Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 13 March 2017

Case Number: T 0725/11 - 3.3.01

Application Number: 04701819.7

Publication Number: 1583542

IPC: A61K31/675, A61K31/513, A61P31/18

Language of the proceedings: EN

Title of invention:
COMPOSITIONS AND METHODS FOR COMBINATION ANTIVIRAL THERAPY

Patent Proprietor:
GILEAD SCIENCES, INC.

Opponents:
Teva Pharmaceutical Industries LTD.
Generics (UK) Limited

Headword:
Combination Antiviral Therapy/GILEAD

Relevant legal provisions:
EPC Art. 56

Keyword:

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0725/11 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 13 March 2017

Appellant: (Patent Proprietor)	GILEAD SCIENCES, INC. 333 Lakeside Drive Foster City, California 94404 (US)
Representative:	Hallybone, Huw George Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent 1: (Opponent 1)	Teva Pharmaceutical Industries LTD. 5 Basel Street 49317 Petah-Tiqva (IL)
Representative:	Keller, Günter Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstrasse 2 80538 München (DE)
Respondent 2: (Opponent 2)	Generics (UK) Limited Albany Gate, Darkes Lane Potters Bar, Herts EN6 1AG (GB)
Representative:	Elend, Almut Susanne Venner Shipley LLP Byron House Cambridge Business Park Cowley Road Cambridge, Cambridgeshire CB4 0WZ (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 14 February 2011 revoking European patent No. 1583542 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: M. Pregetter
L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 583 542 is based on European patent application No. 04701819.7, filed as international application published as WO2004/064845.

II. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(4) Clinical Therapeutics, 2002, 24(10), 1515-1548

(10) Viread® Patient Information Leaflet, 2002

(17) Project Inform Perspective, January 2003, vol. 35, pages 15-16

(20) Antiviral Therapy, 2001, vol. 6, pages 83-88

(24) BioWorld® Today, (5 Dec. 2002) vol. 13, Number 233

(31) Summary of Product Characteristics, Viread®, 2002

(35) EMEA, Scientific Discussion of Truvada®, pages 1-3

(37) BioWorld® Today's website

(41) Handbook of Pharmaceutical Excipients, 3rd ed. 2000, 276-285

(42) Drug-Excipient Interactions, reprint from the March 2001 issue of Pharmaceutical Technology

(43) The Theory and Practice of Industrial Pharmacy, 3rd ed. 1986, 325-326

(44) Arzneiformenlehre 1985, 79, 477

(45) J. Pharm. Sci. 1962, 106-108

(50) Summary of Product Characteristics Epivir® 1997

(51) Nucleosides, Nucleotides & Nucleic Acids, 19(1&2), 189-203 (2000)

(53) Acta Chem. Scand. 43 (1989) 196-202

(56) Pharmaceutical Dosage Forms 1990, 93,98

(57) WO 2007/068934

(61) Summary of Product Characteristics, Truvada®

III. The present appeal lies from the decision of the opposition division to revoke the patent under Article 101(3)(b) EPC.

The opposition division held that the set of claims of the main and sole request lacked inventive step when starting from any of documents (4), (17) or (24) as the closest prior art.

IV. The proprietor lodged an appeal against the decision of the opposition division.

With its statement of grounds of appeal, the appellant (proprietor) requested that the decision under appeal be set aside and that the patent be maintained on the basis of any of auxiliary requests 1 to 7 filed therewith.

Respondent 1 (opponent 1) requested that the appeal be

dismissed.

By letter dated 9 August 2012, the appellant filed a new main request and auxiliary requests 1 to 8.

Summons for oral proceedings were issued on 18 November 2016, accompanied by a communication pursuant to Article 15(1) RPBA.

By letter dated 13 February 2017, the appellant filed a new main request and new auxiliary requests 1 to 6.

V. Oral proceedings were held before the board on 13 March 2017 in the absence of respondent 2, as announced by letter dated 7 March 2017. During oral proceedings the appellant filed a new main request and new auxiliary requests 1 and 5. It also renumbered auxiliary request 7 as auxiliary request 8 and vice versa.

VI. Nine requests, a main request and auxiliary requests 1 to 8, thus form the basis for the present decision.

The independent claims of the **main request** of 13 March 2017 read as follows:

"1. A pharmaceutical co-formulation in the form of a tablet comprising [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxy-methyl ester fumarate (tenofovir disoproxil fumarate) and (2R,5S,cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine) and one or more pharmaceutically acceptable carriers or excipients, wherein tenofovir disoproxil fumarate and emtricitabine are present in a weight ratio from 1:10 to 10:1."

"12. Use of [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate (tenofovir disoproxil fumarate) and (2R,5S,cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1 H)-pyrimidin-2-one (emtricitabine) in the manufacture of a co-formulated tablet composition comprising one or more pharmaceutically acceptable carriers or excipients, wherein tenofovir disoproxil fumarate and emtricitabine are present in a weight ratio from 1:10 to 10:1 for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal."

Auxiliary request 1 of 13 March 2017 differs from the main request in that the product claims have been deleted. Claim 1 is a Swiss-type claim corresponding to claim 12 of the main request.

The independent claims of **auxiliary request 2** of 13 February 2017 read as follows:

"1. A pharmaceutical co-formulation in the form of a tablet comprising 300 mg of [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate (tenofovir disoproxil fumarate) and 200 mg of (2R,5S,cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine) and one or more pharmaceutically acceptable carriers or excipients."

"11. Use of [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate (tenofovir disoproxil fumarate) and (2R,5S,cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-

pyrimidin-2-one (emtricitabine) in the manufacture of a co-formulated tablet composition comprising one or more pharmaceutically acceptable carriers or excipients and 300 mg of tenofovir disoproxil fumarate and 200 mg of emtricitabine for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal."

Auxiliary request 3 of 13 February 2017 differs from auxiliary request 2 in that the product claims have been deleted. Claim 1 is a Swiss-type claim which is based on a reformulation of claim 11 of auxiliary request 2.

Auxiliary request 4 of 13 February 2017 differs from auxiliary request 2 in that the Swiss-type claims have been deleted. Claim 1 is a product claim corresponding to claim 1 of auxiliary request 2.

The independent claims of **auxiliary request 5** of 13 March 2017 correspond to the independent claims of the main request with the further definition that "the pharmaceutically acceptable carriers or excipients comprise lactose monohydrate".

The independent claims of **auxiliary request 6** of 13 February 2017 read as follows:

"1. A pharmaceutical co-formulation in the form of a tablet comprising 300 mg of [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate (tenofovir disoproxil fumarate) and 200 mg of (2R,5S,cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine) and one or more pharmaceutically acceptable carriers or excipients

comprising lactose monohydrate."

"10. Use of [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate (tenofovir disoproxil fumarate) and (2R,5S,cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine) in the manufacture of a co-formulated tablet composition comprising 300 mg of tenofovir disoproxil fumarate, 200 mg of emtricitabine and one or more pharmaceutically acceptable carriers or excipients, comprising lactose monohydrate, for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal."

Auxiliary request 7 of 9 August 2012 consists of a single claim:

"1. A pharmaceutical co-formulation in the form of a tablet comprising [2-(6 amino-purin-9-yl)-1-methyl-ethoxymethyl-phosphonic acid diisopropoxycarbonyloxy-methyl ester fumarate (tenofovir disoproxil fumarate) and (2R,5S,cis)-4 amino-5-fluoro-1-(2-hydroxymethyl-1 , 3-oxathiolan-5-yl)-(1H)-pyrimidin-2 one (emtricitabine), the tablet comprising a total of 1000 mg of

	mg/tablet
Tenofovir Disoproxil Fumarate	300.0
Emtricitabine	200.0
Pregelatinized Starch	50.0
Croscarmellose Sodium	60.0
Lactose Monohydrate	80.0
Microcrystalline Cellulose	300.0
Magnesium Stearate	10.0"

Auxiliary request 8 of 9 August 2012 comprises two independent product claims, the second, claim 3, defining subject-matter based on the examples disclosed in the description as filed. Claim 1 reads as follows:

"1. A pharmaceutical co-formulation in the form of a tablet comprising [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxy-methyl ester fumarate (tenofovir disoproxil fumarate) and (2R,5S,cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine) selected from a tablet comprising in weight percent

a) tenofovir disoproxil fumarate 30.0, emtricitabine 20.0, pregelatinized starch 5.0, croscarmellose sodium 6.0, lactose monohydrate 8.0, microcrystalline cellulose 30.0, magnesium stearate 1.0; and

b) tenofovir disoproxil fumarate 30.0, emtricitabine 20.0, pregelatinized starch 5.0, croscarmellose sodium 6.0, lactose monohydrate 18.0, microcrystalline cellulose 20.0, magnesium stearate 1.0."

VII. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

The new main request and new auxiliary requests 1 and 5 contain minor amendments related to the dependencies of dependent claims.

Main request and auxiliary request 1

With respect to inventive step the appellant considered document (4) to represent the closest prior art but stated that it was prepared to discuss inventive step

starting from document (24). The appellant considered document (24) to be remote from the purpose of the patent in suit, which was described in paragraphs [0010], [0003], [0011] and [0054] of the patent in suit as the provision of a physically acceptable, chemically stable, and effective pharmaceutical composition, involving elements of synergy, for the treatment of HIV. Document (24) was silent on efficacy and contained no technical information. The purpose of document (24) was to attract investments. It required hindsight to consider document (24) as a promising starting point. There was no reasonable expectation of success for providing a pharmaceutical formulation comprising tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). In fact, document (24) only articulated a problem, without providing a solution.

According to the appellant, the difference between the subject-matter of the main request and the disclosure of document (24) lay in the realisation of a concrete form including the choice of tablet and a specific ratio of active pharmaceutical ingredients. A pill was not necessarily a tablet. As could be seen in document (4), table VIII, the pharmacokinetic behaviour of actives was affected by their co-administration, requiring the determination of the respective effective doses.

The technical problem to be solved was the provision of a dosage form of TDF and FTC for once daily administration and that was physically acceptable, chemically stable and effective.

It was not obvious for the skilled person to arrive at the claimed subject-matter. First of all there was no reasonable expectation of success. A skilled person

would consult literature concerning the two active agents. For TNF there was the product Viread on the market (document (31)), tablets comprising 300 mg TDF. No formulation comprising FTC had been approved. A skilled person was aware of pharmacokinetic concerns when combining two active ingredients (document (4), table 8) and of problems related to the rapid absorption of both drugs (document (61), page 24). Of great concern for the skilled person would be the known stability problems. Document (51), see information on compound 6 on page 195, and document (53), see first paragraph and table 4, showed the deamination of cytidine derivatives, FDC being one, under acidic conditions, TDF having acidic groups. This instability would be considered to be aggravated when providing tablets, since the active ingredients had intimate contact in tablets and the manufacture of tablets required harsh conditions. This risk of degradation was confirmed by document (57) page 9 showing brown discoloration of a tablet comprising TDF and lamivudine. Due to the inherent chemical incompatibility of TDF and FTC a skilled person would have avoided tablets.

The same argumentation applied to auxiliary request 1.

Auxiliary requests 2 to 4

Auxiliary request 2 further defined the amounts of TDF and FTC to be formulated. In view of document (4), a change in pharmacokinetics would be expected and a skilled person would thus not have considered the doses of the single active-containing forms.

Auxiliary requests 5 to 8

According to the appellant, it was generally known that it was not possible to use lactose monohydrate as an excipient for active pharmaceutical ingredients with primary amino groups. Several documents representing common general knowledge, i.e. document (41), page 283, document (42), second page, document (43), page 326 and document (44), page 79, taught that the Maillard reaction was likely to occur between lactose (monohydrate) and actives having primary amino groups, such as FDC, exacerbated in the presence of basic lubricants, such as magnesium stearate, and by tabletting. Lamivudine, which differed from FDC only by the absence of a fluorine substitution, was formulated without lactose, see document (50), page 7. The "simple" testing for predicting incompatibility, suggested on page 108 of document (45) did not make it possible to judge the impact of tabletting. Success could thus not be predicted rationally, as required by the case law, before a research project was started. The perception of the skilled person was thus that a tablet comprising FDC and lactose monohydrate and possibly magnesium stearate (as in auxiliary requests 7 and 8) would fail. The fact that certain excipients were used in Viread was irrelevant when looking at a co-formulation with FTC. The respondent's arguments were based on hindsight knowledge. The skilled person would not generate the claimed tablets as a matter of routine, since there was a certainty of failure and not an expectation of success.

VIII. Respondent 1's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

There were no objections concerning the admission of any of the requests.

Main request and auxiliary request 1

Respondent 1 argued that the closest prior art was document (24), a well-known journal employing journalists with experience in biotechnology and having a scientific background. The information in document (24) was reliable. A company would not start to develop a co-formulation of TDF and FTC and publicly state that it was doing so, if it did not have a reasonable expectation of success.

The only difference between the subject-matter of the main request and the disclosure of document (24) was the ratio of the active ingredients.

The technical problem was thus to find the optimal concentrations of the active agents.

Document (10) taught to formulate 300 mg TDF in a tablet for once daily administration, and document (20) disclosed 200 mg of FTC as the optimal dosage for once daily administration (paragraph bridging pages 86 and 87). It was obvious for the skilled person to start with known doses of the two active agents and thus to provide the claimed ratio. Tablet form was the first choice of a skilled person, especially when reading the term "pill" in document (24). The independent claims of the main request defined hardly any galenic features, with the exception of the tablet form. Problems, in particular in view of stability, had only been shown for other compounds, not specifically for the compounds TDF and FTC and their combination. Tablets could have many technical features for overcoming the problems discussed by the appellant, such as coatings or disintegrating agents, e.g. when fast dissolution with a view to high concentrations of active agents was

required. The appellant was speculating about problems whose solution was not reflected in the claims. Document (24), a reliable source, led to almost certain success when putting its disclosure into practice. Consequently, no inventive step could be acknowledged.

The same argumentation applied to auxiliary request 1.

Auxiliary requests 2 to 4

The arguments for the main request applied, as the values of 300 mg TDF and 200 mg FTC were already disclosed in the prior art, see documents (10) and (20).

Auxiliary requests 5 to 8

Respondent 1 submitted that lactose monohydrate was one of the most commonly used excipients. The documents and passages cited by the appellant only raised a *caveat*, but did not actually teach that the Maillard reaction always arose. These documents only disclosed that the Maillard reaction was likely to arise and also taught that it could be avoided by the use of microcrystalline lactose or anhydrous lactose. Furthermore, document (45) provided information on a fast routine test for predicting instability of tablets comprising lactose (page 108, last paragraph). No effect had been shown to be associated with the use of certain excipients. The respondent pointed again to document (10), disclosing to formulate TDF in a tablet comprising lactose monohydrate and magnesium stearate as excipients. It was obvious to use certain excipients that were already being used for one of the two actives. The subject-matter of auxiliary requests 5 to

8 also did not involve an inventive step.

IX. The appellant (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the following requests:

- the main request and auxiliary request 1 filed at the oral proceedings,
- auxiliary requests 2 to 4 filed with letter dated 13 February 2017,
- auxiliary request 5 filed at the oral proceedings,
- auxiliary request 6 filed with letter dated 13 February 2017,
- auxiliary request 7 filed as auxiliary request 8 with letter dated 9 August 2012,
- auxiliary request 8 filed as auxiliary request 7 with letter dated 9 August 2012.

Respondent 1 (opponent 1) requested that the appeal be dismissed.

Respondent 2 (opponent 2) did not take an active part in the proceedings and did not file any requests.

Reasons for the Decision

1. The appeal is admissible.

Oral proceedings were held and the proceedings were continued in the absence of the duly summoned respondent 2 in accordance with Article 15(3) RPBA and Rule 115(2) EPC.

The main request and auxiliary requests 1 and 5 are admitted into the proceedings. Compared to the corresponding requests previously on file they contain

minor amendments in the dependent claims that do not raise any new issues (Article 13(3) RPBA).

2. *Inventive step (Articles 52(1) and 56 EPC)*

2.1 The present invention is directed to a pharmaceutical co-formulation in the form of a tablet comprising tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) for the treatment or prevention of the symptoms or effects of an HIV infection. The pharmaceutical composition should provide enhanced therapeutic safety and efficacy, impart lower resistance, and lead to higher patient compliance (see patent in suit, paragraph [0010]). Concerning the efficacy, synergy is mentioned (paragraphs [0003] and [0011]). It is intended to provide a "one pill, once daily" dosage regimen (paragraph [0054]). An important issue is the chemical stability of the composition (paragraph [0011]). In sum, a physically acceptable, chemically stable and effective composition is to be provided.

2.2 *Closest prior art*

Document (24) represents the closest prior art. Document (24) is an issue of BioWorld® Today. According to document (37), BioWorld® Today is read by biotechnology professionals (first complete paragraph). It publishes information that is researched and written by the top business and science reporters in industry (second complete paragraph).

Document (24) reports on the intention of the biopharmaceutical company Gilead Sciences, Inc., citing both the President and CEO of Gilead and the firm's executive vice president of research and development, to start developing a co-formulation of Coviracil (FTC)

and Viread (TDF), to be dosed as one pill, once daily. Apart from stating this intention, preliminary and optimistic statements about compatibility in view of resistance mutations and physical chemical properties of the drugs are made. The co-formulation work is described as "currently ongoing"; testing of FTC and TDF in combination for HIV is "under way" (document (24), page 6, right column, paragraphs 2 to 5).

A skilled person working in the field of antiviral therapy, especially HIV therapy using reverse transcriptase inhibitors, would consult all available literature dealing with this topic, including literature providing information on the research pipelines of companies working in this field. Such information is essential in order to keep abreast of the latest developments.

The appellant argued that document (24) did not qualify as closest prior art because its content was remote from the purpose of the patent in suit. Furthermore, document (24) was silent on important issues such as efficacy. Also, according to the appellant, it provided no actual technical information.

Indeed, document (24) does not provide any technical details on how the co-formulation is actually put into practice. Document (24) discloses a project. It clearly states that the company having in its portfolio the two active pharmaceutical ingredients under consideration, FTC and TDF, is about to develop a co-formulation of these two actives for the treatment of HIV. Such a statement by a pharmaceutical company implicitly amounts to a concrete plan to develop a commercially viable product. A commercially viable product is one that has the stability required for transport together

with a certain shelf life and having a usable level of efficacy. Further, document (24) is a public statement of intent made by Gilead's CEO and its executive vice president of research and development. It therefore carries weight and would not be dismissed by the skilled person as mere speculation. Instead, a skilled person would regard this plan of co-formulating FTC and TDF as a promising approach. In summary, document (24) relates to providing a co-formulation for the same purpose as the patent in suit and its content would be considered by the skilled person.

The appellant has stated that it considered document (4) to be more suitable as the closest prior art document. Document (4) describes the use of TDF for the treatment of HIV infections and discusses in particular the pharmacological properties of TDF. The results of pharmacokinetic drug interactions of TDF and other antiretroviral drugs are examined, and presented in table VIII. Document (4) is therefore a document a skilled person trying to treat HIV infections would consult. However, the board considers that document (24) is even closer, since it relates to both claimed active ingredients in the context of HIV infections and explicitly mentions co-formulations of TDF and FTC. The appellant has agreed to follow the problem-and-solution approach starting from document (24) as the closest prior art.

2.3 *Main request*

2.3.1 Claim 1 of the main request defines a pharmaceutical co-formulation in the form of a tablet comprising carriers or excipients and TDF and FTC in a weight ratio from 1:10 to 10:1.

Claim 1 of the main request differs from the disclosure of document (24) in the definition of the weight ratio between the two active pharmaceutical ingredients and the specific galenic form of a tablet. Also, document (24) does not disclose an actual and reworkable pharmaceutical composition comprising FTC and TDF.

2.3.2 *Technical problem*

The problem to be solved may be defined as putting into practice the co-formulation taught by document (24).

2.3.3 *Proposed solution*

The solution proposed by the subject-matter defined in claim 1 of the main request consists in the selection of a tablet and the requirement of a certain weight ratio of the two active pharmaceutical ingredients. The problem has been solved. This has not been contested. Evidence is found in document (35).

2.3.4 Obviousness

The skilled person, faced with the task of providing an actual formulation comprising TDF and FDC, will look for guidance in the prior art, i.e. in documents relating to actual formulations in the field of reverse transcriptase inhibitors, and especially to formulations comprising TDF or FDC.

One of the active agents, TDF, has already been formulated as a tablet, comprising 300 mg of TDF, and is available under the trade name "Viread" (document (10), page 2, second last paragraph; document (31), page 2, "2. Qualitative and quantitative

composition"). The form of a tablet and the amount of 300 mg are thus highlighted and constitute a starting point for the skilled person's routine developments.

The second active pharmaceutical agent, FTC, has been tested in various amounts. For once-daily use 100 mg and 200 mg have been tested and 200 mg has been identified as the optimal dose (document (20), figure 1 and sentence bridging pages 86 and 87). Consequently, a weight ratio close to 300:200, or 3:2, i.e. within the range 1:10 to 10:1, would have been considered by a person skilled in the art as a starting point for routine tests.

The selection tablet form and of a weight ratio of TDF to FTC within 1:10 to 10:1 is thus the result of the routine approach taken by the skilled person when formulating a pharmaceutical composition comprising these two actives. No inventive step can be acknowledged.

2.3.5 *Further arguments*

Any effects related to synergy are inherent to the two active ingredients used in the co-formulation and thus already covered by the disclosure of the two specific active agents to be combined, TDF and FTC, in the closest prior art document (24). The appellant's arguments concerning reservations by the skilled person about combining TDF and FTC, due to expected stability problems, can be disregarded. The combination of TDF and FTC is already part of the disclosure of the closest prior art and would thus not be questioned by the skilled person.

The appellant has further argued that tabletting would exacerbate the stability problems arising from the combination of TDF and FTC, since in a tablet the two incompatible active agents were situated in intimate proximity and during the tabletting very harsh conditions applied. Thus, according to the appellant, a skilled person was aware of the stability problems of TDF and FTC and would have avoided the galenic form of tablets. TDF and FTC were inherently incompatible due to the free acid group in TDF which would lead to a degradation of FTC.

Documents (51) and (53) relate to degradation of cytidine derivatives and show the degradation rates of certain cytidine derivatives under acidic conditions. When considering table 1 of document (51), it can be seen that the actual conditions are important. The pH values influence the degradation considerably, as does the temperature. Also of great influence is the actual structure of the hexopyranosyl-like unit. The rate of degradation or-to put it another way-the stability thus depends both on the actual compound and on the reaction conditions, such as pH and temperature. Table 4 of document (53) gives the rate constants for the deamination of cytidine and several of its derivatives. The deamination rate constant depends on the actual structure of the compound. Both the cytosine-like part of the structure (compare for example compounds (1), (2) and (4)) and the substitution on the 6 position (compare compounds (1) (as there is no data for compounds (6)) and (7)) influence the deamination rate. For lamivudine, a compound differing from FTC by the absence of a fluorine substitution in ortho position of the amino group, stability problems in tablets comprising TDF have been observed in document (57) by the appearance of a brown colour (paragraph bridging

pages 8 and 9). However, none of these documents directly concerns FTC.

In view of the fact that Gilead's executive vice-president of research and development has advertised the co-formulation of TDF and FTC, the board cannot follow the argumentation that a skilled person, having in mind stability problems of other, albeit structurally related substances, would not follow the teaching of document (24). It is a matter of routine for a skilled person to carry out stability tests and to find an adequate galenic form. The mere speculation that tabletting might exacerbate potential stability problems would not deter a skilled person trying to realise the teaching of the closest prior art as a tablet, which is one of the most common and convenient galenic forms and comprised by the term "pill".

The disclosure of document (61) concerning the rapid absorption of TDF and FTC is post-published. It has thus not been established that at the priority date of the patent in suit the skilled person would have been aware of problems possibly arising from the rapid absorption of both drugs (document (61), page 24, "5.2 Pharmacokinetic properties"). Consequently, the arguments based on document (61) cannot be taken into account.

The board notes that the appellant has neither argued that the invention lies in the field of galenics, nor invoked any effects due to concentrations or other technical features that may be considered to pertain to the field of galenics.

2.3.6 In view of the disclosure of HIV therapy in document (24), the same reasoning applies mutatis mutandis to

claim 12 of the main request.

2.3.7 *Conclusion*

The subject-matter of claims 1 and 12 of the main request does not involve an inventive step (Article 56 EPC).

2.4 *Auxiliary request 1*

Claim 1 of auxiliary request 1 corresponds to claim 12 of the main request. Its subject-matter does not involve an inventive step (Article 56 EPC) for the same reasons as given above.

2.5 Auxiliary requests 2 to 4

Auxiliary requests 2 to 4 differ from the main request by the definition of the actual amounts of TDF and FTC in the tablet, namely 300 mg TDF and 200 mg FTC. No surprising effect has been demonstrated for these amounts. They correspond exactly to the amounts used when providing a mono-formulation of the actives (see documents (10) and (20) as discussed under point 2.3.4 above). These amounts were thus known to the skilled person and consequently among the obvious amounts to be tested in routine formulation. Consequently, the same reasoning as for the main request applies.

The subject-matter of auxiliary requests 2 to 4 does not involve an inventive step (Article 56 EPC).

2.6 *Auxiliary request 5*

Auxiliary request 5 differs from the main request in that the carriers and excipients comprise lactose

monohydrate.

The appellant has not argued that a surprising technical effect is linked to the presence of lactose monohydrate. The problem to be solved by claim 1 of auxiliary request 5 is thus identical to the problem defined for the main request, see point 2.3.2 above.

As already discussed, see points 2.2 and 2.3.2 above, a person skilled in the art trying to put into effect the teaching of document (24) is in fact trying to provide a commercially viable product, i.e. a product having both efficacy and stability. Such a product normally comprises carriers and/or excipients. A well-known excipient is lactose monohydrate.

The appellant has argued that the skilled person trying to provide a stable pharmaceutical product comprising FTC would have avoided the use of lactose monohydrate. It bases its argumentation on the warning in various textbooks, documents (41), (43) and (44), concerning the formation of Maillard side-products due to the reaction of lactose (monohydrate) and active pharmaceutical ingredients having primary amino groups. Basic lubricants, such as magnesium stearate, may exacerbate incompatibility. Also, the appellant invoked document (50), which shows that lamivudine is formulated in the absence of lactose. Respondent 1 takes the position that lactose monohydrate is one of the most commonly used excipients. All the documents cited by the appellant presented incompatibility only as a possibility. Further, according to documents (41) and (42), the use of crystalline lactose avoided the problem.

The question to be answered is whether a skilled person would consider the use of lactose monohydrate as a carrier or excipient when providing a co-formulation of TDF and FTC. On the one hand, the warning in the textbooks about combining amino-group containing compounds with lactose has to be taken into account, on the other hand the fact that one of the two active pharmaceutical agents is already marketed in a tablet comprising lactose monohydrate cannot be discounted. For the second active pharmaceutical ingredient, FTC, no product had been commercialised at the priority date of the patent in suit. A skilled person, see also point 2.3.4 above, would simply start with a formulation that is known to be effective and stable, i.e. the commercially available formulation comprising TDF (Viread, see document (10)). Document (10) provides thus an incentive to use lactose monohydrate when trying to put the teachings of document (24) into practice.

The subject-matter of auxiliary request 5 does not involve an inventive step (Article 56 EPC).

2.7 Auxiliary request 6

Auxiliary request 6 defines the actual amounts of TDF and FTC in the tablet and the presence of lactose monohydrate as carrier or excipient.

The appellant has not invoked any inter-dependencies between the amounts of active pharmaceutical ingredients and the type of carrier or excipient used. The two aspects can thus be seen as a simple juxtaposition. Consequently, the argumentation for auxiliary request 2 together with that for auxiliary request 5 applies.

The subject-matter of auxiliary request 6 does not involve an inventive step (Article 56 EPC).

2.8 *Auxiliary request 7*

Auxiliary request 7 contains a single claim in the form of a product claim. A tablet comprising the features of the tablet described in table 1 as filed is defined. The carriers and excipients of the tablet correspond to the carriers and excipients of the core of the tablet sold as Viread, which comprises TDF as pharmaceutical active ingredient (document (10), page 18, last paragraph). As already stated above under point 2.3.4, a skilled person would consider starting his routine testing by considering known formulations comprising one of the two pharmaceutical active ingredients. It forms part of the routine testing to determine the optimal amounts of each excipient/carrier.

The combination of excipients and carriers claimed in claim 1 of auxiliary request 7 is thus obvious for the skilled person. The same reasoning as for the main request applies.

The subject-matter of auxiliary request 7 does not involve an inventive step (Article 56 EPC).

2.9 *Auxiliary request 8*

The claims of auxiliary request 8 define product claims having specific weight percentages or concentrations of ingredients. The optimisation of the concentrations of the excipients and carriers is within the routine work of the skilled person. The same reasoning as for auxiliary request 7 applies.

The subject-matter of auxiliary request 8 does not involve an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated