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Datasheet for the decision of 28 February 2025

Case Number: T 0992/22 - 3.3.10

Application Number: 14767892.4

Publication Number: 2970101

IPC: C07C219/08, C07C229/16, C07C309/18, C07C229/12, A61K31/221

Language of the proceedings: EN

Title of invention:
PRODRUGS OF FUMARATES AND THEIR USE IN TREATING VARIOUS DESEASES

Patent Proprietor:
Alkermes Pharma Ireland Limited

Opponents:
Teva Pharmaceutical Industries Ltd.
Hexal AG
Generics (UK) Ltd

Headword:
FUMARATES / Alkermes

Relevant legal provisions:
EPC Art. 123(2), 83, 54, 56

Keyword:
Amendments - combinations of substituent definitions in Markush formula - added subject-matter (no)
Sufficiency of disclosure - (yes)
Novelty - overlapping Markush formulae - (yes)
Inventive step - (yes) - non-obvious alternative

Decisions cited:
T 0012/90

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 0992/22 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 28 February 2025

Appellant: (Opponent 1)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. Tel Aviv 6944020 (IL)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
Appellant: (Opponent 2)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Appellant: (Opponent 3)	Generics (UK) Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Alkermes Pharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 (IE)
Representative:	Pohlman, Sandra M. df-mp Patentanwälte Rechtsanwälte PartG mbB Theatinerstraße 16 80333 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 February 2022 concerning maintenance of the European Patent No. 2970101 in amended form.**

Composition of the Board:

Chairman P. Gryczka
Members: M. Kollmannsberger
L. Basterreix

Summary of Facts and Submissions

I. The opponents appealed the Opposition Division's decision to maintain EP 2 970 101 in amended form pursuant to Article 101(3)(a) EPC, based on the patentee's auxiliary request 1 as submitted during the opposition procedure.

II. The patent deals with fumarate prodrugs which may be used in the treatment of neurological diseases, in particular multiple sclerosis. The prodrugs are metabolized in vivo to the active principle, monomethyl fumarate (MMF), which is responsible for the therapeutic activity.

III. The following documents are referred to in the present decision:

D1: WO 2010/022177 A2

D2: Saari et al., J. Med. Chem. 21(8), 1978; 746-753

D3: WO 02/081466 A1

D4: WO2013/181451 A1

D11: B. Testa and J.M Mayer "Hydrolysis in Drug and Prodrug Metabolism Chemistry, Biochemistry and Enzymology", Verlag Helvetica Chimica Acta, Zürich Switzerland, 2003

D12: Bonina et al., International Journal of Pharmaceutics 156 (1997) 245-250

D19: N.M. Nielsen and H. Bundgaard, Journal of Pharmaceutical Sciences 77(4), 1988, 285-298

D29: B. M. Liederer, R. T. Borchardt, Journal of Pharmaceutical Sciences 95(6), 2006, 1177-1195

D32: Gottlieb et al., October 2017 (poster) (online available via https://www.researchgate.net/publication/320697500 "XP-23829, a novel fumaric acid ester, is efficacious in reducing psoriatic lesions: Results from a phase 2 randomized controlled study". SKIN The Journal of Cutaneous Medicine, Vol. 1 (3.1): 33

D33: Evolve-MS-2 Study press release, Biogen, July 30, 2019. "Diroximel Fumarate Demonstrated Significantly Improved Gastrointestinal Tolerability Profile Compared to Dimethyl Fumarate in Patients with Multiple Sclerosis"

D40: Declaration of Prof. Roberts, 22 September 2021

D41: Annex to the declaration

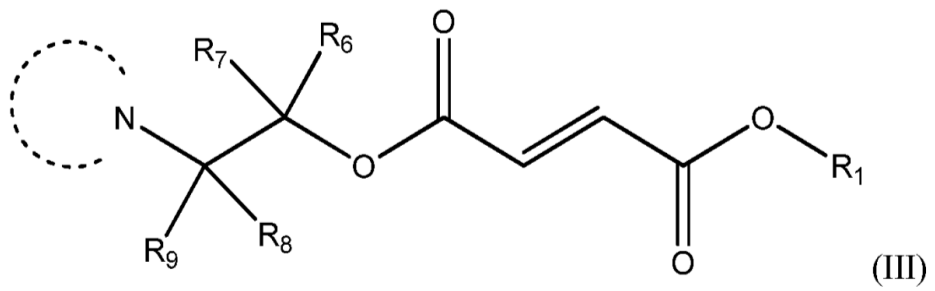
D49: Declaration of Prof. Roberts, 1 July 2022

IV. The patent had been opposed by three opponents under Articles 100(a)-(c) EPC for lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC), insufficient disclosure (Article 83 EPC) and unallowable amendments (Article 123(2) EPC). The Opposition Division concluded that dependent claims 3-6 of the granted patent contained unallowable amendments contravening Article 123(2) EPC. The claim set of auxiliary request 1, in which claims 3-6 were amended and dependent claim 11 deleted, was considered to

comply with Article 123(2) EPC and also with the other relevant provisions of the EPC. In particular the Opposition Division concluded that the claimed invention was sufficiently disclosed in the granted patent, that the claimed compounds were novel over D4 and also inventive starting from D1 as closest prior art document. The Opposition Division held that, although no unexpected improvements could be substantiated for the whole of claim 1 with respect to the closest prior art document D1, the claimed prodrugs were nevertheless a non-obvious alternative to the ones disclosed in D1.

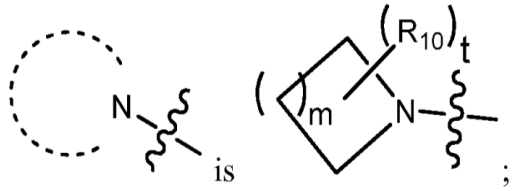
V. Independent claim 1 of the patent as maintained in amended form, which corresponds to claim 1 of the patent as granted, reads as follows:

"*A compound of Formula (III), or a pharmaceutically acceptable salt thereof:*



(III)

wherein:



;

R_1 is unsubstituted C_1-C_6 alkyl;

R_6, R_7, R_8 and R_9 are each, independently, H, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl or $C(O)OR_a$;
R_a is H or substituted or unsubstituted C_1-C_6 alkyl;
m is 0, 1, 2, or 3;
t is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10; and
each R_{10} is, independently, H, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_3-C_{10} carbocycle, substituted or unsubstituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or substituted or unsubstituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S;
or, alternatively, two R_{10}'s attached to the same carbon atom, together with the carbon atom to which they are attached, form a carbonyl, substituted or unsubstituted C_3-C_{10} carbocycle, substituted or unsubstituted heterocycle comprising one or two 5- or 6-member rings and 1 -4 heteroatoms selected from N, O and S, or substituted or unsubstituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S;
or, alternatively, two R_{10}'s attached to different atoms, together with the atoms to which they are attached, form a substituted or unsubstituted C_3-C_{10} carbocycle, substituted or unsubstituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or substituted or unsubstituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S."

Dependent claims 3-6 of the patent as maintained in amended form read as follows:

Claim 3:
"*The compound of claim 1 wherein R_6, R_7, R_8 and R_9 are each H.*"
Claim 4:
"*The compound of claim 1 wherein m is 2 or 3.*"
Claim 5:
"*The compound of claim 1 wherein t is 0, 1, 2, 3, or 4.*"
Claim 6:
"*The compound of claim 1 wherein two R_{10}'s attached to the same carbon atom, together with the carbon atom to which they are attached, form a carbonyl.*"

Independent claim 12 of the patent as maintained in amended form, which corresponds to claim 13 of the patent as granted, reads as follows:

"*A compound of Formula (III), a pharmaceutically acceptable salt thereof, according to any one of claims 1-11, or a composition according to claim 12, for use in treating a neurological disease.*"

VI. The appellants contested all the Opposition Division's findings. They argued that amended claims 3-6 still contravened Article 123(2) EPC. Appellant 2 (former opponent 2) submitted that the therapeutic use of the compounds as defined in claims 12-14 was insufficiently disclosed and that the prodrugs defined in claim 1 lacked novelty over D4. All appellants argued that these claimed prodrugs lacked an inventive step over D1.

VII. The respondent submitted that the Opposition Division's decision to maintain the patent in the form of auxiliary request 1 lying before it was correct.

VIII. The parties' requests were the following:

The appellants (opponents) requested the decision of the Opposition Division to be set aside and the patent to be revoked. Furthermore, the appellants requested documents D51-D58 not to be admitted into appeal proceedings as well as "Annex A".

The respondent (patent proprietor) requested the appeals to be dismissed. Should the appeals not be dismissed the respondent requested to maintain the patent in amended form based on auxiliary requests 2-5, as submitted already in opposition proceedings and resubmitted together with its reply to the statements setting out the grounds of appeals.

IX. Oral proceedings were held on 28 February 2025. The decision was announced at the end of the oral proceedings.

Reasons for the Decision

1. The appeals are admissible.

The patent as maintained by the Opposition Division in the form of auxiliary request 1 (AR1) before it

2. Amendments (Article 123(2) EPC).

2.1 The appellants objected to dependent claims 3-6, and to claims 11-14 insofar as they refer to these claims. Claim 1, which is unamended compared to granted claim 1, was not objected to.

2.2 Claim 1 defines compounds (III) as disclosed on pages 24 and 25 of the original PCT-publication. In claim 1 the N-containing cyclic group is restricted to the first of the four possibilities given there. The appellants' argument was that this first selection of substituents is then combined with the features of dependent claims 3-6, which themselves result from one or a multitude of selections of substituent definitions from the respective broader definitions in the original disclosure. According to the appellants there was no pointer to these specific selections in the originally filed documents. They resulted thus in originally undisclosed subject-matter.

2.3 The Opposition Division decided that no double selection took place since the selection of the N-containing ring was already individualized on the bottom of page 25. The respondent added that there were various pointers to the resulting combination and referred to the example compounds. The appellants deny any individualisation of the claimed N-containing ring already in the original application documents.

2.4 Claims 3-6 comply with the provisions of Article 123(2) EPC, for the following reasons:

2.4.1 Claims 4 and 5 define lists for the variables m and t. These lists are obtained restricting the original lists, e. g. on the bottom of page 24, to fewer members. No specific values have been selected, and thus no specific selection has been made. The appellants' arguments fail already for this reason alone.

2.4.2 The Board does not deny that some selections from the original disclosure have been made in arriving at the structural definition of dependent claims 3 and 6, in combination with claim 1. For the N-containing cycle one of the four described rings has been selected in claim 1, for the values of R_6-R_9 hydrogen has been selected in claim 3 and in claim 6 two groups of R_{10} have been selected to form a carbonyl group together. It is the combination of the selection of the specific ring system with the values of R_6-R_9 and R_{10} respectively that the appellants consider to create originally undisclosed subject-matter.

2.4.3 However, Article 123(2) EPC does not prohibit selecting a part of the originally disclosed subject-matter and specifically claiming it. The decisive question is not whether selections have been made, and if yes, how many. The decisive question is whether the amendments result in subject-matter extending beyond the original disclosure, i. e. whether they add information that is not directly and unambiguously derivable from the original application documents.

2.4.4 The Board is at loss to identify any subject-matter or technical information that is present in claims 3 and 6 of AR1 but not in the original disclosure. The generic group defining the compounds of claims 3 and 6 may not have been originally disclosed in form of the specific

Markush formula now claimed, but the formula defined in claim 3 as well as the formula defined in claim 6 can be obtained from the original disclosure, formula (III) on page 25, by simply deleting substituent definitions from lists. The groups of compounds obtained in this way do not contain any originally undisclosed structural feature, e. g. a specific combination of substituents. This is evident already from the fact that there are numerous example compounds encompassed by claims 3 and 6. The combination of substituents selected from the original disclosure to form the groups defined in claims 3 and 6 was thus already originally disclosed. Such an amendment does not generate originally undisclosed subject-matter.

2.5 Thus, the provisions in Article 123(2) EPC do not prejudice the maintenance of the patent in the form of AR1.

3. Sufficiency of disclosure, Article 83 EPC

3.1 Claim 12 is directed to compounds (III) for use in the treatment of a neurological disease. According to appellant 2 this use is insufficiently disclosed as far as compounds (III) with R_1 other than methyl are concerned. The same applied to claims 13 and 14 which further specify the neurological disease. Appellant 2 argued that compounds for R_1 other than methyl will not hydrolyse in vivo to MMF, unlike what is stated in the patent in [0017].

The patent stressed in paragraphs [0002] and [0059] that the active agent was MMF which was not obtained by hydrolysis if R_1 was other than methyl. At least there was no teaching in the patent how MMF should be

obtained under these circumstances. On the other hand, there was no proof in the patent or anywhere else on file that C_1-C_6 monoalkyl fumarates other than MMF would be effective as active species in the treatment of neurological diseases. The treatment of neurological diseases using such compounds was however a functional feature of claims 12-14. In the absence of any disclosure of a relevant activity a skilled person would be at loss as to how such a treatment should be put into practice.

3.2 The Opposition Division had rejected these arguments, see point 37 of its decision. The Opposition Division concluded that a skilled person would realize that MMF was a representative of monoalkyl fumarates which were known to have relevant pharmaceutical activity, e. g. from D1.

3.3 The Board concurs with the decision of the Opposition Division.

3.3.1 Appellant 2 is of course correct to state that compounds (III) for R_1 other than methyl will not hydrolyse in vivo to MMF, but to other monoalkyl fumarates. A skilled person would know that and would read the disclosure in paragraphs [0002] and [0017] of the patent accordingly. The statement in paragraph [0059] refers to the example compounds for which it is correctly described that they will hydrolyse to MMF.

3.3.2 The essence of appellant 2's argument is that there is no proof of pharmaceutical activity for compounds (III) for R_1 other than methyl. All the examples in the patent, and also the examples in the prior art related to MMF as an active species.

3.3.3 However, while it is correct that all specific disclosures relate to MMF as an active agent it is not the patent proprietor who states for the first time that C_1-C_6 monoalkyl fumarates may have a relevant activity. The same is stated in D1, see the definition of R^5 in claim 1 there, even if not backed up by experimental evidence. The claimed invention in fact starts from the compounds disclosed in D1, see paragraph [0003] of the patent, and the idea of the patent is to change the prodrug moiety on the other side of the molecule. The suitability of this different prodrug moiety was uncontested throughout the proceedings.

It is beyond doubt that compounds with R_1 being methyl, hydrolysing to form MMF, have relevant pharmaceutical activity. A skilled person would read from D1 and from the patent that MMF is a preferred representative of C_1-C_6 monoalkyl fumarates which generally have such pharmaceutical activity.

Appellant 2 has not substantiated that such a reading derived from the patent and the prior art is wrong, i. e. that no relevant activity is present. As an opponent it would have been incumbent on the appellant to show that the generalisations made in the patent and in D1 are not justified. A mere allegation that without experimental proof no pharmaceutical activity can be expected for compounds with R_1 being C_2-C_6 alkyl instead of methyl is insufficient and cannot justify a finding of insufficient disclosure of the claimed invention.

3.4 Thus, the provision of compounds (III) for treating neurological diseases, as claimed in claims 12-14, is disclosed in a manner sufficiently clear and complete

for it to be carried out, as required by Article 83 EPC.

4. Novelty (Article 54(3) EPC)

4.1 Appellant 2 submitted that the claims lacked novelty over D4, which is a document relevant for novelty under Articles 153(5) and 54(3) EPC.

It is undisputed that D4 discloses a generic formula in claim 5 which overlaps with the generic formula of present claim 1 in case of (nomenclature of D4) X representing two hydrogen atoms, n being 0 and R^3 and R^4 forming a heterocycloalkyl ring.

Appellant 2 argued that D4 was novelty destroying in the overlapping region for the present claims. In particular it was referred to decision T 12/90 which elaborated some principles when dealing with overlapping generic Markush formulae.

4.2 The Opposition Division denied any novelty destroying effect of the disclosure of D4 and the Board agrees.

4.2.1 None of the example compounds of D4 illustrates the overlapping region. Most examples in D4 are amides which are not covered by the present claims because R_8 and R_9 (nomenclature of the present patent) cannot form a carbonyl group together. Those which are not, examples 9-12, have a morpholino group as an N-containing ring, which is also not covered by the present claims. This is unlike the situation underlying T 12/90 where the overlapping region was illustrated by two example compounds and novelty was intended to be based on a disclaimer excluding these specific

compounds. The Board in T 12/90 did not see any new technical teaching characterizing the claim at stake in the overlapping region. After all, the combination of structural features selected to define the generic formula in the claim had already been made in the prior art document by means of the two example compounds, see point 2.6 of the reasoning. Thus, the claim in the overlapping region just repeated the teaching of the prior art.

4.2.2 The present case is different. In order to arrive at subject-matter falling into claim 1 of AR1 from the general formula in claim 5 of D4 one has to proceed as follows: restrict n to zero, X to two hydrogen atoms and R^3 and R^4 together with the nitrogen atom to form a N-heteroaliphatic cycle not containing any further hetero atoms. The latter possibility for R^3 and R^4 is not even specifically mentioned in claim 5 of D4. Moreover, in contrast to the case underlying T 12/90 there is no pointer in D4 to proceed in this way, since neither any preferred subgroups nor any of the example compounds have such a combination of features. This specific combination of structural features is simply not described in D4. This represents a new technical teaching in the sense of T 12/90. In the region of overlap with D4 the Markush formula (III) of present claim 1 is not a mere repetition of the teaching of D4 but contains something new, namely a specific combination of structural features not disclosed in D4. Thus, claim 1 is novel over D4 already for this reason alone. Considerations about activities of example compounds, as made by the Opposition Division and appellant 2, are not necessary.

4.2.3 Appellant 2 pointed to example 15 of D4 and argued that this example was included in the present claims were it

not for the oxo group adjacent to the nitrogen atom. A skilled person would read from the definition of X in D4, or from example 9, that also two hydrogen atoms were possible at this position. A skilled person, replacing the oxo group by two hydrogen atoms, would thus arrive at subject-matter included in the claims.

4.2.4 However, the decisive question is whether D4 specifically discloses subject-matter included in the region of overlap of the claims. This is not the case. Modifying the specific teaching of D4 to arrive at something included in the present claims is not what is derivable in a direct and unambiguous way from D4. The question of whether a skilled person would have done so or not would rather be relevant when assessing inventive step.

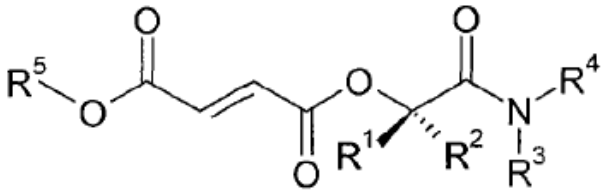
4.3 In summary, the claims of the patent as maintained are novel over the disclosure of D4.

5. Inventive step (Article 56 EPC)

5.1 The patent deals with compounds that act as prodrugs for monomethyl fumarate (MMF), an active agent used in the treatment of neurological diseases, in particular multiple sclerosis. The compounds defined in the independent claim, compounds (III), are double esters that are hydrolysed *in vivo* to form a monoalkyl ester, i. e. MMF or alkyl analogues thereof, which then exert their therapeutic activity inside the body. MMF is usually administered as dimethyl fumarate (DMF) which is rapidly hydrolysed to MMF inside the body. The use of DMF as a prodrug has some drawbacks including gastrointestinal side effects, see paragraphs [0004] and [0009] to [0014] of the patent.

5.2 Closest prior art

It was uncontested that the document representing the closest state of the art is D1. D1 is referred to in paragraph [0003] in the introductory part of the patent and likewise deals with prodrugs of MMF. Similar to the present patent D1 aims to provide prodrugs of MMF having lesser side effects, see page 4 line 25 to page 5 line 1. D1 proposes, among others, acylamino ester prodrugs for this purpose, see formula (I) on page 5.



(I)

This formula is illustrated by various example compounds, one of which (example 1) is used as reference compound A in the present patent, see [0136].

5.3 Objective technical problem and its solution

5.3.1 The difference of the present claims with respect to the compounds disclosed in D1 is that the present claims relate to ester prodrugs wherein an alicyclic nitrogen containing ring is attached via an *alkyl* spacer. In contrast, D1 discloses corresponding compounds where the nitrogen atom is attached via an *acyl* group. This was likewise uncontested. Regarding this difference it is not decisive whether one takes claim 1, example 1, example 20 or any other disclosure of D1 as a starting point.

5.3.2 From the arguments brought forward by the patent proprietor and the opponents in opposition proceedings the Opposition Division concluded that the data on file could not prove any improved properties for compounds according to claim 1 of AR1 compared to those of D1, see point 47 of the decision under appeal. The data concerning aqueous stability, physical stability, oral bioavailability (all in the patent itself), or gastrointestinal tolerability (D32, D33) could show such improvements at most for individual compounds, but not for the entire scope of claim 1.

5.3.3 If this analysis is followed, the objective technical problem to be solved by the compounds defined in claim 1 when starting from the disclosure of D1 is the provision of alternative prodrugs for MMF. Since the Board comes to the conclusion that this technical problem was solved in a non-obvious way (see below), there is no need to decide whether improvements shown for individual compounds, such as for diroximel fumarate (compound 14), versus example compounds of D1 may be generalized to compounds (III) of claim 1 or not, and whether the claimed compounds thus are the solution to any more ambitious technical problem than that of an alternative.

5.3.4 It was common ground that the claimed compounds indeed are a solution to technical problem of providing alternative prodrugs starting from D1. The dispute was whether this technical problem has been solved in an obvious way or not.

5.4 Obviousness

5.4.1 It was undisputed that the prodrug moiety which is used in the claimed compounds is known as such. It has been

used in some compounds of D2 (compound 4d), D3 (compounds 8, 9, 14), D11 (page 433) or D12. The cited compounds in D3 however are carbamates rather than esters and differ in the mechanism of hydrolysis. They undergo decarboxylation, unlike the compounds of the present claims. The appellants focussed thus on the disclosures of D2, D11 and D12.

5.4.2 The question to be decided is whether a skilled person would have chosen such a moiety for preparing a prodrug of MMF.

5.4.3 The Opposition Division had concluded that a skilled person would not have taken the prodrug moieties from the above cited compounds and attached them to MMF in the expectation to obtain suitable alternative prodrugs. The Opposition Division stated that the relevant compounds were not prominent ones in the teaching of the cited documents, so a skilled person had no special reason to consider them. Furthermore, a prodrug of MMF required to be selectively hydrolysed to cleave the pro-moiety without compromising the methyl ester at the other end of the fumarate. None of the prior art documents related to unsymmetrical prodrugs.

5.4.4 The Board agrees to the Opposition Division's analysis.

D2 discloses various prodrugs for Methyldopa, an antihypertensive agent. The compounds are synthesized in the hope of improving efficiency of absorption from the gastrointestinal tract. Compound 4d has a prodrug moiety according to the claims. Two out of the compounds synthesized in D2 are selected for further development, however not compound 4d.

D12 discusses 1-ethylazacycloalkan-2-one (ethyllactam) prodrugs of indomethacin, a condensed heteroaromatic antiinflammatory agent. The prodrug moiety is included in the prodrug part of formula (III) of the claims. The prodrugs are intended to reduce gastrointestinal side effects. The gastrointestinal side effects are in fact lowered, at the expense of reduced activity, as outlined in the "results and discussion" part of the article.

D11 is a textbook on prodrug hydrolysis that refers in the relevant part to the disclosure of D12, see reference [43] in chapter 8.2.3.3 "Amidoalkyl esters" on pages 433/434.

D1 describes acylamino esters (I) and acetal-type compounds (IV) as prodrugs for MMF. None of the other cited documents deals with prodrugs for MMF, so a skilled person would have had no guidance about which other prodrug groups might be suitable for this active agent. Without knowledge of the claimed invention a skilled person would not have had any reason to pick out the rather isolated disclosures of D2, D11 or D12 from the vast amount of literature on prodrug design and transfer the moieties described therein to MMF. Neither are the active agents discussed in D2, D11 or D12 structurally similar to MMF, nor do they have two different hydrolysable ester groups, nor are they used in the treatment of multiple sclerosis or are disclosed as acting via the same mechanism as MMF. Attaching a prodrug moiety as defined in present claim 1 to MMF could have been done with hindsight knowledge of the invention, but was not rendered obvious by the cited prior art.

5.4.5 Appellant 1 argued that starting from D1 the ethyllactam prodrugs disclosed in D12 would have lead the skilled person to the claimed compounds.

It was submitted that, in general, esters were the most prominent prodrugs for carboxylic acid group containing drugs since esterases were widely distributed throughout the body (D29, pages 1177-1180). Esters were routinely used and ester moieties were considered to be transferable between different active agents (D41). The prodrugs of D12 were disclosed as being stable in aqueous media and readily hydrolysed by ubiquitous esterases. The textbook D11 showed (chapters 8.2.3.2 and 8.2.3.3) that morpholinoalkyl or alkyllactam esters could be transferred between various nonsteroidal anti-inflammatory drugs (NSAID) in the expectation of improving oral bioavailability. Thus, a skilled person would have tried such esters with a reasonable expectation of success, in particular because the problem to be solved only related to the provision of alternative prodrugs.

The Board disagrees. The disclosures of D11 and D12, and the table showing transferability of ester prodrugs in D41 concern prodrugs of structurally remote NSAIDs. There is no evidence on file which would show that the prodrug moiety used in D12 has been transferred to any active agent other than indomethacin and naproxen. It was referred to compound 8 of D3, however, firstly the prodrug moiety of compound 8 in D3 is not the same as the one used in D12 and secondly the compounds of D3 are not esters but carbamates. Although also MMF is believed to have at least some anti-inflammatory activity, as mentioned in paragraph [0003] of the patent, MMF is not a classical NSAID.

The appellants are of course correct in stating that esters are a generally used prodrug form of carboxylic acid drugs. However, starting from D1 a skilled person would not have had any reason to turn to the disclosure of D12. There is no link between D1 and D12. A general transferability of prodrug moieties between any arbitrary kind of active agent is not derivable from the cited documents. Even if a skilled person, as submitted in the expert declarations D40 and D49, would know that some ester moieties had been transferred from one drug to another, it is not established that a skilled person would have considered such a concept to be universally applicable, in particular not in the case at stake. On the contrary, the textbook D11, to which also the expert declarations refer, presents the morpholinoalkyl (which are not even according to the claims) or alkyllactam esters in the chapters cited above and continues by stating that "*the various examples presented in this section illustrate the diversity of molecular factors that influence the many physicochemical and biochemical properties of significance in prodrug design. Many items of information are reported in this section, but the partial and fragmentary character hinders comprehensive understanding. (...)*"

5.4.6 Appellant 2 stressed that the difference of the claims with respect to D1 was only the replacement of a carbonyl by a methylene group. Starting from D1 a skilled person would have considered the prodrug moieties of D12 to have similar properties when applied to MMF since the kinetics of ester hydrolysis was not affected by the replacement of a carbonyl by a methylene group. To prove this, appellant 2 pointed to table II of D19 which compares rates of hydrolysis of various benzoic acid esters. The appellant referred to

compounds 52 and 53 which contained ester moieties only differing in the replacement of a carbonyl by a methylene group. The appellant argued that since the rates of hydrolysis of the two compounds were similar, a skilled man would have known that replacing the carbonyl group with a methylene group in the structurally closest compounds of D1, or applying the moieties of D12 to MMF instead of the glycolamides of D1, would result in compounds with similar properties, i. e. suitable prodrugs for MMF.

D19 is an article on glycolamide ester prodrugs, i. e. the prodrug moieties used in D1. In fact, D1 acknowledges D19 in the introductory part of the description, see page 4 lines 21 and 22, so its teaching was known to the inventors of D1. D19 concludes (see abstract) that "*the most prominent structural requirement needed for a rapid rate of hydrolysis was found to be the glycolamide ester structure combined with the presence of two substituents on the amide nitrogen atom*", see abstract. Compound 53 is a reference compound included in D19 for comparative purposes and is stated to have reduced enzymatic reactivity compared to the title compounds of D19, see page 291, right hand column. Compound 53 of D19 neither has the structural requirements stressed in D19 to be important, nor a prodrug moiety as defined in the present claims since it is linear, not cyclic. There is no relation whatsoever between D19 and D12. A skilled person could not have derived from D19 that starting from the cyclic compounds disclosed in D1 replacement of the carbonyl by a methylene group, or application of the prodrug moieties of D12, would equally lead to suitable prodrugs.

Even more importantly, the question to be decided is not whether a skilled person, being presented with the present claims, would have expected the claimed compounds to differ from the compounds in D1 only slightly in hydrolysis kinetics, or whether a skilled person would have reasonably expected them to be suitable prodrugs of MMF. This is a hindsight analysis. The question is whether a skilled person, considering the relevant prior art, would come up with the claimed compounds as a solution to the technical problem in the first place. This is not the case, as outlined above.

5.4.7 Appellant 3 submitted that ester prodrug moieties were freely transferable between active moieties, since the only function they needed to fulfil was to be hydrolysed upon administration. The relative order of hydrolysis between the two ester groups in MMF prodrugs was known already from D1; the second methyl esters was stable whereas the glycolamide ester was cleaved. A skilled person would expect this order to be maintained also for other easily cleavable esters as the ones disclosed in D12. Thus, basically any mixed ester of MMF would solve the non-ambitious problem of providing alternative prodrugs when starting from D1, and the ester moieties known from D12 would have been chosen by a skilled person and expected to work.

However, the important point is not so much whether a skilled person would have expected the order of ester hydrolysis in the unsymmetrical prodrugs of MMF disclosed in D1 to change or not if carrying out structural modifications on the prodrug moiety. Even assuming that the appellant is correct in this point, the statement that any ester would lead to suitable prodrugs of MMF, as long as it may be somehow hydrolysed, is not backed up by the cited prior art. If

this was the case, any research into prodrug design would be superfluous. As shown above, a general transferability of prodrug moieties between any arbitrary kind of different active agents is not what is generally believed in the art, and in particular not for the moieties discussed in D11 and D12.

5.4.8 The appellants also referred to D2, compound 4d, which likewise has a prodrug moiety as defined in the claims.

However, as for D12, starting from D1 there is no reason for a skilled person to consider D2. Compound 4d in D2 is one out of many esters synthesised as prodrugs of Methyldopa, an antihypertensive agent. Compound 4d is neither presented as a prominent example, not chosen for further development. There is no structural relationship between MMF and Methyldopa, nor do these drugs act via a similar mechanism.

5.5 To summarize, a skilled person, starting from D1 and looking for alternative prodrugs of MMF, would not have arrived at the compounds defined in claim 1 in an obvious way in view of the cited prior art.

6. Thus, the appellants' requests for revocation of the patent cannot be granted. The Opposition Division's decision to maintain the patent in amended form based on auxiliary request 1 lying before it was correct. The respondent's auxiliary requests do not need to be considered. Documents D51-D58 and "Annex A", which were requested not to be admitted to appeal proceedings are irrelevant for the decision and do not need to be commented on.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka

Decision electronically authenticated