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Datasheet for the decision of 11 October 2007

Case Number: T 1001/01 - 3.3.02

Application Number: 92907833.5

Publication Number: 0572557

IPC: A61K 31/535

Language of the proceedings: EN

Title of invention:
Treatment of ovarian cancer

Applicant:
SMITHKLINE BEECHAM CORPORATION

Opponent:
-

Headword:
Treatment of ovarian cancer/SMITHKLINE BEECHAM CORPORATION

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

Keyword:
"Admissibility of not justified late-filed requests: no"
"Allowability under Article 123(2): (yes) for the sixth auxiliary request"
"Novelty and inventive step of the sixth auxiliary request: yes, improved indication"

Decisions cited:
T 1020/03, G 0005/83, G 0002/88

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1001/01 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 11 October 2007

Appellant: SMITHKLINE BEECHAM CORPORATION
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 9 March 2001 refusing European application No. 92907833.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

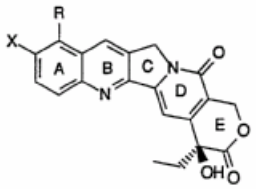
Chairman: U. Oswald
Members: M. C. Ortega Plaza
P. Mühlens

Summary of Facts and Submissions

I. European patent application No. 92 907 833.5 based on international patent application WO 92/14469 was filed with 30 claims.

Claim 1 as originally filed read as follows:

1. A method of treating ovarian cancer in a human afflicted therewith which comprises administering to such human an effective amount of a compound of the formula:



wherein:

a) X is hydroxy and R is trimethylammoniummethyl;

b) X is hydroxy and R is N-methylpiperazinylmethyl;

c) X is hydroxy and R is N-methylanilinomethyl;

d) X is hydroxy and R is cyclohexylaminomethyl;

e) X is hydroxy and R is N,N-dimethylaminoethyloxymethyl;

f) X is hydroxy and R is cyclopropylaminomethyl;

g) X is hydroxy and R is morpholinomethyl;

h) X is hydroxy and R is aminomethyl;

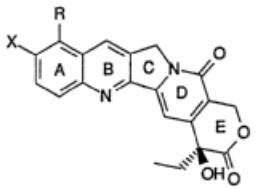
i) X is hydroxy and R is cyanomethyl; or

j) X is hydroxy and R is dimethylaminomethyl

or any pharmaceutically acceptable salts, hydrates and solvates thereof.

Independent claim 19 as originally filed read as follows:

"19. Use of a compound of the formula



wherein:

a) X is hydroxy and R is trimethylammoniummethyl;

b) X is hydroxy and R is N-methylpiperazinylmethyl;

c) X is hydroxy and R is N-methylanilinomethyl;

d) X is hydroxy and R is cyclohexylaminomethyl;

e) X is hydroxy and R is N,N-dimethylaminoethyloxymethyl;

f) X is hydroxy and R is cyclopropylaminomethyl;

g) X is hydroxy and R is morpholinomethyl;

h) X is hydroxy and R is aminomethyl;

i) X is hydroxy and R is cyanomethyl; or

j) X is hydroxy and R is dimethylaminomethyl

or any pharmaceutically acceptable salts, hydrates and solvates thereof, in the manufacture of a medicament for use in the treatment of ovarian cancer.

II. The following prior art documents were cited inter alia during the proceedings:

(1) (Proc. Annu. Meet. Am. Cancer Res., vol. 31, 1990, page 431, abstract No 2558)

(2) (EP-A-0 321 122)

Among the numerous exhibits cited during the proceedings the following are relevant for the present decision:

(5) Wim ten Bokkel Huinink et al, Journal of Clinical Oncology, vol. 15, No 6 (June), pages 2183-2193 (1997)

(20) Abstract from the database PubMed about the article on Ann. Oncol. 1995 Oct; 6(8): 844-6

(21) Abstract from the database PubMed about the article Am. J. Clin. Oncol. 1999 Jun; 22(3): 218-222

(22) E. G. Levine, et al., American Journal of Clinical Oncology, Cancer clinical trials, volume 22(3), June 1999, pages 218-222

(23) J. Carmichael, Exp. Opin. Invest. Drugs (1997), 6(5), pages 593-608

(26) Robbins Pathologic Basis of Disease, Ramzi S. Cotran, M.D., Vinay Kumar, M.D., and Stanley L. Robbins, M.D., 4th edition 1989, pages 240-243

(27) Van Nostrand's Scientific Encyclopedia, fifth edition, 1976, pages 38, 413-417

(28) Collins English Dictionary 21st Century edition pages 242, 1366

III. The present appeal lies from a decision of the examining division refusing the patent application under Article 97(1) pursuant to Article 56 EPC.

The examining division considered that the subject-matter of claim 1 of the main and sole request (set of claims filed with the letter dated 7 July 1998) met the requirements of novelty. In particular, in the examining division's opinion document (1) was not considered to be novelty destroying since it disclosed *in vitro* use of topotecan in preclinical studies. Furthermore, the examining division considered that the dosage ranges specified in claim 1 established the

novelty of the claimed subject-matter over the content of document (2).

As regards inventive step, the examining division considered document (2) to represent the closest prior art. The examining division defined the problem to be solved as to provide the use of certain known compounds in the manufacture of a medicament for use in the treatment of ovarian cancer in an effective dosage regimen.

The examining division considered that to find the tolerated dosage range *in vivo* was normal practice which did not require any inventive skills for the skilled person in the knowledge of the preclinical tumour model studies mentioned in document (1).

IV. The appellant lodged an appeal against this decision and filed grounds of appeal.

V. In the course of the appeal proceedings oral proceedings took place on 12 August 2005 in which the board decided that the proceedings were to be continued in writing, starting with a communication of the board.

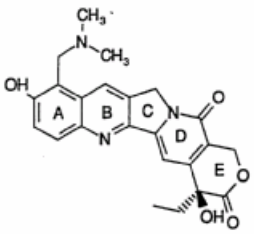
VI. A substantive communication of the board was sent informing the appellant *inter alia* that the subject-matter claimed lacked novelty vis-à-vis the content of document (2).

VII. As a response to a communication concerning loss of rights pursuant to Rule 69(1) EPC, the applicant filed its letter of 19 February 2007 with a request for further processing pursuant to Article 121 EPC and paid

the corresponding fees. It also filed as an annex to this letter a main request and five auxiliary requests.

Claim 1 of the main request and of the first auxiliary request and fourth auxiliary request (filed as second auxiliary request and renumbered during the oral proceedings before the board) read as follows:

"1. Use of topotecan that is a compound of the formula:



or any pharmaceutically acceptable salt, hydrate or solvate thereof,
in the manufacture of a medicament for use in the treatment of ovarian cancer in a human afflicted therewith by intravenous administration to the human."

Dependent claims 2 and 3 of the main request and first auxiliary request read as follows:

"2. The use according to claim 1, wherein the topotecan is in the form of the hydrochloride salt, acetate salt or methanesulfonic acid salt."

"3. The use according to claim 2, wherein the topotecan is in the form of the hydrochloride salt."

Claim 1 of the third auxiliary and second (filed as fourth auxiliary request and renumbered during the oral

proceedings before the board) requests differed from claim 1 of the main request in that the expression "or oral administration" was inserted between the words "intravenous" and "to the human".

Dependent claims 2, 4 and 5 of the third auxiliary request read as follows:

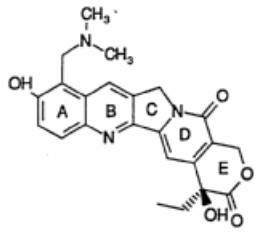
"2. "The use according to claim 1, wherein the medicament is for use in the treatment of ovarian cancer in the human afflicted therewith by intravenous administration to the human.

"4. The use according to claim 1, 2 or 3, wherein the topotecan is in the form of the hydrochloride salt, acetate salt or methanesulfonic acid salt."

"5. The use according to claim 2, wherein the topotecan is in the form of the hydrochloride salt."

Claim 1 of the fifth auxiliary request read as follows:

"1. Use of topotecan, that is a compound of the formula:



or any pharmaceutically acceptable salt, hydrate or solvate thereof,
in the preparation of an intravenous or oral pharmaceutical composition comprising topotecan and an

inert, pharmaceutically acceptable carrier or diluent, and wherein the pharmaceutical composition is for use in the treatment of ovarian cancer in a human afflicted therewith by intravenous or oral administration to the human."

Dependent claims 2, 4 and 5 of the fifth auxiliary request read as follows:

"2. The use according to claim 1, wherein the pharmaceutical composition is an intravenous pharmaceutical composition for use in the treatment of ovarian cancer in the human afflicted therewith by intravenous administration to the human."

"4. The use according to claim 1, 2 or 3, wherein the topotecan is in the form of the hydrochloride salt, acetate salt or methanesulfonic acid salt."

"5. The use according to claim 4, wherein the topotecan is in the form of the hydrochloride salt."

VIII. The appellant was informed in a brief communication dated 5 April 2007 that further processing under Article 121(3) EPC had taken place.

IX. A communication from the board was sent on the 19 April 2007 as an annex to the summons to oral proceedings. In said communication, the board expressed its preliminary opinion in respect of Articles 123(2), 52 and 54 EPC for the sets of claims filed with the letter of 19 February 2007.

X. The appellant filed a letter on 9 October 2007 accompanied by several exhibits, a main request and seven auxiliary sets of claims.

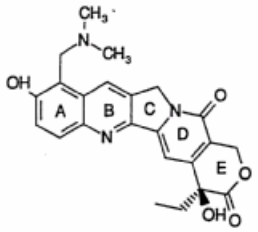
XI. Oral proceedings took place on 11 October 2007.

XII. At the beginning of the oral proceedings a discussion about the admissibility of the requests and exhibits filed on 9 October 2007 took place and the board decided not to admit these late-filed requests and exhibits into the proceedings.

Later on during the oral proceedings, the appellant filed a sixth auxiliary request.

Claim 1 of the sixth auxiliary request reads as follows:

"1. Use of topotecan, that is a compound of the formula:



or any pharmaceutically acceptable salt, hydrate or solvate thereof,
in the manufacture of a medicament for use in the treatment of ovarian cancer in a human afflicted therewith by intravenous administration to the human, wherein the term "ovarian cancer" means adenocarcinoma of the ovary."

XIII. The appellant's arguments as far as relevant for the present decision may be summarised as follows:

In respect of the admissibility of the eight new sets of claims and exhibits filed on 9 October 2007, the appellant said that it had received them late from the American applicant.

As regards the issue of Article 123(2) EPC, the appellant mentioned the example on page 7 as implicitly disclosing topotecan hydrochloride. Furthermore, if a selection had taken place in respect of two lists of options, the selection was to be found allowable since the lists were very short. The appellant also cited in this respect decisions T 12/81, OJ EPO, 1990, 093, and T 7/86, OJ EPO, 1988, 381.

In relation to novelty of the subject-matter claimed the appellant invoked that, in view of the decision T 1020/03, OJ EPO, 2007, 4, the specification of the administration route was always to be considered a novelty-bringing feature for medical use claims in "Swiss-type form". Document (2) did not disclose a preferred administration route for the treatment of ovarian cancer. Moreover, the experimental part of document (2) concerned animal models relating to a sarcoma cell line. The appellant also stated the view that document (2) did not include any clinical data on human patients.

In relation to the inventive step issue, the appellant stated that document (2) was the closest prior art.

The appellant defined the problem to be solved as to finding a cancer that topotecan treats particularly well in a human and the corresponding route of administration for it.

The appellant further stated that although it was not explicitly mentioned which was the specific ovarian cancer type in the utility example on pages 8 and 9 of the description of the application in suit, the woman treated was suffering from adenocarcinoma of the ovary. The ovarian cancer from which this woman was suffering had been refractory to two previous platinum-containing regimens, i.e. the ovarian cancer was much harder to treat than usual ovarian cancers and also extremely difficult to treat. The objective for the course of therapy was the long-term treatment. The results showed that greater than 50% tumour size regression was obtained and this clinically significant response was sustained.

The appellant further argued that apart from the great success in the third-line treatment supported by the example in the description, topotecan also showed a "fantastic" efficacy in first-line treatment and very good efficacy in second-line setting topotecan monotherapy. In this context it cited exhibit (5) and explained that the malignant and serious ovarian cancer tumour tested concerned adenocarcinoma of the ovary.

The appellant also explained that, as shown *inter alia* by the exhibits (20), (21), (22), (23), when using a directly comparable course of therapy for topotecan in the treatment of different cancers such as colorectal cancer (response was rate 7%), breast cancer (response

rate 10%), pancreas cancer (very poor response), and finally, soft tissue sarcoma (response rate 10%), the response rate was poor.

The appellant further argued that the skilled person was not in a position to extract any valuable knowledge from document (1) in order to arrive at the proposed solution, since this abstract did not give any information about the compound mentioned as a number other than that it was a semisynthetic analogue of campothecin. At the time, there were at least two other topoisomerase inhibitors which may have been referred to.

Furthermore, the appellant also stressed that adenocarcinoma of the ovary was not the only ovarian cancer possible and hence document (1) gave no hint in respect of its treatment since it related to *ex vivo* preclinical models of cancer in general terms, without any detail about their nature.

XIV. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of one of the main, first, second (filed as fourth), third, fourth (filed as second) or fifth auxiliary requests filed with the letter dated 19 February 2007, or on the basis of the sixth auxiliary request filed in the appeal proceedings.

Reasons for the Decision

1. *Admissibility*

1.1 The present appeal is admissible.

1.2 Admissibility of the late-filed requests

The admissibility of late-filed requests is at the board's discretion and depends upon the overall circumstances of the case under consideration, a general principle being that the later the requests are filed, the less likely they are to be held admissible. Moreover, account has to be taken, *inter alia*, of whether they could have been filed earlier and if so the reason why they were not, and of whether they immediately appear to fulfil the formal criterion for allowability.

The board had written a detailed communication dealing with the requests filed with the letter of 19 February 2007, which was sent to the appellant on 5 April 2007. The appellant chose to file six months later, and only two days before the date of the oral proceedings, a letter with several exhibits and eight new sets of claims. At the oral proceedings the appellant's representative gave as justification that it had received them very late from the American applicant. However, this cannot serve to justify the appellant for such a late-filing. The communication of 5 April 2007 was sent within the meaning of Article 11(1) of the Rules of Procedure of the Boards of Appeal as an annex to the summons to oral proceedings. Having regard to the fact that the present appeal proceedings were filed

in 2001, the version of the Rules of Procedure of the Boards of Appeal is that published in OJ 1980, 171, as amended in OJ EPO 1983, 7, OJ EPO 1989, 361, and OJ EPO 2000, 316.

Hence, the board's communication was sent with the summons to oral proceedings with the intention of allowing the board to come to a conclusion at the end of the oral proceedings, scheduled for 11 October 2007. The board was taken by surprise by the filing of the eight new sets of claims and the several exhibits two days before the oral proceedings. To admit these late-filed documents and exhibits into the proceedings would have made impossible to arrive at a final conclusion at the end of the oral proceedings in view of the complexity of the case.

Therefore, all the requests and new material filed without justification two days before the oral proceedings were not admitted into the proceedings.

The appellant filed the sixth auxiliary request at the oral proceedings after the discussion in relation to Articles 123(2), 52 and 54 EPC had taken place in its full length for the requests filed on 9 February 2007. The sixth auxiliary request was a clear, simple and direct response to the discussions during the oral proceedings and thus it is found to be admissible.

The extracts from dictionaries exhibits (26), (27) and (28), were also admitted into the proceedings, since they were intended to support the common general understanding of the expressions used in the claims in relation to the definition of the disease.

2. *Article 123(2) EPC*

2.1 Claim 1 of the main request has been worded as a "Swiss-type form" claim and relates to the use of topotecan or any pharmaceutically acceptable salt, hydrate or solvate thereof in the manufacture of a medicament for use in the treatment of ovarian cancer in a human afflicted therewith by intravenous administration to the human.

An inspection of the application as filed (WO 92/14469) shows topotecan as the "most preferred" active compound of the "water soluble camptothecin analog class" represented by the formula appearing in the originally filed medical use claim 19 (see last paragraph of page 3, top of page 4).

Furthermore, it can be directly derived from page 4 of the application as originally filed that not only the free base of topotecan, represented by the structural formula now depicted in claim 1 of the main request, but also pharmaceutically acceptable salts, hydrates and solvates thereof are meant to be included (page 4, lines 20-23, and lines 12-19).

Furthermore on page 4 of the application as filed reads: "Topotecan is water-soluble by virtue of the presence of the basic side-chain at position 9 [*sic, position 10*] which forms salts with acids. Preferred salt forms of topotecan include the hydrochloride salt, acetate salt and methanesulfonic acid salt. A(n) alkali metal salt form of the carboxylate formed on alkaline hydrolysis of the E-ring lactone of topotecan would also yield a

soluble salt, such as the sodium salt" (page 4, lines 12-19).

The way of administration generically disclosed, according to the application as filed, is either oral **or** parenteral. By "parenteral" is meant intravenous, subcutaneous and intramuscular administration (page 5, lines 16-19).

Therefore, the choice of "intravenous" in claim 1 of the main request concerns a mono-dimensional restriction, i.e. the choice of the way of administration among the options disclosed in the application as originally filed. Hence, claim 1 meets the requirements of Article 123(2) EPC.

2.1.1 However, as regards dependent claim 3 of the main request, the situation differs. Claim 3 finds no support in the set of claims as originally filed. Furthermore, no basis can be found in the application as filed either for the selection of the specific salt **topotecan hydrochloride** as most preferred salt, or for the selection of the type of salt together with a particular administration way, namely the intravenous administration route.

Hence, the subject-matter of claim 3 which relates to a singling-out concerning specifically the use of topotecan **hydrochloride** (for treating ovarian cancer) by means of intravenous administration was not foreseen in such a specific way in the application as originally filed.

Therefore, dependent claim 3 contravenes the requirements of Article 123(2) EPC.

2.2 The appellant's arguments in favour of claim 3 do not hold for the following reasons:

As regards the argument that the example on pages 7 and 8 of the application as originally filed could serve as a basis since it relates to the use of topotecan hydrochloride, an inspection of the content of the said example shows the following passages: "Clinical Pharmaceutical Information" "Topotecan is currently undergoing Phase I clinical investigation. The following pharmaceutical information is being supplied to the clinicians:
How supplied - As a vial containing 5 mg (**of the base**) with 100 mg mannitol. The pH is adjusted to 3.0 with HCl/NaOH. Lyophilized powder is light yellow in color. Intact vials should be stored under refrigeration (2-8 degrees Centigrade).
Solution Preparation -When the 5mg is reconstituted with 2 ml Sterile Water for Injection, USP, each ml will contain 2.5 mg of **topotecan as the base** and 50 mg of mannitol, USP. Topotecan **must not be diluted or mixed with buffered solutions because of solubility and stability considerations**". (emphasis added)

First of all, the said example clearly refers to **the base** which is topotecan itself and it does not refer to the hydrochloride salt. Secondly, the vial disclosed contains topotecan and **mannitol**. Thirdly, there is no information concerning the method for adjusting the pH with HCl/NaOH. Hence, the pH value 3.0 cannot be directly and unambiguously linked to the transformation

of topotecan into topotecan hydrochloride. Furthermore, as acknowledged in the passage of the description mentioned above, topotecan may have stability problems in solution. Indeed, it is well known to the skilled person that the lactone ring may undergo hydrolysis leading either to the free acid form or to opened-ring salts such as the sodium salt (see also page 4, lines 16-19, of the application in suit).

Additionally, the application as originally filed refers to the content of document (2) for the preparation of topotecan and its pharmaceutically acceptable salts (page 4, lines 20-29). A reading of document (2) clearly shows that the preparation of topotecan hydrochloride (preparation of topotecan monohydrochloride in example 18 and topotecan dihydrochloride in example 19 of document (2)) requires a different technology (starting from topotecan acetate) than just adjusting the pH of a preparation containing *inter alia* topotecan free base and mannitol.

As regards the argument that the selection from two lists (type of salt and administration route) should be considered as allowable since the lists were very short, the following has been considered:

The present claims derive from an originally filed claim 19 which related to the use of a generically defined compound class in the manufacture of a medicament for the treatment of ovarian cancer. The disclosure made in the description in relation to the administration route as either oral or parenteral referred to the generic compound class appearing in originally filed claims 1 and 19 (see also originally

filed claims 26 and 27). Hence, in order to arrive without contravention of Article 123(2) EPC at the second medical indication now claimed in claim 3 of the main request the intellectual exercise of choosing each time one item from two apparently "short" lists of options (type of salts and type of administration route respectively) would not suffice but would require the skilled person to be able to derive such a specific singling out (topotecan **hydrochloride and** intravenous administration route) in a direct and unambiguous manner from the content of the application as originally filed. This is not the case for the application in suit.

2.3 Therefore, the main request fails for non-compliance with Article 123(2) EPC.

2.4 The first auxiliary request merely differs from the main request in that claims 7 to 12 have been deleted. Therefore, the analysis made above for claim 3 of the main request is identical and the conclusion directly applies to the first auxiliary request.

2.5 The analysis made above for claim 3 of the main request applies *mutatis mutandis* to claim 3 of the third auxiliary request and to claim 5 of the fifth auxiliary request, which are dependent on claim 2 which specifically relates to the intravenous administration.

2.6 Consequently, the sets of claims of the first, third and fifth auxiliary requests fail since they contravene Article 123(2) EPC.

2.7 The arguments given above in favour of the allowability of claim 1 of the main request in relation to the requirements of Article 123(2) EPC apply *mutatis mutandis* to claim 1 of the second (filed as fourth) auxiliary request with the additional comment that not only the intravenous administration but also the oral administration is included.

Moreover, the set of claims of the second auxiliary request no longer includes a dependent claim relating to topotecan hydrochloride.

Hence, this request meets the requirements of Article 123(2) EPC.

2.8 Having regard to the fact that the fourth (filed as second) auxiliary request only contains a single claim which is identical to claim 1 of the main request, which has been found to be allowable, the fourth auxiliary request meets the requirements of Article 123(2) EPC.

2.9 Claim 1 of the sixth auxiliary request differs from claim 1 of the main request in that the following has been added at the end of the claim: ", wherein the term "ovarian cancer" means adenocarcinoma of the ovary". This specification undertaken in claim 1 finds a clear basis on page 5, lines 8-9, of the application as originally filed.

Moreover, this set of claims only consists of two claims, claim 2 is identical in its wording to claim 2 of the main request and its basis is to be found in

particular on page 4, lines 14-16, of the application as originally filed.

2.10 Therefore, the set of claims of the sixth auxiliary request meets the requirements of Article 123(2) EPC.

3. *Novelty*

Only two documents (document (1) and document (2)) were cited during the procedure by the first instance. These documents form part of the prior art within the meaning of Article 54(2) EPC and their content has to be investigated when assessing novelty for the subject-matter claimed.

3.1 Document (2) is a European patent application, published before the priority date of the application in suit, by the same applicant. Document (2) relates to water-soluble camptothecin analogs of formula I and pharmaceutically-acceptable salts, hydrates and solvates thereof (claim 1). Topotecan is the preferred compound (claims 3 and 5). Topotecan is exemplified, inter alia, in examples 21 (free base), 3 and 17 (acetate salt), 8 (methanesulfonate salt), 18 (monohydrochloride salt) and 19 (dihydrochloride salt).

Moreover, document (2) discloses these compounds as inhibitors of the growth of animal tumour cells and as useful in the manufacture of a medicament having tumour cell growth inhibiting activity (claims 12 and 13). Hence, document (2) clearly discloses the use of topotecan and its derivatives as anticancer agents.

Furthermore, document (2) specifically discloses citotoxicity results based on *in vitro* and *in vivo* (animal models) experiments of, *inter alia*, topotecan acetate (compound "1S", page 8), showing the potent antiproliferative and antitumour activity of topotecan.

Additionally, document (2) also discloses some preclinical studies using animal models employing different implanted tumours for the compound "1S" (i.e. topotecan acetate). Among these preclinical studies disclosed in document (2), there is a preclinical model for ovarian cancer (namely, M5076 Sarcoma, which is "a metastatic reticulum cell sarcoma which arose in the ovary of a C57B1/6 mouse and was established as a transplanted tumor". Document (2) further states that "compound No 1S is reproducibly active in this tumor model" (page 12, lines 42-55).

In view of the above analysis, document (2) clearly and unambiguously discloses topotecan (in particular its pharmaceutically acceptable salt topotecan acetate) as an anticancer agent against ovarian cancer.

Pharmaceutical formulations comprising the exemplified topotecan and topotecan derivatives mentioned above are disclosed in examples A and B (for parental administration and for oral administration respectively) (page 41).

Document (2) further makes a generic recommendation: "during the course of treatment the active ingredient will be administered **parenterally or orally** on a daily basis in an amount selected from about 20 mg/m^2 to about 150mg/m^2 of body surface area for one to five days, with

courses of treatment repeated at appropriate intervals" (page 29, lines 33-35).

The appellant put forward several arguments for its novelty analysis. However, when questioned by the board as to the new purpose described in the application in suit which could amount to a technical effect and hence be considered as a new functional feature, the appellant answered that it was the treatment of adenocarcinoma of the ovary.

It has to be stressed that there are in principle two basic categories for claims: claims directed to an entity and claims directed to an action. Use claims and process claims are claims directed to actions.

As expressed in the "Order" (point (iii)) of the decision of the Enlarged Board of Appeal G 2/88, OJ EPO 1990, 093:

"(iii) A claim to the use of a known compound for a particular purpose, which is based on a technical effect which is described in the patent, should be interpreted as including that technical effect as a functional feature, and is accordingly not open to objection under Article 54(1) provided that such technical feature has not been made available to the public."

Moreover, the well-established jurisprudence of the boards of appeal confirms that a new function (corresponding to a technical effect) may confer novelty on the use of known compounds.

In case of medical use claims a "European patent may be granted with claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application" (G 5/83, OJ EPO, 1985, 64). This is the case of the "Swiss-type form".

The purpose alleged by the appellant as novelty bringing is not reflected in claim 1 of the sets of claims of the second and fourth auxiliary requests (Articles 52 and 54 EPC) which address the treatment of ovarian cancer in general terms.

Correspondingly, document (2) anticipates the subject-matter claimed in claim 1 of the sets of claims of the second and fourth auxiliary requests (Articles 52 and 54 EPC).

3.2 The appellant's arguments in favour of novelty do not hold for the following reasons:

As regards the argument that document (2) does not specifically mention any administration route as preferred for the treatment of ovarian cancer, the following has been considered. Document (2) discloses the pharmaceutical formulations for parental or oral administration within the context of the anticancer uses disclosed in that document. Although it is a fact that document (2) does not specifically disclose a particular administration route as preferred, nor a preference for parenteral *versus* oral, **this is also the case for the disclosure of the application in suit as filed**.

Indeed, the description of the application in suit states: "By the term "administering" is meant parenteral or oral administration. By "parenteral" is meant intravenous, subcutaneous and intramuscular administration", without given any preference whatsoever of one mode of administration over the others (page 5, lines 16-19).

Novelty cannot be acknowledged for the use claimed in claim 1 of the second auxiliary request for the mere reason that the oral administration was specifically mentioned in document (2) as administration route.

Furthermore, in the case of claim 1 of the fourth auxiliary request, where the administration route has been specified as intravenous, the assessment of novelty requires in-depth technical analysis which goes beyond the mere linguistic differences between the amended claim and the textual expressions employed in document (2).

In the present case, it has not been demonstrated that the choice of a parenteral route is a purposive choice over the oral administration route and it has not been shown that it is linked to the technical effect intended to characterise the second medical indication as a new functional feature.

Document (2) discloses the parenteral administration without going into deeper detail because it does not include experiments *in vivo* on humans but animal models and *in vitro* tests.

Furthermore, the intravenous administration of topotecan and its pharmaceutically acceptable salts, solvates and hydrates **addresses both the treatment of ovarian cancer and the treatment of adenocarcinoma of the ovary**. Hence, the feature "by intravenous administration" cannot serve to establish the novelty over the content of document (2).

Additionally, the formulations for parenteral administration disclosed in document (2) are suitable for the intravenous route and the choice of this route, in the absence of any explicit teaching in the application in suit of a technical effect linked thereto, would only depend on the medical practitioner's freedom of decision for each individual patient when putting into practice the treatment of ovarian cancer disclosed in document (2).

Furthermore, it has to be reminded that it is common practice that a patent literature document, in order to be an enabling disclosure of a medical indication for pharmaceutically active compounds, such as the treatment of ovarian cancer disclosed in document (2), does not necessarily need to include either clinical tests (Phase I, II or even III) or *in vivo* human assays.

In view of the above it can be concluded that the information that document (2) discloses in respect of the treatment of ovarian cancer is sufficient and thus is enabling for the skilled person in the technical field. Therefore, this document is novelty destroying for the use claim directed to the treatment of ovarian cancer in a human.

The appellant has disputed the experimental data disclosed in document (2) as a useful preclinical model for adenocarcinoma of the ovary but it did not produce any convincing argument why they should not be valid for any other possible ovarian cancers encompassed by the claims. The experiments disclosed in document (2) employ a metastatic reticulum cell sarcoma which arose in the ovary of a C57B1/6 mouse. It is to be stressed that, as expressed by the appellant, not every ovarian cancer is an adenocarcinoma.

As regards the appellant's argument that decision T 1020/03, OJ EPO 2007, 204, concludes that the specification of the "route of administration" is always a novelty-bringing feature for second medical use claims in the "Swiss-type form", the following has to be said.

Board 3.3.04 does not conclude on the question of novelty in its decision T 1020/03, as is shown clearly in the last point of the "Reasons for the decision":

"79. In view of the foregoing the board concludes that claims 1 and 13 of the main request are directed to potentially patentable subject matter avoiding the prohibition of Article 52(4) EPC first sentence, and **remits the case for further consideration of novelty and inventive step**, depending on whether the intended method of therapy is itself novel and inventive, taking into account all the features of the use in the claim, as well as for consideration of the other requirements of the EPC mentioned in point 9 above". (emphasis added)

Hence, the appellant's argument that said decision was cited in the Case Law of the Boards of Appeal of the EPO, fifth edition, 2006, in the chapter I.C.5 (novelty of use), as taking "a new approach to the concept of "new therapy" "(page 109 of the Case law report) is not relevant, since the comments on novelty in decision T 1020/03, in the absence of a conclusion by Board 3.3.04 on Article 54 EPC, can only be taken as *obiter dicta*.

In fact, the assessment of novelty remains a decision to be taken **on a case-by-case basis after making a careful and detailed technical (and not only linguistic) analysis of the features appearing in a particular claim and when the relevant piece of prior art is read by the skilled person**.

Indeed, the conclusions reached at by decision T 1020/03 are irrelevant for the claims on file, since the wording of the sets of claims serving as a basis for the present decision has not been challenged under Article 52(4) EPC because they are medical use claims in an acceptable "Swiss-type form".

3.3 Consequently, the sets of claims of the second and fourth auxiliary requests are refused for lack of novelty (Article 54 EPC).

3.4 Since claim 1 of the sixth auxiliary request incorporates the specification of the type of ovarian cancer as "adenocarcinoma of the ovary", novelty can be acknowledged over the content of document (2).

Document (2) does not specifically disclose topotecan and its salts, solvates and hydrates to be useful for the treatment of adenocarcinoma of the ovary. The board is satisfied by the appellant's arguments and submitted exhibits (inter alia exhibit 26) that the preclinical model using metastatic reticulum cell **sarcoma** cannot serve as model for adenocarcinoma of the ovary which is of epithelial cell origin and has a glandular growth pattern. Moreover, the board is convinced that the skilled person is able to differentiate when an ovarian cancer is an adenocarcinoma of the ovary.

3.5 Document (1) relates to an abstract of the "Eighty-first Annual Meeting of the American Association for Cancer Research on May 23-26, 1990 in Washington, DC". Abstract N° 2558 reports on preclinical *in vitro* assays for a compound SKF 104864 (SKF) which is defined as a semisynthetic analogue of the natural product campothecin and is an inhibitor of topoisomerase I.

However, the appellant has denied that it was public knowledge on the effective filing date of the application in suit that the compound SKF was topotecan and the board does not dispose of any evidence to the contrary.

The sparse information about compound SKF in document (1) does not make the compound available to the public. Hence, document (1) does not disclose the use of topotecan or its derivatives for treating adenocarcinoma of the ovary.

3.6 Therefore, the subject-matter claimed in the sixth auxiliary request meets the requirements of novelty (Article 54 EPC).

4. *Inventive step*

Document (2) represents the closest prior art.

As is evident from the comments made about the content of document (2) in point 3.1 above, document (2) discloses the use of topotecan and its pharmaceutically acceptable salts, hydrates and solvates thereof for the treatment of cancer and in particular of ovarian cancer.

Therefore, the problem to be solved lies in the provision of an improved use of topotecan in a specific cancer therapy.

The solution lies in the treatment of adenocarcinoma of the ovary.

Having regard to the clinical experimental results in the "utility" example of the description which show the excellent and sustained clinically significant response in third-line treatment of adenocarcinoma of the ovary (topotecan administered by intravenous injection), the board is satisfied that the problem has been plausibly solved.

It remains to be investigated whether the proposed solution is obvious to the skilled person in the light of the prior art.

As becomes evident from the analysis of the content of document (2) made in point 3.1 above, the skilled person is taught to use topotecan when treating ovarian cancer among other cancer types, but there is no information or anything in said document which could have induced the skilled person to think about the excellence and improvement achievable when using topotecan in the treatment of adenocarcinoma of the ovary.

As expressed already in point 3.4 above, the tumor models disclosed in document (2) relying on reticulum cell sarcoma do not serve as models for adenocarcinoma of the ovary.

Moreover, the mention in document (2), page 16, of ovarian adenocarcinoma relates to a general teaching in connection with anti-cancer drugs in general and multidrug resistant sublines, and the wish to find new agents, but the teaching in relation to topotecan in document (2) refers to the cell lines and models detailed in the experimental part of document (2). Hence, document (2) cannot serve the skilled person further when looking for the specific use of topotecan defined in claim 1 of the sixth auxiliary request.

Additionally, as analysed in point 3.5 above, the board does not dispose of any proof that the skilled person knew at the effective date of the application in suit that the abstract numbered as document (1) related to topotecan. Moreover, the *in vitro* tumour models mentioned therein suggest a preference for ovarian cancer rather than for breast or cell lung cancers for the derivative SKF but they do not give the skilled

person any information in respect of their usefulness in respect of predicting the excellent use of topotecan for adenocarcinoma of the ovary.

Consequently, in view of the above, the board concludes that the subject-matter claimed in the sixth auxiliary request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of the sixth auxiliary request filed in the oral proceedings and a description to be adapted.

The Registrar The Chairman

A. Townend U. Oswald