii) a unit dose of less than or equal to 20 mg, (iv) an "orally dispersing tablet" as defined in the Patent, that is (v) suitable for topical administration of budesonide in the upper GI tract, i.e. this combination amounts to an undisclosed selection of individual elements from multiple lists. The claimed tablets therefore constitute a novel selection (under the "two-lists principle").

7.41 It is also noted that D2 provides no examples at all and, as such, there is no enablement of its disclosure, taking into account also the general knowledge in the field of orally dispersing tablets at the relevant time. The subject matter disclosed in D2 thus cannot be regarded as comprised in the state of the art.

7.42 In summary, therefore, the subject matter claimed in claim 1 of the Patent is novel over that disclosed in D2. Naturally, the same also applies for claims 2-19, which are dependent from claim 1.

D4

7.43 The Opponent has alleged that paragraph [0043] of D4 discloses budesonide as an active ingredient. Whilst this may be true, it is only disclosed as part of a long list of active ingredients and, in fact, only as an anti-asthma agent. In order to be effective, an anti-asthma agent must either be inhaled so that it contacts the inflamed tissue of the lung directly or be adsorbed systemically in order to also reach the lung. On the publication date of D4 (29 May 2003), budesonide was, in fact, formulated as an aerosolised composition and inhaled to contact the lungs.

7.44 Consequently, it is not directly and unambiguously taught in D4 that any pharmaceutical composition comprising budesonide would be suitable for topical administration to the upper GI tract (feature 1.2).

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7.45 The Opponent has also alleged that paragraph [0035] of D4 discloses an orally dispersing tablet. Whilst this may also be true, the tablet is not disclosed in combination with budesonide or the dose amount recited in claim 1 of the Patent (feature 1.1.1).

7.46 The Opponent has alleged that paragraphs [0010] and [0055] of D4 disclose orally dispersing tablets comprising mannitol or sorbitol and/or disintegrants. Whilst this may be true, it is again not in combination with budesonide or the dose amount recited in claim 1 of the Patent (feature 1.1.1).

7.47 Furthermore, with respect to the amount of active ingredient to be included in the disclosed compositions, paragraph [0044] of D4 teaches the skilled person to include: "*at least the effective amount in terms of treatment and no more than 80 w/w % tablet weight*." It is not disclosed in D4 in any case, therefore, that any pharmaceutical composition should contain less than or equal to 20 mg budesonide.

7.48 Moreover, the treatment of asthma (which is the target indication for budesonide disclosed in D4), however, would rely on a systemic effect of any tablets. If the skilled person had wanted to treat asthma using an orally dispersing tablet at the publication date of D4, therefore, s/he would have known that systemic absorption is necessary to reduce the inflammation in the lungs and consequently would have selected a corticosteroid having higher systemic activity (as the Opposition Division will appreciate, the corticosteroid in an orally dispersing tablet, being swallowed, would never contact the lungs).

7.49 The skilled person hence would have known that corticosteroids which have low systemic activity and primarily act topically – such as budesonide - would not work in this regard, as corticosteroids with low systemic activity must topically contact inflamed tissue to be effective at low doses (which is why budesonide was since formulated as the aerosolised composition, Pulmicort®, in order for the budesonide to topically contact the inflamed lung tissues, in the treatment of asthma).

7.50 The skilled person would therefore never have understood D4's teaching to actually include an orally dispersing tablet comprising budesonide, even though this may be theoretically encompassed.

7.51 In any case, even if the skilled person had decided to prepare an orally dispersing tablet comprising budesonide (as an anti-asthma agent) on the basis of D4, s/he would clearly have included much more than 20 mg budesonide in the tablet, so as to ensure a therapeutically effective amount of drug being systemically available to ultimately treat asthma.

7.52 In summary, therefore, the subject matter claimed in claim 1 of the Patent is novel over that disclosed in D4. Naturally, the same also applies for claims 2-19, which are dependent from claim 1.

7.53 As such, the Patent is compliant with the provisions of Article 54 EPC.

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8. Inventive Step (Articles 100(a) and 56 EPC)

8.1 The Opponent has alleged that the subject matter claimed in the Patent, if novel, lacks an inventive step in the light of D1 in combination with one or more of D4-D6.

8.2 As the Opposition Division will be aware, in order to assess inventive step, the correct approach to adopt is the problem and solution approach. This consists of identifying the closest prior art, assessing the technical results or effect achieved by the claimed invention when compared with the closest state-of-the-art established, defining the technical problem to be solved as the object of the invention to achieve these results and examining whether or not a skilled person, having regard to the state of the art within the meaning of Article 54 (2) EPC, would have suggested the claimed technical features in order to obtain the results achieved by the claimed invention. It is also well established according to Board of Appeal case law that the assessment of inventive step has to be based on the objective, not subjective, achievement of the inventor (T1/80, T20/81, T24/81, T248/85).

8.3 In accordance with the problem and solution approach, it is well established case law of the Boards of Appeal that the closest prior art for assessing inventive step is normally a prior art document disclosing subject matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, therefore requiring the minimum of structural modifications (T606/89, T834/91, T897/92, T380/93, T1040/93 and T795/93). In selecting the closest prior art, the first consideration is that it must be directed to the same purpose or effect as the invention, otherwise it cannot lead the skilled person in an obvious way to the claimed invention. According to T506/95, the closest prior art is therefore that most suitable for the purpose claimed by the invention, not that superficially showing structural similarities with the solution as claimed.

D1 - Closest Prior Art

8.4 In the case of the invention claimed in the Patent, the person skilled in the art is a PhD-trained pharmacologist or biochemist with several years of experience in treating inflammatory diseases in the upper GI tract.

8.5 At the priority date of the Patent, there was no approved treatment for inflammation of the upper part of the GI tract with topically-administered anti-inflammatory drugs (see paragraph [0002] of the Patent). Only experimental and "off-label" treatments were known, which attempted to somehow administer steroid drugs, formulated for inhalation, in the upper area of the GI tract or treat the inflammation with systemically-acting corticosteroid tablets (see paragraphs [0003] and [0004] of the Patent).

8.6 The invention claimed in the Patent was therefore conceived to provide patients with oral dosage forms for a topical treatment of inflammatory disorders of the GI tract, particularly the upper GI tract (see paragraph [0005]).

8.7 D1 is concerned with a similar problem (see title and paragraphs [0002], [0005], [0009] and [0010]); hence it is a suitable choice as the closest prior art.

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8.8 By comparison, D2 and D3 are not available for the inventive step assessment. D4 and D6 are concerned with increasing tablet strength for orally dispersing tablets in general and improving their friability (in D4, see the abstract and paragraphs [0003] and [0004], and in D6, see the abstract and paragraphs [0002], [0003]). D5 is concerned with avoiding the problematic manufacture of orally dispersing tablets in general, which typically includes sticking and binding of ingredients to the tableting machine and a consequent lack of tablet hardness (see paragraphs [0003], [0005] and [0006]).

8.9 For the reasons provided above in section 7 of these submissions, D1 does not directly and unambiguously disclose an orally dispersing tablet having the particular combination of features recited in claim 1 of the Patent. Indeed, in contrast to D1, the Patent relates to orally dispersing tablets that *inter alia* contain an amount of up to 20 mg budesonide. As described below, such tablets are associated with advantages over the compositions disclosed in D1. Indeed, these orally dispersing tablets quickly disintegrate in the mouth or dissolve to form a solution or dispersion of the corticosteroid that can be easily swallowed (see paragraph [0022] of the Patent).

Objective technical problem

8.10 The Opponent's identification of the problem underlying the claimed invention as merely the provision of an "alternative embodiment" to the compositions disclosed in D1 is therefore incorrect.

8.11 The objective technical problem may actually be formulated as the provision of an improved orally administered budesonide formulation that provides topical treatment of inflammatory disorders of the GI tract, particularly the upper GI tract.

Solution

8.12 As detailed below, the solution to this problem is an orally dispersing tablet as claimed in claim 1 of the Patent.

Solution not obvious – D1

8.13 Taking D1 as the starting point for the evaluation of inventive step, one notices first of all that, in D1, the focus is on the use of liquid formulations like a viscous budesonide suspension. This is already expressed in the title of D1, and liquid formulations are also used in all experimental examples of D1. A clear preference for liquid dosage forms also emerges from paragraph [0009] (the stated object: "*A liquid, long-acting topical corticosteroid preparation is needed*"). Further, it is described in paragraph [0021] of D1 that: "*A viscous oral suspension of budesonide improved symptoms, resolved endoscopic abnormalities, and markedly reduced or eliminated esophageal eosinophils…*"

8.14 Contrastingly, D1 describes no such advantageous effects when it comes to any other dosage form, e.g. an orally dispersing tablet. The Opponent's inventive step analysis is therefore fundamentally flawed at the outset because it starts from a tablet for which there is no

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pointer in D1. Choosing to start from the tablet, in particular, out of the different pharmaceutical compositions disclosed in D1 amounts to an impermissible *ex post facto* analysis.

8.15 The analysis should, of course, correctly start from the preferred liquid dosage form disclosed in D1. This preferred approach described in D1, in which a budesonide solution provided for inhalation is further suspended with a sweetener (sucralose), is one of the experimental (but not approved) approaches for treatment of inflammations of the upper GI tract mentioned in paragraph [0003] of the Patent.

8.16 It is true that solid dosage forms are mentioned in D1, such as in dependent claims 19-22 and paragraphs [0013], [0032], [0035], [0037], [0039] and [0040], but not in detail and always secondary to corresponding liquid formulations, as described below.

8.17 The dependent claims 19-22, which relate to a dissolving tablet, dissolving wafer, capsule and gel capsule, are preceded by a whole series of claims relating to liquid compositions, e.g. claims 1-14 and claim 18. The very limited number of claims inherently related to solid dosage forms shows that solid dosage forms in the sense of the teaching of D1 are a secondary aspect described in little detail. Furthermore, in the claims 19-22 it is left open whether the solid dosage forms dissolve rapidly or slowly, or whether the solid dosage forms dissolve in the mouth, in the oesophagus or in a liquid vehicle prior to administration.

8.18 A liquid dosage form is described first in paragraph [0013] of D1, which deals with the pharmaceutical compositions of D1, and solid dosage forms are mentioned last. Thus, not only are liquid dosage forms preferred, but the liquid dosage forms are mentioned before solid dosage forms and described in significantly more detail.

8.19 It is described in paragraph [0032] of D1 how the solid dosage forms act in an embodiment: "*The lozenge or other similar tablet, capsule or other solid, wo[u]ld dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.*"

8.20 Interestingly, the term "solution" was chosen here in D1, which a person skilled in the art would understand to mean that the solid dosage forms, or at least the active ingredient (budesonide) contained in them, dissolve completely, i.e. are in solution, and the oesophagus is coated with this solution.

8.21 However, the skilled person would have known that budesonide is very poorly soluble in water. This is shown, for example, by the online PubChem entry for budesonide submitted as D10, which says "*practically insoluble in water.*"

8.22 Consequently, given the stipulation in D1 that the budesonide should be "rapidly" dissolved, the skilled person would have been able to formulate only very small amounts of budesonide in the dosage form. Even if a very small amount of budesonide would dissolve rapidly in a small volume of saliva, a person skilled in the art would have realised right away that such small amounts would not be enough to thus provide effective amounts of budesonide for treatment in the upper GI tract.

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8.23 It is only with the teaching disclosed in the Patent, with a sufficient budesonide suspension created by the rapid disintegration of the tablets (see paragraph [0022] of the Patent) suitable for topical administration in the upper GI tract, that the skilled person is able to produce an effective orally dispersing tablet.

8.24 In other words, based on the teaching in [0031] of D1, the skilled person would have had no motivation to produce a corresponding tablet that could achieve a therapeutic effect, and would have had no reasonable expectation of success in doing so.

8.25 This is especially true given that it is already warned in paragraph [0007] of D1 that it is frequently difficult to deliver an effective amount of corticosteroid to specific areas of the oesophagus: "*It is often difficult to deliver an effective dose of corticosteroid to the targeted area of the esophagus*."

8.26 As a result, a person skilled in the art would have wanted to change the explicit examples of D1 that relate exclusively to liquid dosage forms as little as possible since the liquid dosage forms are already shown to deliver an effective dose of the corticosteroid to the targeted area of the oesophagus.

8.27 Moreover, in paragraph [0006] of D1, the deficiencies of a "puff and swallow" method are noted, in which the attempt is made to swallow, rather than inhale, an aerosolised composition prepared for inhalation and thereby provide an effective amount of a topical steroid to the oesophagus. However, the "puff and swallow" technique "*results in a less than effective dose of the topical steroid being delivered to the esophagus*" (paragraph [0006] of D1). D1 teaches that an effective amount is best assured by formulating the corticosteroid in a precisely defined volume (e.g. as used in the examples, 4 ml or 7-8 ml or 8-12 ml liquid with precisely defined components) of a viscous liquid (see e.g. claims 2 and 3 of D1; see also paragraph [0021] of D1). As discussed below, D1 teaches that the precise volume delivers budesonide throughout the oesophagus, thus ensuring contact of the drug with the inflamed mucosa, while also providing a dosage form that can be easily swallowed by patients who have difficulty swallowing. In this regard, paragraph [0067] describes these advantages of the disclosed liquid formulations: *"It may have advantages over other therapies in that it is palatable, its volume (8-12 ml) provides pan-esophageal mucosal coverage and…"*

8.28 But such an approach is only possible with liquids and, without hindsight analysis, a person skilled in the art would have had no reason to choose an alternative formulation that does not follow this approach. In contrast to D1's liquid formulation, the claimed orally dispersing tablets are formulated as a solid that disintegrates in the oral cavity in a very small volume of saliva that is not exactly defined, with an unknown portion of the budesonide dissolved in the saliva, and which possibly may be transported to the oesophagus in varying budesonide concentrations with several swallows (instead of the bolus dose administered via D1's liquid composition). Given this, a person skilled in the art could not have estimated whether such an orally dispersing tablet could likewise be suitable for topical administration of the budesonide to the upper GI tract.

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8.29 A person skilled in the art would have realised that one cannot predict if an orally dispersing tablet can provide an effect equivalent to D1's precisely-defined viscous budesonide suspension. This is because D1's liquid composition delivers a bolus dose of budesonide, whereas the claimed orally dispersing tablet delivers varying budesonide concentrations with several swallows. Furthermore, poorly water-soluble active ingredients like budesonide make it particularly hard to estimate if, by disintegration and dissolution, the orally dispersing tablet can provide an effect equivalent to the precisely-defined viscous budesonide suspension of the examples in D1. It is therefore not surprising either that D1 provides no express instruction to reformulate the viscous budesonide suspension used in the examples as a different dosage form.

8.30 Furthermore, a symptom of inflammation of the oesophagus is dysphagia (disrupted swallowing), as is also mentioned in paragraph [0003] of D1: "*The disorder may present with reflux-like symptoms, pain and dysphagia*."

8.31 Consequently, without hindsight, the skilled person would not have deviated from the viscous budesonide suspension demonstrated in the examples – which is formulated in 4-12 ml to provide an obviously easy-to-swallow dosage form – to replace it with a solid dosage form in which only the slightest amounts of saliva (i.e. much less than 4-12 ml bolus volume) must suffice to gradually swallow the dispersing tablet.

8.32 This is especially true given that, in paragraph [0032] of D1, it is recommended *inter alia* that the solid dosage forms described therein also be crushed <u>in the volumes described in D1</u> (i.e., for example, 5-50 ml (see paragraph [0031]) or preferably between 4 and 12 ml as used in the examples) <u>before being taken</u>. This again shows a person skilled in the art the importance of the ingestion volume, and thus discourages the skilled person from using the tablets described in paragraph [0032] of D1 with a reasonable expectation of success by dissolution in the oral cavity.

8.33 Furthermore, D1 teaches that solid dosage forms ("pills") can even cause oesophagitis (inflammation of the oesophagus) if, for example, the pill gets stuck in the oesophagus while being swallowed. The inflammation can remain even if the pill is later removed (see paragraph [0007] of D1).

8.34 For this reason as well, a person skilled in the art would have refrained from using orally dispersing tablets according to the Patent for a topical treatment of an inflammation of the upper GI tract because disintegration of the dosage form in a very small, imprecisely-defined volume of saliva by repeated swallowing creates a rather imprecisely-defined suspension with possibly large particles and possibly not fully-dissolved budesonide and other components of the solid pharmaceutical composition. This is possibly "too solid" in the mouth or oesophagus when swallowing and carries a risk of triggering a pill-induced oesophagitis.

8.35 In the overall view of the teaching of D1, there was no motivation for the skilled person to have replaced the viscous budesonide suspension of the examples with a tablet of the Patent.

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8.36 Furthermore, the orally dispersing tablets claimed in the Patent offer advantages that were not obvious to a person skilled in the art from the teaching of D1.

8.37 The orally dispersing tablets claimed in the Patent do not need to be freshly prepared for use by the patient. In contrast to this, the patient must mix the Pulmicort® suspension – described in the examples of D1 as actually intended for inhalation – fresh with sucralose, which can naturally entail mistakes. Moreover, budesonide is not very stable in aqueous solutions and is, for example, light-sensitive. This is described, for example, in D11: "*As we know from previously reported result…, rapid degradation of budesonide after light exposure made photoprotection mandatory*." (page 94, left column, second paragraph; emphasis added).

8.38 The preparation of the viscous budesonide suspension must therefore be done quickly by the patient to avoid light damage. In contrast to this, the orally dispersing tablets claimed in the Patent, which do not need further processing, can be directly stored light-protected with simple means until oral ingestion.

8.39 Furthermore, with the viscous budesonide suspension used in D1, there is the risk that parts of the active ingredient of the viscous suspension will remain as residue on the vessel wall, so that imprecise active ingredient amounts, and potentially less than an effective dosage, are ingested, whereas this problem does not exist with administration of a tablet according to the Patent – the total effective dose is necessarily administered with the claimed tablets.

8.40 Overall, taking the drug is made much easier for the patient by the compositions provided by the Patent.

8.41 It is therefore not surprising that, in a direct comparison study between an oral viscous budesonide suspension and an orally dispersing tablet in the sense of the Patent, 80% of the patients preferred the solid composition.

8.42 The comparison study by Mielke *et al*. is submitted as D12. Three of the 21 co-authors, Ralph Mueller, Karin Dilger and Roland Greinwald, are associated with the Opponent.

8.43 The study was designed as a placebo-controlled double-blind study in which the patients always took two dosage forms (solid and liquid) as "double dummy", but the active ingredient, budesonide, was only contained in one of the two. The patients were supposed to hold the tablet in the mouth, on their tongue, until it completely disintegrated by contact with the saliva, and swallow 5-10 times. After at least 15 minutes, 5 ml of a viscous suspension was then administered (see page 391, right column, second paragraph, sentences 3 and 4).

8.44 The study showed that EE could be effectively treated with both the viscous suspension and the oral dispersing tablet (see, for example, the abstract of D12). Furthermore, the tablet form was preferred by 80% of the patients over the suspension (see, for example, page 397, left column, first complete paragraph).

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8.45 Given the clear preference for the liquid dosage form in D1, such an excellent acceptance of the orally dispersing tablet over the suspension was not to be expected.

8.46 To summarise, the subject matter claimed in the Patent would not have emerged for a person skilled in the art based on the teaching of D1. The skilled person would not have been motivated to deviate from a liquid viscous budesonide suspension of the D1 examples and instead choose an orally dispersing tablet in the sense of the Patent, nor would the associated advantages over the liquid formulations preferred in D1 have been obviously evident to him/her.

Solution not obvious – D4-D6

8.47 First of all, and as aforementioned, it must be noted that D4-D6 deal with a different technical objective than the Patent or D1, namely a technical field remote to the skilled person (D4-D6 concern the field of galenics and not the field of treatment of inflammation in the upper GI tract). Due to a lack of motivation put forward in D1, a person skilled in the art would not have dealt with these documents or possibly combined them with D1.

8.48 D4 and D6 are based on the same priority application and are addressed together below.

8.49 D4/D6 deals generally with raising the tablet strength of orally disintegrating tablets and, in particular, improving brittleness (see, for example, the abstract and paragraphs [0003] and [0004] in D4). A treatment of the upper GI tract is not mentioned in D4/D6. As already mentioned in section 7 above, budesonide is described only as an anti-asthma means, so that, at most, a person skilled in the art can learn from D4/D6 that an orally disintegrating tablet with budesonide according to D4/D6 would be suitable for treating asthma, either by inhalation of the disintegrated tablet or systemic action after ingestion of budesonide. But for the latter, much more than 20 mg budesonide is needed due to its low systemic action.

8.50 Consequently, following the teaching of D4/D6, a person skilled in the art would not have arrived at a composition that would be suitable for topical administration to the upper GI tract or contain less than or equal to 20 mg budesonide to be able to have the effect on inflammation of the respiratory tract.

8.51 Furthermore, D4/D6 discloses none of the specific advantages of the pharmaceutical compositions claimed in the Patent over the oral viscous budesonide suspensions preferred in D1. At most, the dosage forms of D4/D6 are seen as alternatives to the liquid dosage forms. On the whole, D4/D6 provides no motivation to modify the preferred embodiment of D1.

8.52 The same is true for D5. Here, too, the teaching concerns more the (problematic) production of an orally disintegrating tablet. Problems in the production include, for example, the contents remaining stuck in the tableting machine and an insufficient hardness of the tablets (see, for example, paragraphs [0003], [0005] and [0006] of D5).

8.53 It is true that a long list of active ingredients is disclosed in paragraph [0012] of D5, but this list contains no budesonide and no advantages of a budesonide-containing disintegrating

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tablet over a viscous suspension can be learned. Nor is it mentioned in D5 that, with a dosage form, an active ingredient can be topically applied in the upper GI tract. Consequently, a person skilled in the art would not have deviated from the liquid dosage form preferred in D1 and modify it *as per* D5.

8.54 Overall, a person skilled in the art would not (without a pointer to do so) have modified the teaching of D1 based on D4-D6 to obtain an orally dispersing tablet as claimed in the Patent.

Problem solved

8.55 As set out above in section 6 of these submissions, the example in the Patent at least plausibly demonstrates that the Patentee has produced tablets that disintegrate rapidly in the oral cavity after administration, without chewing (see paragraph [0079]). Surprisingly, the disintegration and dissolution of the budesonide tablet is so efficient that the claimed amounts of budesonide in the orally dispersing tablet are sufficient to achieve the desired therapeutic effect. Indeed, rapid tablet dispersal in the oral cavity means the formulation can be readily swallowed; upon mixing with saliva in the oral cavity, a smooth, easy-to-swallow suspension results (see paragraph [0022]). Hence the claimed tablets provide a topical treatment of inflammatory disorders of the GI tract, particularly the upper GI tract.

8.56 The skilled person would also consider it entirely reasonable to extrapolate the results demonstrated in the example using fluticasone propionate as the active ingredient to budesonide (and any other topically administrable corticosteroid, for that matter).

8.57 In this latter regard, fluticasone and budesonide are both topically administrable corticosteroids with anti-inflammatory activity and no significant systemic glucocorticoid or mineralocorticoid activity after oral administration (see page 4, lines 9-21, page 10, lines 10-15 and claims 3 and 27 in the original application). They are both poorly soluble in water and thus they share this common feature too. As such, it is at least plausible that the claimed tablets comprising budesonide have the same properties as shown for the tablets comprising fluticasone in the example.

8.58 Reference is also again made to D7 and D8, which provide substantive evidence to show that an orally dispersing tablet as claimed in the Patent provides a topical treatment of EE.

8.59 D12 also teaches that orally dispersing tablets were preferred by 80% of patients compared to a viscous budesonide suspension.

8.60 The claimed tablets clearly, therefore, constitute an improved orally administered budesonide formulation that provides topical treatment of inflammatory disorders of the GI tract, particularly the upper GI tract, compared to the compositions disclosed in D1. The identified objective technical problem has therefore been solved by the tablets claimed in the Patent.

8.61 In summary, therefore, the subject matter claimed in the Patent is inventive in the light of D1 alone or in combination with one or more of D4-D6.

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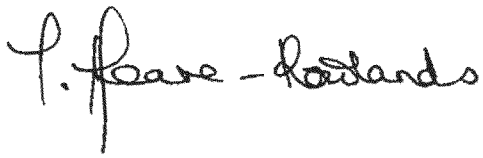
8.62 As such, the Patent is compliant with the provisions of Article 56 EPC.

9. Conclusion

9.1 The invention as set out in the claims of the Patent is clearly patentable, novel, inventive and sufficiently disclosed in the specification. The claimed subject matter finds basis in the original application, and it does not represent new subject matter in addition to that originally disclosed.

9.2 The opposition should thus be rejected in its entirety.

Yours faithfully,



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