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# Datasheet for the decision of 29 October 2009

**Case Number:** T 0682/06 - 3.3.02

**Application Number:** 98907722.7

**Publication Number:** 0973527

**IPC:** A61K 31/704

**Language of the proceedings:** EN

**Title of invention:**
Extended release formulations of clarithromycin

**Patentee:**
ABBOTT LABORATORIES

**Opponent:**
Sanovel Ilac Sanayii ve Ticaret A.S.

**Headword:**
Extended release formulations/ABBOTT LABORATORIES

**Relevant legal provisions:**
EPC Art. 100 (c), 123 (2)

**Relevant legal provisions (EPC 1973):**
-

**Keyword:**
"Claim 1 of all requests: Added matter (yes)"

**Decisions cited:**
-

**Catchword:**
-

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**Case Number:** T 0682/06 **-** 3.3.02

# D E C I S I O N
## of the Technical Board of Appeal 3.3.02
## of 29 October 2009

**Appellant**: (Patent Proprietor)
ABBOTT LABORATORIES
CHAD 0377/AP6D-2
100 Abbott Park Road
Abbott Park IL 60064-3500 (US)

**Representative**:
Wright, Robert Gordon McRae
Elkington and Fife LLP
Prospect House
8 Pembroke Road
Sevenoaks
Kent TN13 1XR (GB)

**Respondent**: (Opponent)
Sanovel Ilac Sanayii ve Ticaret A.S.
Buyukdere Cad. Dereboyu Sok
Zadra is Merkezi C Blok
TR-34398 Maslak-Istanbul (TR)

**Representative**:
Vossius & Partner
Siebertstraße 4
D-81675 München (DE)

**Decision under appeal:**
**Decision of the Opposition Division of the European Patent Office posted 2 March 2006 revoking European patent No. 0973527 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairman:** U. Oswald
**Members:** M. C. Ortega Plaza
J.-P. Seitz

## Summary of Facts and Submissions

I. European patent No. 0 973 527, which was filed as application number 98 907 722.7, based on international application WO 98/46239, was granted on the basis of eleven claims.

Claim 1 as granted read as follows:

"1. A pharmaceutical composition for extended release of clarithromycin in the gastrointestinal tract, to be administered orally, comprising clarithromycin and a pharmaceutically acceptable, hydrophilic, water-soluble polymer,
which releases clarithromycin so that after a regimen of a single 1000 mg dose on day 1 and a multiple dose regimen of 1000 mg on days 3, 4 and 5, the maximum plasma concentration is reached after 6.9±3.3 hours, and the area under the plasma concentration time curve 0-24 hours is 40.2±13.8 µg.h/mL, or
which releases clarithromycin so that after a single 500 mg dose, the area under the plasma concentration time curve 0-∞ is 15.0±6.5 µg.h/mL".

II. The following documents and exhibits cited during the proceedings are relevant for the present decision:

(21) Product information of The Dow Chemical Company with the heading: "Formulating for Controlled Release with METHOCEL$^{R}$ Premium Cellulose Ethers".
The opposition division mentioned this document in its decision as being published in 1989; however, the last digit of the year on the right-hand bottom of the page after the cover page is illegible. The parties present

at the oral proceedings before the board did not know either whether it was a seven or a nine.

(E1) Extract of Dow Company leaflet with the heading "Dow Excipients METHOCEL™ Products". Available in the internet on 12 October 2009 under the link corresponding to dow.com/dowexcipients.

III. Opposition was filed and revocation of the patent in its entirety was requested pursuant to Articles 100(c) (added matter), 100(b) (insufficiency of disclosure) and 100(a) EPC (lack of novelty and inventive step).

IV. The present appeal lies from a decision of the opposition division revoking the patent under Article 102(1), (3) EPC 1973.

The opposition division considered that the subject-matter of claim 1 as granted extended beyond the content of the application as filed (Article 100(c) EPC).

As regards the auxiliary requests 1 to 3 also serving as basis for the opposition division's decision, the opposition division found that they were not allowable since they contained added matter (Article 123(2) EPC). Moreover, in the opposition division's view the third auxiliary request did not meet the requirements of Article 123(3) EPC.

V. The patent proprietor (appellant) filed an appeal against the said decision. The appellant filed with its grounds of appeal a main request and eight auxiliary requests.

VI. The respondent filed counterarguments thereto.

VII. The board sent a communication as an annex to the summons for oral proceedings expressing its preliminary opinion in relation to added matter. In this communication the board expressly mentioned that the opposition division's findings (unallowable generalisation of the examples in the application as originally filed) in relation to the issue of added matter (Article 100(c) EPC) were correct.

VIII. The appellant filed with the letter dated 29 September 2009 a new main request and three auxiliary requests in order to replace all requests previously on file.

IX. Oral proceedings took place on 29 October 2009.

At the oral proceedings the appellant filed a new main request and three auxiliary requests and withdrew its previous requests.

Claim 1 of the main request read as follows:

"1. A pharmaceutical tablet formulation for extended release of clarithromycin in the gastrointestinal tract, to be administered orally, comprising clarithromycin and a pharmaceutically acceptable, hydrophilic, water-soluble polymer, which is hypromellose 2208, with a methoxyl content of 19-24%, a hydroxypropoxyl content of 7-12% with a particle size 90% <100 mesh screen and a viscosity of 100 cps, as a 2% solution in water, the tablet formulation comprising 500.0 mg clarithromycin,

and either 200 mg of the polymer, 260.00 mg lactose monohydrate, 30.00 mg talc, USP and 10.00 mg magnesium stearate (formulation A) or 100 mg of the polymer, 360.00 mg lactose monohydrate, 30.00 mg talc, USP and 10.00 mg magnesium stearate (formulation B), obtainable by wet granulation,
wherein formulation B releases clarithromycin so that after a regimen of a single 1000 mg dose on day 1 and a multiple dose regimen of 1000 mg on days 3, 4 and 5, the maximum plasma concentration is reached after 6.9±3.3 hours, and the area under the plasma concentration time curve 0-24 <hours> (*sic*) is 40.2±13.8 µg.h/mL, the maximum plasma concentration is 2.6±0.87 µg/mL, the minimum plasma concentration is 0.67±0.39 µg/mL, and the fluctuation index is 1.24±0.37 and formulation A releases clarithromycin so that after a single 500 mg dose, the area under the plasma concentration time curve 0-∞ is 15.0±6.5 µg.h/mL, the maximum plasma concentration is reached 5.0±1.7 hours after dosing and the maximum plasma concentration is 1.19±0.60 µg.h/mL".

Claim 1 of the first auxiliary request differed from claim 1 of the main request in that the "product-by-process features" before the pharmacokinetic profiles had been specified as follows: "obtainable by wet granulation and coating with an aqueous coating,"

claim 1 of the second auxiliary request differed from claim 1 of the main request in that the "product-by-process features" before the pharmacokinetic profiles had been specified as follows: "obtainable by dry blending the polymer, lactose and clarithromycin, followed by granulating the mixture using water until

proper granulation is obtained, then drying, sifting and grinding the granulation to appropriate size, blending the talc and magnesium stearate with dried granulation, compressing the granulation into tablets and coating with an aqueous coating".

Claim 1 of the third auxiliary request differed from claim 1 of the second auxiliary request in that it had been restricted to formulation (A) and its pharmacokinetic profile.

X. The appellant's arguments, as far as relevant for the present decision, can be summarised as follows:

The appellant acknowledged that the pharmacokinetic profiles appearing in granted claim 1 corresponded to particular formulations of the examples (namely formulations A and B of example 1, Table 1 of the application as filed). The examples in the application as filed referred to Methocel$^{R}$ K 100 LV. Hence the appellant had to deal with the problem of having one of the constituent products defined in the examples as a trade mark product. This was the reason why the claim now gave the definition "hypromellose 2208, with a methoxyl content of 19-24%, a hydroxypropoxyl content of 7-12% with a particle size 90% <100 mesh screen and a viscosity of 100 cps, as a 2% solution in water".

It had been acknowledged on page 3, lines 25, 26 of the application as filed that the hydrophilic, water-soluble polymer was "hydroxypropylmethyl cellulose K 100 LV".

The term "hypromellose" was a generally known short term for "hydroxypropylmethyl cellulose". Moreover, the further specifications appearing in connection with the hydrophilic, water-soluble polymer were generally known to the person skilled in the art. This applies in particular to the substitution type as being 2208 and to the substitution degree in relation to the methoxyl content and the hydroxypropoxyl content. As regards the viscosity the value stated in the claim was perfectly derivable from the application as filed (page 5, lines 17-20). From this passage it was clear that the viscosity was "about 100 cps", and hence the meaning corresponded to that appearing in document (21).

CR grade was a more refined grade as reflected in the claim by means of the particle size 90% <100 mesh screen. This was the product description definition given on the top (right-hand) of page 4 in document (21).

Although the formula of trade mark products may vary as time elapses this was not the case for Methocel$^{R}$ which was a pharmaceutical excipient, namely hypromellose, having the standards defined in the US Pharmacopeia (USP). The appellant submitted that, in the case of pharmaceutical products, if the product changed then the name changed as well.
The appellant denied that the CR grade Methocel$^{R}$ might have a different viscosity to that appearing in table 1 of document (21). The appellant argued that the product description in the product leaflet (E1) supported their assertion that the Methocel$^{R}$ K 100 LV had not changed over time (in particular the type and degree of substitution). As regards the viscosity, the appellant

did not deny that it referred to a range, but this was also stated in the application as filed with the expression "about".

XI. The respondent's arguments as far as relevant for the present decision can be summarised as follows:

Claim 1 of all requests contravenes the requirements of Article 123(2) EPC. In particular the definition of the "hydrophilic, water-soluble polymer" incorporated in claim 1 of all requests found no basis in the application as filed. The hydrophilic, water-soluble polymer employed in the exemplified formulations (Table 1 on page 8 of the application as filed) was a commercial product, namely Methocel K 100 LV Premium CR Grade and the definitions now appearing in claim 1 did not necessarily correspond to the actual polymer used in the examples. The respondent submitted that it could not read the date of document (21) and that this was a document of the eighties, whereas the priority date claimed in the patent in suit was a decade later. Moreover, even if considering document (21) not all the features had been incorporated into claim 1. Document (21) clearly expressed that it was the "nominal" viscosity which meant that the value appearing in table 1 of document (21) was not a single value but related to a range. In contrast to that the viscosity was defined in claim 1 as a single value. Moreover, the Methocel$^{R}$ product employed in example 1 was a CR Grade type, and this was essential for the extended release and the pharmacokinetic profile attained. According to document (21) Methocel$^{R}$ CR Grade had particular hydration characteristics which were not mentioned in the amended claims.

The opponent submitted that the trademark Methocel$^{R}$ was not one single product but a palette of products encompassed by the generic definition of "hypromellose" as a pharmaceutical excipient and it denied that Methocel$^{R}$ K 100 LV had never changed over time. The respondent submitted document (E1) in order to support its position. This document clearly supported the view that the viscosity of the commercial product Methocel$^{R}$ K 100 LV appearing in document (21) was only nominal, and the viscosity varied, according to (E1), within the range 80 to 120 cps. Hence, the actual viscosity of the Methocel$^{R}$ K 100 LV CR grade employed in example 1 in the application as filed was not necessarily 100 cps.

The respondent submitted that the teaching of the application as filed referred to very specific formulations and that this teaching, which implied specific limitations, was not reflected in the amended claims. Thus, claim 1 of all requests related to an unallowable generalisation of the examples.

The respondent denied the definition of the particle size as a synonym for CR grade and mentioned that there was no proof that particle size of Methocel$^{R}$ CR grade had not varied over time. It also mentioned that the exhibit (E1) did not contain this data.

XII. The appellant (patentee) requested that the decision under appeal be set aside and that the case be remitted to the first instance for further prosecution on the basis of the main request or one of the three auxiliary requests filed during the oral proceedings held before the board on 29 October 2009.

The respondent requested that the appeal be dismissed.

## Reasons for the Decision

1. *Admissibility*

1.1 The appeal is admissible.

1.2 *Admissibility of the auxiliary requests and the document filed at the oral proceedings before the board*

The appellant did not contest the admissibility of the document filed by the respondent at the oral proceedings before the board and the board sees no reason to differ.

The respondent did not contest the admissibility of the requests filed at the oral proceedings before the board and the board sees no reason to differ.

2. *Claims' history*

2.1 The appellant's attempt to specify in the amended claims the exact composition of the extended release formulations A and B in accordance with example 1 and table 1 of the application as filed is justified by the fact that claim 1 as granted contains added matter (Article 100(c) EPC) owing to an unallowable generalisation of the examples. The unallowable amendment introduced during the examination proceedings, involved the incorporation of specific pharmacokinetic profiles (only disclosed in the application as filed

for the specific formulations A and B of example 1) as a feature of the generic formulation claimed in claim 1. The said unallowable amendment implied for the claimed subject-matter a teaching undisclosed in the application as filed, namely that each and every formulation encompassed by the generic claim was able to attain one of the two specific pharmacokinetic profiles in the claim.

2.2 Furthermore, the appellant had to abandon several sets of claims filed during the appeal procedure in which the commercial product definition "Methocel$^{R}$ K 100 LV Premium CR grade" in table 1 of example 1 had been replaced in the claims by the term "hydroxypropyl methylcellulose", since this amendment would also have amounted to an unallowable generalisation of the examples.

2.3 Finally, it has to be stressed that the specific nature and identity of the hydrophilic, water-soluble polymer employed in formulations A and B of example 1 have a direct bearing on the extended-release pharmacokinetic profile of the formulations.

2.4 As a consequence of the above situation, the appellant defined the "hydrophilic, water-soluble polymer" in claim 1 of all requests (main request and auxiliary requests 1 to 3) as follows:

"hypromellose 2208, with a methoxyl content of 19-24%, a hydroxypropoxyl content of 7-12% with a particle size 90% <100 mesh screen and a viscosity of 100 cps, as a 2% solution in water".

3. *Added matter (Article 123(2) EPC)*

3.1 In order to assess the issue of added matter in relation to Article 123(2) EPC it has to be investigated whether or not the definition (which is now incorporated in claim 1 of all requests), mentioned in point 2.4 above, unequivocally identifies the "Methocel$^{R}$ K 100 LV Premium CR Grade" used in the exemplified formulations A and B and whether or not it is unambiguously derivable from the application as originally filed.

3.2 The term "hydroxypropylmethylcellulose" (HPMC, or "hypromellose") is the non-proprietary name given to cellulose, 2-hydroxypropyl methyl ether. It is well known that these non-proprietary terms (hydroxypropylmethylcellulose and its synonym hypromellose) relate to pharmaceutical excipients in the pharmacopoeias and are also terms appearing in the handbooks of pharmaceutical excipients. In contrast thereto, the term "Methocel$^{R}$ K 100 LV Premium CR Grade" identifies a specific commercial product of a specific company, which (according to the application as filed) was available from The Dow Chemical Company in 1997 (priority date of the patent in suit).

Moreover, although the appellant repeatedly invoked the US Pharmacopeia (USP) as a source for the common general knowledge of the person skilled in the field, in order to validate the specific definition now appearing in claim 1 of all requests for the hydrophilic, water-soluble polymer employed it never filed a copy thereof and referred instead to document (21) which relates to a product information leaflet

about the METHOCEL™ series and which was published by The Dow Chemical Company in the eighties. This document (21) is neither a pharmacopoeia nor a handbook of pharmaceutical excipients and hence it cannot be seen as forming part of the common general knowledge of the skilled person.

3.3 It is well known that the term "hydroxypropyl methylcellulose" (HPMC, or "hypromellose") in the pharmacopoeias and handbooks of pharmaceutical excipients is in fact a generic term which describes hydroxypropyl methylcellulose as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose which is commercially available in several grades which vary *inter alia* in viscosity and extent of substitution. Additionally, since hydroxypropyl methylcellulose is a very versatile pharmaceutical excipient (commonly used in oral and topical pharmaceutical formulations, e.g. as tablet binder, film coating, extended-release matrix) the palette of commercially available products reflects a multitude of variations in substitution degree, molecular weight, viscosity, particle size, hydration degree etc., addressing the different uses and purposes.

3.4 It is not disputed that the commercial products of the Methocel® series which were and are sold as pharmaceutical excipients by The Dow Chemical Company are encompassed by the generic definition "hydroxypropyl methylcellulose" appearing in the pharmacopoeias and meet the pharmaceutical purity standards required, but what is at stake in the present case is the identification of one particular commercial product, namely Methocel® K 100 LV Premium CR Grade, as regards its specific physical and chemical

characteristics. These characteristics of the particular polymer used in the examples are not shared by each and every Methocel$^{R}$ product commercially available, nor are they shared by every hydroxypropyl methylcellulose excipient defined in the pharmacopoeias.

The Methocel$^{R}$ product specifically used in example 1 was Methocel$^{R}$ K 100 LV Premium CR Grade available from The Dow Chemical Company in 1997 and it has inevitably a particular and **individualised** chemical (e.g. substitution type and degree, molecular weight) and physical (viscosity, particle size, hydration degree) **identity**.

3.5 The application as filed does not contain any explicit definition of the identity of the specific polymer employed in example 1 apart from its commercial name. The passage on page 5, lines 15 to 20, merely reads:

"Most preferably, the polymer is a low viscosity hydroxypropyl-methyl cellulose with viscosity ranging from about 50 cps to about 200 cps. The most preferred low viscosity polymer is a hydroxypropylmethylcellulose with a viscosity of about 100 cps, commercially available under the Tradename Methocel$^{TM}$ K 100 LV from The Dow Chemical Company".

However, the mention of a viscosity of "about 100 cps" on page 5, without any reference in the whole application as filed to the measurement conditions, is not meaningful.

3.6 Furthermore, even supposing in favour of the appellant, that this reference in the application as filed to the commercially available product from The Dow Chemical Company equates to the content of The Dow Chemical Company's document (21) as "incorporated by reference" in the application as filed*, the following considerations apply:

(*This premise is however not confirmed by the board since document (21) was not identified in the application as filed and it corresponds to a specific document about "Formulating for Controlled Release with METHOCEL Premium cellulose ethers" published by The Dow Chemical Company in the eighties, which means that there is an additional problem left open: whether or not the products sold a decade later remained exactly the same.)

Document (21) explains on page 2 "Why HPMC is Often the Controlled Release Agent of Choice" and on page 3 "Why METHOCEL Premium Products are Often the Brand of Choice": "METHOCEL™ Premium cellulose ethers, specifically the K and E **series of products**, have been the preferred brand of HPMC in matrix systems for many years. And for many good reasons. First, the **family** of METHOCEL™ Premium products is the **broadest** in the industry. More than a **dozen separate** products are currently available. And this means **unmatched flexibility for the fine-tuning matrix release profiles**..." (*emphasis added*).

Document (21) page 4 gives "An overview of METHOCEL Premium products for matrix systems": "In controlled release formulations, only the premium grades of

METHOCEL can be used. These include METHOCEL Premium K100LVP, K4MP, K15MP, K100MP and E4MP. All of these products in addition to METHOCEL E10MP CR are available in CR (Controlled Release) grades which are specially produced, ultra-fine particle size materials".

Page 4 further contains a Table 1 concerning "Properties of Select Premium (USP) METHOCEL Premium Cellulose Ethers[1] ".

Footnote[1] reads: "Also available in EP and JP grades to meet the requirements of the European and Japanese pharmacopoeias".

The entry in Table 1 of document (21) for METHOCEL[R] Premium Product Grade K100LVP refers to a footnote[2] which reads: "Also available in faster hydrating CR (Controlled release) grades". It can be accepted that the substitution type identified in table 1 as 2208 is the same for both grades of the K100LVP Methocel[R] product (CR grade and non-CR grade). Moreover, it is generally known that the four-digit number defined in connection with a hydroxypropyl methylcellulose product reflects its substitution type in the following way: the first two digits (i.e. 22) refer to the approximate content of methoxy group and the second two digits (i.e. 08) refer to the approximate content of hydroxypropoxy group. This means that it can also be accepted that the ranges expressed as % for the methoxyl content and hydroxypropoxyl content in table 1 apply to both grades. However, the viscosity in table 1 is a "Nomimal viscosity, 2% in water" (emphasis added). This means that the number 100 stated in table 1 (***the units have to be assumed to be cps***) does not necessarily

correspond to the exact viscosity value of the polymer, i.e. the value 100 is of an approximate nature and does not represent a definite value.

The appellant has not denied this fact and has pointed to the expression "about 100 cps", appearing on page 5 of the application as originally filed, alleging that it was a synonym thereof. However, the description in the application as filed did not mention that the viscosity "about 100 cps" related to a "2% solution in water", and the expression "nominal" does not appear in amended claim 1 of the requests on file. In fact, the viscosity of the polymer is expressed in the amended claims as a single specific value. Thus, the viscosity value 100 cps, as a 2% solution in water, is a condition ***sine qua non*** in the amended claim 1 (which defines the hypromellose polymer) for which there is no disclosure in the application as originally filed.

Additionally, it has not been proven, nor has it been plausibly argued, that the specific polymer in the specific grade employed in example 1 for formulations A and B inevitably has a viscosity of "100 cps, as a 2% solution in water", since the value in table 1 of document (21) was of an approximate nature. However, to choose an HPMC polymer with a particular viscosity is essential for the formulation to attain a particular extended release profile.

This view concerning the approximate value of the viscosity of Methocel$^{R}$ K100LV in document (21) has been further confirmed by exhibit (E1), where the viscosity of 2% solution in water of Methocel$^{R}$ K100LV is given as the range 80-120.

3.7 As regards the issue of the actual grade of the polymer used in the formulations A and B, the following considerations apply: although document (21) defines the products in "CR grade" as "ultra-fine particle size materials", all the size requirements disclosed in document (21) for the Methocel$^{R}$ K100LV Premium series in the CR Grade have to be met.

However, the appellant took some of the values about particle size appearing on the right-hand top on page 4 as if they were a complete and isolated definition of a product particle size. By doing so, it created a new product definition concerning size requirements beyond the content of document (21).

Thus, the particle size requirements introduced in amended claim 1 of all requests are not acceptable since they are not the complete definition disclosed in document (21), which additionally requires that "100% <30 mesh screen".

Therefore, the specific particle size grade of the specific polymer employed in the examples is not appropriately reflected by the amended claims.

3.8 Consequently, the polymer defined in claim 1 of all requests is not necessarily identical to the polymer employed in the formulations A and B of example 1 in the application as filed.

3.9 For the above mentioned reasons, claim 1 of the main request and each claim 1 of auxiliary requests 1 to 3 do not meet the requirements of Article 123(2) EPC in

view of the definition of the hydrophilic, water-soluble polymer.

## Order

## For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

N. Maslin U. Oswald