English translation

VÉRON & ASSOCIÉS AVOCATS

T R I B U N A L
D E G R A N D E
I N S T A N C E
O F P A R I S

■

3rd Chamber
3rd Section

Docket No.:
08/12537

MINUTES NO.: 1

JUDGMENT
handed down on 7 May 2010

Summons of:
22 August 2008

CLAIMANTS

HEXAL AG
Industriestrasse 25
D-83607 Holzkirchen
Germany

S.A.S SANDOZ
49 avenue Georges Pompidou
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represented by Mr Pierre Cousin, attorney-at-law, member of the Paris Bar, courthouse box #R159

DEFENDANT

Boehringer Ingelheim Pharma GbmH & CoKG
Binger Str 173
55216 Ingelheim am Rhein
Germany

represented by Ms Marianne Schaffner, attorney-at-law, member of the Paris Bar, courthouse box J30

COMPOSITION OF THE *TRIBUNAL*

Agnès Thaunat, Vice-Presiding Judge, *signatory of the decision*
Anne Chaply, Judge
Mélanie Bessaud, Judge

assisted by Marie-Aline Pignolet, Court clerk, *signatory of the decision*

DISCUSSION

At the hearing of 18 January 2010
held publicly

JUDGMENT

Pronounced by delivery of the decision to the Court Clerk's office
After hearing both parties
In first instance

FACTS AND CLAIMS OF THE PARTIES:

Boehringer is the owner of patent EP 874 and in particular of the French designation of this patent:
- filed on 21 June 1991 by Karl Thomae GmbH, claiming priority of application PCT WO 93/00337, published on 7 January 1993, assigned to Boehringer on 9 June 1998,
- granted on 8 September 1999, and entitled "use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid for the preparation of a long-lasting antidiabetic medicament".

The translation into French was filed with the *Institut National de la Propriété Industrielle* (*I.N.P.I*) and published in the *Bulletin Officiel de la Propriété Industrielle* (*B.O.P.I*), in issue No. 51 dated 24 December 1999.

The annual renewal fees to keep the patent in force have been paid to the *I.N.P.I.*

On the basis of this patent, Boehringer commercialised a drug for the treatment of diabetes containing (S)(+)-2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid as the active principle.

This compound is known under the INN (International Nonproprietary Name) repaglinide.

In France, the drug is commercialised by Novo Nordisk Pharmaceutique SAS under the trade name NovoNorm, on the basis of the marketing authorisation granted on 17 August 1998 to Novo Nordisk A/S.

On the basis of this marketing authorisation, Karl Thomae GmbH filed, on 9 December 1998, an application for a supplementary protection certificate (hereinafter referred to as "SPC") in respect of basic patent No. 0 147 850 (hereinafter referred to as "Patent EP 850"), covering the compound called repaglinide, the enantiomers and salts thereof.

The SPC was granted on 5 May 2000 under No. 98 C0044 and remained in force until 26 December 2009.

By way of a summons dated 22 August 2008, Hexal AG and Sandoz brought proceedings against Boehringer Ingelheim Pharma GmbH and CoKG for the invalidity of the claims of the French designation of European No. 0 589 874 for lack of novelty or at least for lack of inventive step.

In the latest pleading notified on 23 December 2009, Hexal AG and Sandoz mainly request that the Judge:

declare claims 1 to 7 of the French designation of European patent No. 0 589 874 to be invalid due to lack of novelty or at least lack of inventive step, pursuant to the provisions of Articles 138-1-a), 52-1, 54-2 and 56 of the European Patent Convention,

order the forwarding of the judgment to be handed down to the *Institut National de la Propriété Industrielle* for entry in the French patents register,

order the defendant to pay to them the sum of €200,000, in accordance with the provisions of Article 700 of the French Civil Procedure Code,

order the defendant to pay the entire costs of the proceedings which will be recovered by Mr Pierre Cousin, local attorney-at-law, pursuant to Article 699 of the New French Civil Procedure Code.

According to its latest pleadings notified on 15 January 2010, Boehringer Ingelheim Pharma GmbH & CoKG mainly requests that the judge:

Hold its pleadings admissible and well-founded.

Hold Hexal AG and SAS Sandoz's requests and claims ill founded.

Hold that claims 1 to 7 of the French designation of European patent No. 0 589 874 are new and involve an inventive step.

Consequently,

Hold that claims 1 to 7 of the French designation of European patent No. 0 589 874 are valid.

Order Hexal AG and SAS Sandoz jointly and severally to pay to Boehringer Ingelheim Pharma GmbH & CoKG the sum of €400,000, pursuant to Article 700 of the French Civil Procedure Code.

Order Hexal AG and SAS Sandoz jointly and severally to pay the entire costs of the proceedings, which will be recovered by Ms Marianne Schaffner (Linklaters LLP), attorney-at-law, within the terms of Article 699 of the French Procedure Code.

In its latest responsive pleading notified on 15 January 2010, Boehringer requested:
- that the pleading notified on 23 December 2009 by the claimants be […][1] from the discussion,
- that exhibits Nos. 24, 24 bis, 25, 25 bis, 26 and 26 bis adduced by the claimants be rejected from the discussion,
- that the decision concerning the costs be postponed.

[1] Translator's note: word missing in the source document

In the latest interlocutory pleading notified on 18 January 2010, the claimants requested that the Judge:

hold Boehringer's claim seeking an order that sets aside its pleading No. 3 as well as exhibits No. 24, 24 bis, 25, 25 bis, 26 and 26 bis, inadmissible and ill-founded, and to dismiss it,

in the alternative, and if the *Tribunal* were inconceivably to reject this pleading and its exhibits, dismiss Boehringer's pleading of 14 December 2009 as well as its exhibits Nos. 3.20, 3.21, 4.28, 5.1 to 5.5 and 6,

in any case, reject on the grounds of lateness and violation of due process: the pleading on the merits of the case notified at the end of the day on 15 January 2010 before the oral proceedings of Monday 18 January at 9.30 a.m., as well as the slides produced in the same circumstances,

order Boehringer to pay the entire costs.

It should be noted that the procedural calendar which scheduled the notification of the claimants' latest pleading on 26 October 2009, that of the defendants' on 14 December 2009 and the pronouncement of the closing order on 12 January 2010, was not respected since after notifying a pleading on 29 October 2009, the claimants notified a fresh pleading on 23 December 2009, hence the defendants which had notified a pleading on 14 December 2009, had to respond to the claimants' latest pleading that occurred outside the calendar, in order to comply with due process.
The pronouncement of the closing order was consequently differed to the day of the oral proceedings. Taking the judicial holiday into consideration, this fresh pleading was notified only on 15 January 2010, that is, three days before the hearing.
Since due process was complied with and the defendant was last to communicate its pleading, the pleading and exhibits exchanged by the parties on 23 December 2009 and 13 December 2010 should be taken into consideration.

The closing order was pronounced on 18 January 2010.

GROUNDS OF THE DECISION

In order to better understand the next developments, the following points should be explained:

A carbon atom is called asymmetric or chiral carbon when it is attached to four atoms or groups of atoms all different from each other. When a molecule has a chiral atom, it exists in two different forms that are mirror images of each other, non-superposable on each other. Those two molecules are called stereoisomers: they are isomers because they are molecules different from each other although they have the same general formula, and are constituted of the same atoms, but with a different spatial arrangement. A sub-category of stereoisomers is known as enantiomers.

The conventional methods of organic synthesis of molecules containing a chiral carbon generally produce a mixture of each of the two enantiomers in equal amounts.
Such an equimolecular mixture (50/50) is called racemate.

The (R)/(S) nomenclature describes the absolute stereochemical configuration of a carbon.
This nomenclature reflects the intrinsic three-dimensional structure and the configuration of a given asymmetric carbon atom.
In addition, the specific rotatory powers of the enantiomers are opposed.
Enantiomers are classified as (+)enantiomer and (-)enantiomer.

The pharmaceutical properties of the two enantiomers can be very different. Very often, one of the enantiomers has a therapeutic activity completely different from that of the other: one can be active and the other inactive, or one can be active and the other toxic; pharmacodynamic interactions may occur between two enantiomers present in a racemate.

The enantiomers interact in a differential way with living systems which are themselves chiral and composed of chiral constituents. This is the chiral recognition phenomenon in biology. It explains why distinct pharmacokinetic responses are expected for enantiomers and why their pharmacokinetic behaviours differ.

On the scope of the patent

The subject-matter of the invention is the "use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid for the preparation of a long-lasting antidiabetic medicament".

The descriptive part of the patent sets out that "EP B 0 147 850 describes inter alia the racemate of 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]benzoic acid (code No. AG EE 388ZW) of the formula (*which follows*) and EP B 0 207 331 describes two other polymorphous forms of this compound. This compound and its physiologically acceptable salts have valuable pharmacological properties, namely an effect on the intermediate metabolism, but more particularly the effect of lowering blood sugar.
The two enantiomers of this compound, namely (S)(+)-2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid (code AG EE 623 ZW) and the (R)(-)–2–ethoxy-4-[N-(1-(2-piperidinophenyl)–3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid (code No. AG EE 624ZW), have been tested for their blood sugar-lowering effect on female rats."

The patent sets out that "it was found, surprisingly, that the (S)-enantiomer (AG EE 623 ZW) is the effective enantiomer and that its effect lasts longer than 6 hours in the rat.
On the basis of these findings in the rat, it seems appropriate to use exclusively AG-EE 623 ZW in humans, thereby reducing the dose by 50%, compared with the dose of AG-EE 388 ZW. This and a relatively long period of activity have

been found in humans. However, it was also found in the human studies that AG-EE 623 ZW has surprising pharmacokinetic properties which could not have been foreseen on the basis of the AG-EE 388 ZW data. AG-EE 623 ZW thus has surprising therapeutic advantages over the racemate AG-EE 388 ZW.
The surprising findings in humans are:
a) the AG-EE 623 ZW levels fall more rapidly towards zero than the AG-EE 388 ZW levels, even when the dosage is absolutely the same, which could not be expected in view of the relatively long period of activity.
b) in relation to the lowering of blood sugar achieved, substantially lower plasma levels of AG-EE 623 ZW occur than might have been expected by halving the dosage of AG-EE 388 ZW.
c) the blood sugar lowering activity occurs more rapidly after the administration of AG-EE 623 ZW than after the administration of AG-EE 388 ZW.

The amazing difference between the two enantiomers is the fact that the effective enantiomer, AG-EE 623 ZW, in spite of having a relatively long period of activity, is surprisingly eliminated more rapidly than the ineffective enantiomer, AG-EE 624 ZW, as demonstrated by Figures 1 and 2.VAfter the administration of the racemate, the ineffective enantiomer, AG-EE 624 ZW, is therefore present not only as an unnecessary additive in plasma concentrations which are just as high as those of the effective enantiomer, AG-EE 623 ZW, but is present in unexpectedly higher maximum and long-lasting levels. The effect of this, e.g. on administration of a tablet containing 2 mg of AG-EE 388 ZW or one tablet containing 1 mg of AG-EE 623 ZW to 12 and 6 test subjects, respectively, is that the maximum concentrations are 84 ± 25 and 28 ± 18 ng/ml, respectively, and the concentrations after 4 hours are 19 ± 8 and 0.7 ± 1.0 ng/ml, respectively, after 5 hours 13 ± 6 and 0.3 ± 0.7 ng/Ml, respectively, and after 6 hours 10 ± 6 and 0.3 ± 0.7 ng/ml (*sic*).

The surprisingly quick onset of the lowering of blood sugar by AG-EE 623 ZW, compared with AG-EE 388 ZW, is particularly advantageous for diabetics, since the rapid onset results in optimum control of the disease.

Thus, compared with the administration of AG-EE 388 ZW, the surprising advantage of the administration of AG-EE 623 ZW is that unnecessarily high and long-lasting levels of the substance in the body are avoided, which is of major importance in long term therapy, such as that of diabetic mellitus.

Human studies have shown that the use of the new (S) – enantiomer, namely (S)(+)-2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid, as a vehicle of blood sugar-lowering activity, is far superior to AG-EE 388 ZW, because of its surprisingly rapid elimination from the blood, which was not foreseeable in view of its relatively long duration of activity, and these superior qualities go far beyond the “normal” advantage of an enantiomer over its

racemate, namely the advantage of halving the dose."

The patent contains 7 claims:

Claim 1:

"Use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid as active substance, or of a physiologically acceptable salt thereof, in the preparation of a long-term antidiabetic agent, characterised in that, compared with double the single dose in the administration of a racemate, unnecessarily high and long-lasting substance loading is avoided, as a result of which substantially lower levels of active substance in the plasma are obtained which go beyond the normal advantage of halving the dose in the administration of enantiomers."

Claim 2:

"Use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid according to claim 1, characterised in that the active substance with an optical purity of at least ee = 95, or a physiologically acceptable salt thereof, is used."

Claim 3:

"Use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid according to claim 1, characterised in that the active substance with an optical purity of at least ee = 98, or a physiologically acceptable salt thereof, is used."

Claim 4:

"Use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid as active substance, or a physiologically acceptable salt thereof, in the preparation of a pharmaceutical composition according to claim 1, 2 or 3, characterised in that the single dose is in the range from 0.25 to 5.0 mg."

Claim 5:

"Use according to claim 4, characterised in that the single dose is 0.5 mg."

Claim 6:

"Use according to claim 4, characterised in that the single dose is 1.0 mg."

Claim 7:

"Use according to claim 4, characterised in that the single dose is 2.0 mg."

On the validity of the patent

The claimants argue that the patent is invalid for lack of novelty and inventive step.

On the lack of novelty of claim 1

In support of their claim for invalidity of the patent for lack of novelty, the claimants assert the following prior art documents:
- European patent No. 0 147 850 filed on 27 December 1984, granted on 14 June 1989, which expired on 27 December 2004, (EP 850);
- European patent No. 0 207 331, filed on 10 June 1986, published on 7 January 1987 (EP 331).

It is well established pursuant to Article 54 of the European Patent Convention that the novelty of an invention can only be taken away by a novelty-destroying prior art document which should be taken as is without having to be supplemented.

It means that to be comprised in the state of the art and to lack novelty, the invention must be found entirely in a single prior art document, with definite character, with the elements which constitute it having the same form, the same arrangement and the same function in view of the same technical result.

Patent EP 850 relates to "Phenylacetic-acid derivatives, medicines containing these compounds and process for their preparation". As claimed in claim 1 "Phenylacetic acid derivatives of general formula (…)" wherein R_4 represents a hydrogen atom, a methyl, ethyl or allyl group."

Claim 6 of this patent relates to "2-Ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid, the enantiomers and salts thereof" and its claim 9 to "Use of the compounds as claimed in claims 1 to 6, wherein R_4 represents a methyl, ethyl or allyl group, or a physiologically acceptable salt thereof for the preparation of a pharmaceutical composition which is suitable for treating Diabetes mellitus."

The defendant vainly argues that claim 9 relating to the use of a compound for the preparation of a pharmaceutical composition refers to a R_4 group and that only claims 1 to 4 of patent EP 850 mention such a R_4 group, so that claim 9 cannot depend on claims 5 and 6 but only on claims 1 to 4 and that consequently, the combination of claim 9 referring to the R_4 group with claim 6 which does not mention a R_4 group is impossible.

In fact, claim 1 of patent EP 850 specifies that in the general formula claimed "R_4 represents a hydrogen atom, a methyl, ethyl or allyl group."

Yet the descriptive part of the contested patent EP 874 includes the 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid formula which enables to find that the R_4 group is constituted by C2H5, which corresponds to the formula of an ethyl group.

2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid is a compound of the formula claimed in claim 1 of patent EP 850 wherein:
R_1 represents a piperidino

R_2 represents a hydrogen atom
R_3 represents a 3-methyl-n-butyl group
R_4 represents an ethyl group
W represents a carboxy group

Therefore, claim 9 of the said patent relating to "use of a compound for the preparation of a pharmaceutical composition which is suitable for treating diabetes mellitus" does refer to 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid, object of claim 6.

Under these conditions, it is well established that patent EP 850 discloses the active principle as well as the use of this active principle as a pharmaceutical composition for treating diabetes mellitus.

The claimants maintain that patent EP 850 also discloses the means for obtaining the enantiomers of the racemates which it discloses.

It should be emphasised that in fact the descriptive part of patent EP 850 describes in its example 2 a way of separation of a compound B structurally very close to the racemate of repaglinide to lead to compound E, (+)(S) enantiomer, the only difference between the racemate of repaglinide and compound B being the absence of a methyl group on the R_3 butyl chain.

In addition, European patent EP 0 207 331 filed on 10 June 1986, discloses in claim 1 "Two new solid forms of 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid characterised by the IR-KBr) spectrum according to Figure B' and C', the enantiomers and salts thereof" and in claim 6 "the use of one of the compounds according to claims 1 to 3 or its physiologically acceptable salts according to claim 4 for the treatment of diabetes mellitus".

The descriptive part of this patent points out that in the EP A2-147 850 document, 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]benzoic acid compound (…) is described (…) that it is obtained according to example 10 by hydrogenation catalyst of 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid; that it presents, like its physiologically-acceptable addition salts and their enantiomers, the pharmacological intermediate properties, in particular a hypoglycemic effect (…). The hypoglycemic effect was tested on rats as well as the toxic effect. After 14 days no rat was dead.

The *Tribunal* observes that none of these two patents studied the specific effect of the S(+) enantiomer compared with the racemate of 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid.

Therefore, not being novelty-destroying prior art documents, patents EP 850 and EP 331 are not relevant to destroy the novelty of claim 1 asserted.

On the inventive step of claim 1

The claimants consider that claim 1 of patent EP 874 is invalid for lack inventive step since the patented invention would result in an obvious manner to the person skilled in the art from the combination of earlier patents EP 850, EP 331, and from different articles published at the date of the filing of the patent application.

Article 56 of the European Patent Convention provides that an "invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art."

To assess the inventive step, one should find out if the person skilled in the art who was able to identify a technical problem was led in an obvious manner to find the solution by combining various teachings.

The person skilled in the art, who is in this case an organic chemist specialised in organic molecular synthesis for therapeutic purposes, informed of the structure and activity of the pharmaceutical active substances still in development and already used, and of the preparation of agents containing such active substances, and who is part of a team of experts involved and informed of the discovery of new active substances and of their development, this team also including, given the objective, pharmacologists, medical doctors and veterinary surgeons involved in clinical research as well as chemists and analysts, sought to resolve the problem posed, namely: to prepare an antidiabetic agent suitable for long-term treatment using an appropriate active substance, this antidiabetic agent having beneficial pharmacological properties with respect to the state of the art.

The literature adduced by the claimants contains three articles by E.J. Ariens:
- "Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology" (1984) published in the *European Journal of Clinical Pharmacology*;
- "Chirality in bioactive agents and its pitfalls" (May 1986) published in *TIPS*
- "Stereochemistry: A source of problems in medical chemistry" (1986) published in *Medical research reviews*,

- and an article by F. Jamali, R. Mahvar and F.M. Pasuito, entitled "Enantioselective aspects of drug action and disposition: therapeutics pitfalls" (1989) published in the *Journal of Pharmaceutical Sciences*.

- the February 1987 guideline published by the Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Service, Rockville, Maryland, entitled "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substance" sets out that "the regulations require a full description of the physical and chemical characteristics of the drug substance" and in particular "stereochemistry (identifying chiral centers, cis-trans isomerism, etc.); enantiomer or solid-state form ratios (e.g., for racemates, and for defined

admixtures of isomers or enantiomers or solid-state forms)" and pointed out that "the impurities may have significant clinical or toxicological effects. It should be noted that (even in racemates) enantiomers may be considered as impurities".

The various articles published by E. J. Ariens show that for a chiral therapeutic molecule "often only one isomer is therapeutically active, but this does not mean that the other is really inactive. It may very well contribute to the side-effects", "Enantiomers, and stereoisomers in general, must be regarded as different chemical compounds, particularly for biological purposes. Racemic drugs (…) usually contain 50 % or more of an inactive isomer (…). The enantiomers must, particularly from the biological point of view, be regarded as different substances. The neglect of stereochemistry in the development and application of drugs and bioactive agents leads to serious misconceptions and is a source of problems in pharmacokinetics".

In the conclusion of the article published in 1989, F. Jamali explains that "the scientific community is generally aware that the enantiomers of a drug may have different pharmacodynamic and pharmacokinetic properties (…) There have been very significant improvements in the commercial availability of the chromatographic columns and agents required for the separation of enantiomers. Consequently, the analytical knowledge required no longer belongs to the exclusive area of "experts"[2].

Boehringer argues that in fact, at the time of the filing of the application of the contested patent, the question of the relevance of the systematic separation of the enantiomers from a racemic mixture was vigorously debated and adduces in support of its allegations two articles: one by Professor Tessa entitled "Chiral aspect of drug metabolism" published in February 1986 in *TIPS*, the other by A.M. Krstulovic, published in 1986 in the *Journal of Chromatography* entitled "Racemates versus enantiomerically pure drugs: putting high-performance liquid chromatography to work in the section process".

In support of its argumentation, Boehringer refers to two passages from the articles which it adduces:
- an extract taken from Professor Tessa's article explaining that: "to state indiscriminately that racemic drugs contain 50 % impurities, constitutes a gross simplification and to want to make the separation of all the chiral drugs on the market compulsory would considerably increase their cost"[3].
- an extract from Mr Krstulovic's article, according to which: "the concept of contamination at 50 % was suggested for drug substances containing a chiral centre and regulatory bodies are expected to continue to be interested in this subject. However, this perspective must be considered as a last resort, for with the development of highly potent drugs, the administered doses and therefore the probability of undesirable side-effects also diminish. The exceptions concern the drugs for which the pharmaceutical effects are not well defined or those for which the undesirable effects would be stereoselective[4]".

[2] Translator's note: free translation
[3] Translator's note: free translation
[4] Translator's note: free translation

For a better understanding of the importance of those articles, one should refer to their contents.

The *Tribunal* observes that Mr Krstulovic's article emphasised in particular "that the stereometric composition of the drug (has) become a key subject in development, regulatory approval and marketing" and that "since the demand for drug purity is increasingly higher, the question is whether a racemic mixture must be automatically considered as impure at 50 %. The answer is complex and requires careful comparative evaluations of the two enantiomers' activities, toxicities and pharmacokinetics" and pointed out that "considering the foregoing even if the final decision is to commercialise a racemic mixture rather than the enantomerically pure drug, the pharmacokinetic studies and clinical pharmacology of a drug must be conducted on distinct isomers to justify the decision taken" (then the article set out a certain number of processes to prepare pure enantiomers (…) and explained that "the final choice between the pure enantiomer and the racemate will have to be made on the basis of risk-benefit and cost-benefit considerations"[5].

Furthermore, Professor Tessa indicated that the person skilled in the art must ask himself the following questions:
- "is the therapeutic activities of the active principle enantioselective, in other words, is the therapeutic activity carried more by one enantiomer rather than the other?
- is he inactive or less active enantiomer the cause of pharmacodynamic and pharmacological side-effects?
- are there pharmacodynamic interactions between the two enantiomers present in the racemate?
- what are the therapeutic consequences of the interaction noted between the enantiomers?

Under these conditions, the claimants rightly point out that the person skilled in the art who was prompted by Professor Tessa's article to study if "the therapeutic activity of the active principle was enantioselective", should, in order to do so, evaluate each enantiomer.

Mr Krstulovic's article prompted him in the same way to undertake this study before making a final decision.

Consequently, those articles did not dissuade the person skilled in the art from studying each enantiomer.

The person skilled in the art therefore had, at the time, no prejudice to overcome to undertake the study of the two enantiomers, even if the result obtained, had it been of no particular relevance, could have dissuaded him from going further and try to commercialise the S+ enantiomer.

The parties make opposite interpretations of the results provided in patent EP 850 of the study of compound B, which has a formula very similar to that of 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid and of its S+ enantiomer. The claimants consider that this study shows that only the S+ enantiomer is active which could but prompt the person skilled in the art to think that such was the

[5] Translator's note: free translation

case for the S+ enantiomer of the racemate of repaglinide. The defendant claims that on the contrary the results obtained would have dissuaded the person skilled in the art from undertaking the study of the S+ enantiomer of the racemate of repaglinide.

The *Tribunal* observes that in fact the results obtained in this study are little significant. These results show that there is no dose effect between what is measured for 1 mg/Kg of racemate and 0.5 mg/Kg as the plateau of the effect is probably reached.
Consequently, the person skilled in the art could not reach a conclusion, for when comparing a 0.5 mg/Kg dose of S enantiomer:
- it is either responsible for the entire effect and what can be observed is what can be seen with 1 mg/Kg of racemate (which is the case)
- or it shares the effects with the R racemate and what can be observed is what can be seen with the 0.5 racemate (which is also the case).
Under these conditions, this data does not allow to find which enantiomer is active.

Therefore, this could but prompt to perform the same experiment at doses at which a difference in the effect can be seen between the two doses of racemate and could not dissuade the person skilled in the art from studying the S+ enantiomer of repaglinide.

Boehringer maintains that a prejudice had to be overcome to undertake the study of the S+ enantiomer of 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid, since having at his disposal a very effective racemate, in the crystalline form, about which the studies had shown that it had no toxic effect, it therefore had no reason to undertake the study of the S+ enantiomer.

The *Tribunal* observes that the prior art document EP 331 teaches that the racemate of repaglinide is far more efficient than compounds B and E studied in patent EP 850.

The experimental data of the animal tests of the racemate of 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid is also taught by patent EP 331 and shows that it has no toxic effect.

This compound is the object of a further selection because it already generates in the racemic form a high, continuous and lasting action, lowering blood sugar, already to a fifth or a tenth of the single dose of other derivatives of the benzoic acid.

Furthermore, the pharmacological action with the determining parameters is obtained in EP 331 as a solution and is thus independent from the properties of the solid substance of either the crystalline forms or of other particular aspects of 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid.

Under those conditions, the person skilled in the art, aware of the literature published on the relevance of whether or not the therapeutic activity of the active principle is enantioselective, and who wanted to prepare a suitable antidiabetic agent for a long-term treatment by using an appropriate active substance

this antidiabetic agent having beneficial pharmacological properties with respect to the state of the art, had no prejudice to overcome to study the effects of the two enantiomers of 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid, the racemate of which proved to be very promising.

On the contrary, it results from the study of the adduced literature available at the time of the filing of the patent application that the person skilled in the art was encouraged to study the action of each enantiomer of a chiral molecule used as a drug, the literature adduced by the defendant not dissuading him from doing so, but on the contrary, prompting him to study each enantiomer.

The claimants rightly emphasise that the person skilled in the art would have undertaken the separation of the enantiomers from 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid by using the method described in the prior art document EP 850 to separate compound E, S+ enantiomer in the racemate which is compound B.

Boehringer claims that the use of repaglinide as an active principle, perfectly appropriate for the preparation of a long-term antidiabetic due to its unexpected pharmacological properties, is inventive.

It should be pointed out that an effect considered as unexpected may involve an inventive step.

However, in the cases where the state of the art is taken into consideration, the person skilled in the art would arrive in an obvious manner at a result which corresponds to the terms of a claim, considering that he could expect the combination of the teachings of the documents comprised in the state of the art to bring an advantage, such a claim lacks inventive step, independently from the fact that a possibly unexpected additional effect is obtained.

In the present case, the hypoglycemic effect of the racemate of repaglinide was disclosed by the prior art documents EP 850 and EP 331, so were the methods that could be implemented to select the enantiomers of a compound close to 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid.
In addition, the person skilled in the art knew how to observe the activity of each of the enantiomers with regard to the glucose rate in the blood by following the protocol described in the prior art document EP 850.

Even if the person skilled in the art were to study the effects of the S+ enantiomer of 2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid and to find that it was the active enantiomer, he could expect to obtain an identical therapeutic effect for a dose half the size.

In the present case, the benefit observed further to the replacement of the racemate by the S+ enantiomer, goes beyond a reduction by half of the plasmatic rates and, consequently, of the substance loading which the active principle is for the body.

The *Tribunal* considers that the additional and unexpected effect obtained according to which "compared with double the single dose in the administration of a racemate, unnecessarily high and long-lasting substance loading is avoided, as a result of which substantially lower levels of the active substance in the plasma are obtained which go beyond the normal advantage of halving the dose in the administration of enantiomers", constitutes a mere additional effect occurring by itself, in the course of the studies suggested by the state of the art, which does not confer any inventiveness.

Consequently, claim 1 of the patent in dispute must be held invalid for lack of inventive step.

On the invalidity of claims 1 and 2

Claims 2 and 3 are worded as follows:

Claim 2:
"*Use of (S)(+)-2-ethoxy-4-[N[1-(2-piperidinopheny1)-3-methy1-1-butyl]aminocarbonylmethy1]-benzoic acid according to claim 1, characterised in that the active substance with an optical purity of at least ee = 95, or a physiologically acceptable salt thereof, is used.*"

Claim 3:
"*Use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid according to claim 1, characterised in that the active substance with an optical purity of at least ee = 98, or a physiologically acceptable salt thereof, is used."*

The claimants allege that these claims are invalid for lack of novelty and lack of inventive step.

It is well established that in synthesis organic chemistry, it is common practice for the person skilled in the art to continue to purify a chemical compound obtained according to a particular process until it reaches the degree of purity required. A known compound does not acquire novelty simply from the fact that it is prepared in a purer form. It results that, generally, a document disclosing a chemical compound makes this product available within the meaning of Article 54 of the European Patent Convention, in all the degrees of purity.

In the present case, the prior art documents EP 850 and EP 331 disclose the racemate of repaglinide in the degrees of purity desired as well as its use as an antidiabetic agent.

Consequently, these claims are invalid for lack of novelty.

On the invalidity of claims 4 to 7

Claim 4:
"*Use of (S)(+)-2-ethoxy-41N-[1-(2-piperidinopheny1)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid as active substance, or a physiologically acceptable said thereof, in the preparation of a pharmaceutical*

composition according to claim 1, 2 or 3, characterised in that the single dose is in the range from 0.25 to 5.0 mg."

Claim 5:"
"*Use according to claim 4, characterised in that the single dose is 0.5 mg*."

Claim 6:
"*Use according to claim 4, characterised in that the single dose is 1.0 mg."*

Claim 7:
"*Use according to claim 4, characterised in that the single dose is 2.0 mg*."

The claimants rightly emphasise that the descriptive part of patent EP 874 does not include any experimental results as to the use of these doses. Consequently, arbitrarily setting the amount of active principle without corroborating experimental results and any pharmaceutical effect being associated to it, cannot on its own be sufficient to show an inventive step.

Under these conditions, claims 4 and 7 of patent EP 874 should be held invalid.

On the application of Article 700 of the French Civil Procedure Code

Article 700 of the French Civil Procedure Code provides that "(..)*in all proceedings, the judge will order the party obliged to pay for legal costs or, in default, the losing party, to pay to the other party the amount which he will fix on the basis of the sums outlayed but not included in the legal costs. The judge will take into consideration the rules of equity and the financial condition of the party ordered to pay. He may, even sua sponte, for reasons based on the same considerations, decide that there is no need for such order*."

Fairness requires that the claimant be awarded an overall compensation of €50,000 pursuant to Article 700 of the French Civil Procedure Code.

On the provisional enforcement

It does not seem necessary in this case to order the provisional enforcement of this decision.

On the costs

The defendant who has been unsuccessful is to be ordered to pay the entire costs which will be recovered by Mr Pierre Cousin, attorney-at-law, pursuant to Article 699 of the French Civil Procedure Code.

ON THESE GROUNDS

The *Tribunal*, ruling publicly, by way of a judgment made in first instance after hearing both parties and delivered to the Court clerk's office,

Holds claim 1 of the French designation of European patent No. 0 589 874 invalid for lack of inventive step;

Holds claims 2 and 3 of the French designation of European patent No. 0 589 874 invalid for lack of novelty;

States that the decision will be entered in the French patents register on the initiative of the most diligent party or upon the court's clerk's request, once the decision has become final;

Orders Boehringer Ingelheim Pharma GmbH & Co to pay to Hexal and Sandoz the overall sum of €50,000 pursuant to Article 700 of the French Civil Procedure Code,

Holds that there is no reason to pronounce the provisional enforcement.

Orders Boehringer Ingelheim Pharma GmbH & CoKG to pay the entire costs, which will be collected by Mr Pierre Cousin, attorney-at-law pursuant to Article 699 of the French Civil Procedure Code.

Ordered and adjudged in Paris on 7 May 2010

THE CLERK THE PRESIDING JUDGE