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Datasheet for the decision of 6 April 2023

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Title of invention:
ENDOXIFEN FOR USE IN THE TREATMENT OF CANCER

Patent Proprietor:
Jina Pharmaceuticals Inc.

Opponents:
Besins Healthcare Monaco S.A.M
Bayer Intellectual Property GmbH /
Bayer Aktiengesellschaft

Headword:
Endoxifen / JINA PHARMACEUTICALS

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 12(4), 13(1)

Keyword:

Inventive step - technical prejudice in the art (no)
Amendment to case - suitability of amendment to address issues (no)

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Case Number: T 1328/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 6 April 2023

Appellant: (Patent Proprietor)	Jina Pharmaceuticals Inc. 28100 North Ashley Circle, Suite 103 Libertyville IL 60048 (US)
Representative:	HGF HGF Limited 1 City Walk Leeds LS11 9DX (GB)
Respondent: (Opponent 1)	Besins Healthcare Monaco S.A.M 2 Av. des Ligures Les Terrasses du Port Rez-de-chaussee - Lot 777 Monaco (MC)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Respondent: (Opponent 2)	Bayer Intellectual Property GmbH / Bayer Aktiengesellschaft Alfred-Nobel-Strasse 10 / Kaiser-Wilhelm-Allee 1 40789 Monheim / 51373 Leverkusen (DE)
Representative:	Maiwald GmbH Grünstraße 25 40212 Düsseldorf (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 2 April 2020 revoking European patent No. 2101731 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	W. Sekretaruk

Summary of Facts and Submissions

I. European patent 2 101 731 ("the patent") was granted on the basis of eleven claims.

Independent claim 1 as granted defined:

> "A composition comprising an effective amount of a complex comprising synthetic endoxifen, wherein said endoxifen is a free base or is in the form of a salt for use in the treatment or prevention of cancer."

II. Two oppositions had been filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed. The patent proprietor filed the appeal against the decision of the opposition division to revoke the patent.

The decision was based on the main request and auxiliary requests 1-15 (as re-numbered in section 1.14 of the decision), which were filed on 4 March 2020.

In the decision the opposition division cited *inter alia* the following documents:

E1: Johnson et al.; Breast Cancer Research and Treatment, 85: 151-159 (2004)
E2: Lim et al.; Cancer Chemother. Pharmacol., 55: 471-478 (2005)
E8: Pujol et al.; Cancer Chemother. Pharmacol., 36: 493-498 (1995)

E23: Ahmad et al.; Clin. Pharmacol. Ther., 88(6): 814-7 (2010)
E26: Declaration by A. Ahmad of 24 December 2019
E27: Drug Absorption Pharmacokinetics: 2015 Merck Manual Professional
E28: Wu et al.; J. Pharm. Sci., 100(9): 2001 3655-3681 (2011)
E29: Kemp et al.; Drug Metabolism and Disposition, 30(6):694-700 (2002)
E30: Mauvais-Jarvis et al.; Cancer Res., 46:1521-1525 (1986)
E31: Zheng et al.; Drug Metabolism and Disposition, 35(10): 1942-48 (2007)
E32: Buzdar et al.; Cancer Chemother. Pharmacol., 33(4): 313-6 (1994) (Abstract)
E33: Buzdar et al.; Breast Cancer Res. Treat., 73(2): 161-75 (2002) (Abstract)

The opposition division arrived at the following conclusions:

(a) In view of documents E1 and E2, which already reported the effect of endoxifen on the proliferation of breast cancer cells, the patent did not present a new technical teaching with respect to the claimed medical use. The subject-matter of claim 1 of the main request therefore lacked novelty.

The subject-matter of auxiliary requests 1 and 2 lacked novelty in view of documents E1 and E2 for the same reason.

(b) The subject-matter of claim 1 of auxiliary request 3, which additionally defined the form of the composition as a tablet or a filled capsule coated

with an enteric material, lacked an inventive step in view of document E1 as closest prior art.

The subject-matter of claim 1 of auxiliary request 3 differed from the teaching of document E1 in the definition of the dosage form. The problem to be solved was the development of further treatment. The skilled person would consider the formulation of a tablet or capsule with an enteric coating obvious as solution, because such forms were well known in cancer treatment, for example for the administration of tamoxifen.

The existence of a prejudice against oral administration of endoxifen had not been demonstrated. Documents E30 and E31, which indicated that 4-hydroxy-tamoxifen (4-OH-Tam) and endoxifen are conjugated and inactivated in the liver, were *a priori* not suitable as evidence for such a prejudice. Moreover, a reduced oral bioavailability of endoxifen due to glucuronidation would not prevent the skilled person from providing endoxifen for oral administration taking account of the effective oral administration of the related agents raloxifene and droloxifene reported in the prior art.

(c) The additional features regarding the optional presence of a lipid and the process for the preparation of the endoxifen composition as defined in the independent claims of auxiliary requests 4-15 did not further distinguish the claimed subject-matter from the prior art. Accordingly, auxiliary requests 4-6, 8-10 and 12-14 lacked novelty and auxiliary requests 7, 11 and 15 lacked an inventive step.

III. With the statement of grounds of appeal the appellant (patent proprietor) filed a new main request and auxiliary requests 1-3.

Claim 1 of the main request defined:

> "A composition comprising an effective amount of a complex comprising synthetic endoxifen, wherein said endoxifen is a free base or is in the form of a salt for use in the treatment or prevention of cancer **by the oral mode of administration.**"
> [highlighting by the Board to indicate the amendment with respect to claim 1 as granted]

Auxiliary request 1 corresponded to auxiliary request 3 on which the decision under appeal was based. Claim 1 of this auxiliary request defined:

> "A composition comprising an effective amount of a complex comprising synthetic endoxifen, wherein said endoxifen is a free base or is in the form of a salt for use in the treatment or prevention of cancer, **and wherein said composition comprises a form selected from the group consisting of a tablet or a filled capsule, wherein said tablet or filled capsule comprises an enteric coating material.**"
> [highlighting by the Board to indicate the amendment with respect to claim 1 as granted]

Claim 1 of auxiliary requests 2 defined:

> "A composition comprising an effective amount of a complex comprising synthetic endoxifen, wherein said endoxifen is a free base or is in the form of a salt, **and with at least one lipid**, for

use in the treatment or prevention of cancer by the oral mode of administration." [highlighting by the Board to indicate the amendment with respect to claim 1 of the main request]

Claim 1 of auxiliary request 3 defined:

"A composition comprising an effective amount of a complex comprising synthetic endoxifen, wherein said endoxifen is a free base or is in the form of a salt, **and with at least one lipid**, for use in the treatment or prevention of cancer, and wherein said composition comprises a form selected from a tablet or a filled capsule, wherein said tablet or filled capsule comprises an enteric coating material." [highlighting by the Board to indicate the amendment with respect to claim 1 of auxiliary request 1]

IV. The following additional documents have been submitted during the appeal procedure:

E39: Jordan; Breast Cancer Res. Treat., 2: 123-138 (1982)
E40: Rochefort et al.; J. Steroid Bioch., 19: 69-74 (1983)
E41: US 4,919,937
E42: Sauvez et al.; Carcinogenesis, 20: 843-850 (1999)
E43: WO 2004/087123
E44: WO 2004/054558
E45: WO 2005/092310
E46: US 2005/0158388
E47: Business Wire press release, 5 February 2004 (accessed at https://www.businesswire.com/news/home/20040205005315/en/ASCENDTherapeutics-Acquires-North-American-Product-Rights, 24 June 2020)

E48: Rouanet et al.; J. Clin. Oncol., 23: 2980-2987 (2005)
E49: WO 2006/040196
E50: Mansel et al.; Breast Cancer Res. Treat., 106: 389–397 (2007), (abstract)
E51: Ogura et al.; Biochem. Pharmacol., 71: 1358–1369 (2006)
E52: Sun et al.; Drug Metab. Dispos., 35: 2006-2014 (2007)
E53: P. Y. Maximov, R. E. McDaniel and V. Craig Jordan, Tamoxifen: Pioneering Medicine in Breast Cancer, Springer, Basel, 2013
E54: Jordan et al.; Eur. J. Cancer, 16: 239–251 (1980)
E55: Steroids, 77(7): 717-718 (2012)
E56: Falany et al.; Drug Metab. Dispos., 34(3): 361-368 (2006)
E57: Malik et al.; Drug Metab. Rev., 48: 281-327 (2016)
E58: Huntjens et al.; Br. J. Pharmacol., 153: 1072-1084 (2008)
E59: Zhang et al.; Life Sci., 78(24): 2772–80 (2009)
E60: Wong, et al.; Int. J. Pharm., 366(1–2): 14–20 (2009)
E61: Rauschning et al.; Breast Cancer Res. Treat., 31: 83-94 (1994)
E62: Jordan; Steroids, 77: 829-842 (2007)

E63: Beland et al.; Carcinogenesis, 20(3): 471-477 (1999)

Documents E39-52 were filed by the appellant (patent proprietor) with the statement of grounds of appeal and documents E53-E62 were filed by the appellant with its letter of 26 May 2021.

Document E63 was filed by respondent 1 (opponent 1) with the letter of 28 October 2021.

V. In its communication pursuant to Article 15(1) RPBA the Board expressed *inter alia* the preliminary opinion that the subject-matter as defined in accordance with the main request and auxiliary requests 1-3 does not involve an inventive step. As regards the admittance of documents D39-D62 the Board expressed doubts whether the filing of these documents for the first time in the appeal proceedings was justified and conducive to the principle of procedural economy.

VI. Oral proceedings were held on 6 April 2023.

VII. The arguments of the appellant relevant to the present decision are summarized as follows:

The subject-matter of claim 1 of the main request differed from the teaching in document E1 in that it related to the actual use of endoxifen in the treatment or prevention of cancer by the oral mode of administration.

The patent expressly disclosed the suitability of endoxifen for oral administration in cancer treatment and presented in examples 11-15 experiments in support of this suitability. Document E23 confirmed that oral administration of endoxifen allows for achieving systemically effective levels of endoxifen in human subjects and surprisingly demonstrated greater bioavailability for endoxifen which is orally administered as compared to endoxifen generated via the metabolism of orally administered tamoxifen.

The problem solved was therefore to be seen in the provision an advantageous administration form for effective cancer treatment with endoxifen.

The compositions used for *in vitro* tests in document E1 provided the skilled person with no suggestion towards any specific form suited for the effective administration of endoxifen, let alone at a composition for use by oral administration.

The skilled person had actually to overcome a technical prejudice against the oral administration of endoxifen. This prejudice was explained in the expert declaration presented in document E26 and supported by documents E8 and E27-E33 as filed before the opposition division. The existence of the prejudice was further substantiated by documents E39-E52 filed with the statement of grounds of appeal in reaction to the findings in the decision under appeal and documents E53-E62 filed with the letter of 26 May 2021 in response to the replies to the appeal by the respondents. These documents demonstrated that the tamoxifen metabolite 4-OH-Tam was well known to be unsuited for oral administration due to its rapid metabolic inactivation and elimination and indicated that similar unsuitability was to be expected for the structurally closely related endoxifen, which is like 4-hydroxy-tamoxifen inactivated by glucuronidation in the liver.

The particular form of a coated tablet or capsule with an enteric coating as defined in claim 1 of auxiliary request 1 allowed for the protection of orally administered endoxifen against degradation in the acid environment of the stomach.

The definition of the presence of a lipid in accordance with the claims of auxiliary requests 2 and 3 corresponded to exemplified compositions in the patent and further distinguished the claimed compositions from the prior art.

VIII. The arguments of respondent 1 (opponent 1) and respondent 2 (opponent 2) relevant to the present decision are summarized as follows:

The patent provided no evidence of any technical effect beyond the qualities of endoxifen already known from document E1. In as far as the defined oral administration was considered to represent a distinguishing feature, the problem solved could only be seen in the provision of an alternative composition of endoxifen for the treatment and prevention of cancer.

The documents presented before the opposition division did not establish any prejudice against the oral administration of endoxifen. Documents E39-E62 filed during the appeal proceedings should not be admitted. These documents did anyway not demonstrate the existence of a prejudice against the oral administration of endoxifen either.

Differences in the C_{max} and the exposure to endoxifen after oral administration of endoxifen as compared to oral administration of tamoxifen could not be considered surprising.

In the absence of any rebutted prejudice or surprising effect the claimed oral mode of administration was to be considered obvious to the

skilled person, because oral administration represented the administration route generally preferred in the art.

Tablets and filled capsules with an enteric coating as defined in claim 1 of auxiliary request 1 represented conventional forms for oral administration. The additional features as defined in claim 1 of auxiliary request 1 did therefore not contribute to an inventive step.

Auxiliary requests 2 and 3 were not to be admitted, because the definition of the presence a lipid, which had not been required according to any of the requests on which the decision under appeal was based, introduced ambiguity and was in the absence of any surprising effect anyway not suitable contribute to an inventive step.

IX. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of

- the main request filed with the statement of grounds of appeal,
- auxiliary request 1 corresponding to auxiliary request 3 in the decision under appeal filed on 4 March 2020 or
- auxiliary requests 2-3 as filed with the statement of grounds of appeal.

X. The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. Main request - inventive step

1.1 Closest prior art

Document E1 reports results of *in vitro* assays for estrogen receptor binding, inhibition of estrogen stimulated breast cancer cell proliferation and regulation of estrogen responsive genes indicating that endoxifen has equivalent activity to 4-OH-Tam, which is known as a potent active tamoxifen metabolite (see E1, abstract and pages 155-156, figure 3).

The identification of document E1 as an appropriate starting point in the prior art was not in dispute.

1.2 Problem to be solved

Document E1 does not describe a composition for use in the treatment or prevention of cancer by the oral mode of administration as defined in claim 1 of the main request.

As pointed out in the decision under appeal (see page 10, section 2.3.3.1) the patent presents in example 10 results of *in vitro* experiments which are in line with the results from the experiments already described in document E1. In example 9 the patent further reports that mice can survive exposure to certain doses of intravenously administered endoxifen, whilst examples 11-15 relate to protocols for testing the effects of endoxifen following oral administration without presentation of any actual results.

In view of document E1 and having regard to the teaching in the patent the Board considers the objective technical problem as the provision of an effective and convenient administration form for endoxifen in the treatment of cancer.

1.3 Assessment of the solution

1.3.1 In view of the pharmacological activity of endoxifen as known from document E1 and taking account of the well known convenience of oral administration the Board considers that the skilled person would, in the absence of any prejudice against oral administration of endoxifen, regard the claimed subject-matter an obvious solution for providing a convenient and effective mode of administration for endoxifen in the treatment of cancer.

In this context the Board observes that endoxifen represents one of various known metabolites of tamoxifen. In view of the required metabolism for its generation following the oral administration of tamoxifen it is not at all surprising that a different endoxifen exposure profile, including a faster onset of the C_{max} , results from the oral administration of endoxifen itself as compared to the oral administration of tamoxifen. Accordingly, the difference in endoxifen exposure profile from oral administration of endoxifen itself as compared to tamoxifen as reported in document E23 does not affect the assessment of the solution.

1.3.2 In accordance with the established jurisprudence a technical prejudice concerns an opinion or preconceived idea widely or universally held by experts in the relevant field. The existence of a prejudice relied upon for meeting the requirement of inventive step

needs to be convincingly demonstrated by the proprietor, typically by reference to the literature or to encyclopedias published before the relevant filing date (see Case law of the Boards of Appeal of the European Patent Office, 10th edition, 2022, section I.D.10.2).

1.3.3 The appellant relied with reference to the declaration in document E26 on the existence of a prejudice against effective oral administration of endoxifen. In view of the common knowledge presented in document E27 (see paragraph "Passage diffusion" on page 1) the skilled person would already expect reduced absorption for endoxifen as compared to the more lipophile tamoxifen. The prejudice would in particular follow from the known unsuitability for oral administration of the closely related tamoxifen metabolite 4-OH-Tam due to its inactivation by the liver as described in documents E8 and E30, the structural similarity between 4-OH-Tam and endoxifen and the known inactivation of 4-OH-Tam and endoxifen by glucuronidation as described in document E31 and cited in the review on first-pass glucuronidation of phenolics as a barrier to oral bioavailability of phenolics in document E28.

The Board observes, however, that the unsuitability of the tamoxifen metabolite 4-OH-Tam for effective oral administration due to extensive hepatic inactivation and elimination as reported in documents E8 (see page 497, left column, third full paragraph) and E30 (see page 1525, left column, last paragraph) may support support the prejudice against oral administration of 4-OH-Tam, but does not necessarily demonstrate the existence of a similar prejudice with respect to endoxifen.

The structures of 4-OH-Tam share a phenolic hydroxy group and only differ in the demethylated amino group in endoxifen. As argued by the appellant with reference to document E26, the skilled person may on the basis of the structural similarity between 4-OH-Tam and endoxifen, have expected that the bioavailability of endoxifen following oral administration is also affected by inactivation and elimination by the liver. Document E31, which relates to a research article published in 2007, the year of filing for the present patent, indeed confirms that endoxifen is glucuronidated and indicates that the glucuronidates of 4-OH-Tamoxifen and endoxifen are inactive at relevant doses (see E31, page 1943, Figure 1 and page 1946, right column). However, the related agents raloxifene and droloxifene, which are also prone to deactivating glucuronidation of their phenolic hydroxy-group, have nevertheless been reported in the prior art as effectively administered in oral dosage forms (see E29, page 694, left column, paragraph 1; see E32 and E33, abstracts). As pointed out in the decision under appeal (see page 14, paragraph 5) oral administration of raloxifen is effective in spite of its reduced (2%) bioavailability (see E29, *supra*), whilst the development of droloxifene was not stopped in view of inadequate bioavailability, but due to its inferior effectiveness with respect to tamoxifen (see E33, "Results" and "Conclusion"). The Board therefore considers that neither the structural similarity of endoxifen with 4-OH-Tam, nor the hepatic inactivation of endoxifen by glucuronidation, nor the more hydrophilic character of endoxifen with respect to tamoxifen convincingly substantiate the existence of a relevant prejudice against the suitability of endoxifen for oral administration.

The review in document E28 indicates that extensive glucuronidation can be a barrier to oral availability of an active agent (see E28, abstract) and confirms with references to document E31 and a further document published in 2007 (E52 as cited by the appellant) that endoxifen is mainly cleared via glucuronidation (see E28, pages 13-14, section 10.7.3). The Board takes the view that document E28 thereby merely indicates that the endoxifen will show a reduced bioavailability after oral administration. Apart from the circumstance that docent E28 was published after the filing for the patent (2011), the Board considers that document E28 does therefore not demonstrate the existence of any relevant prejudice against the oral administration of endoxifen either.

1.3.4 The appellant filed documents E39-E52 with the statement of grounds of appeal. The filing of these documents represents an amendment to the appellant's case under Articles 12(4) RPBA.

The additional documents E53-E62 were filed with the appellant's letter of 26 May 2021. The filing of these documents represents an amendment to the appellant's appeal case under Articles 13(1) RPBA.

Document E39 merely indicates that it is possible that tamoxifen metabolites are rapidly conjugated and excreted via the bile duct (see page 134, left column) and may therefore not enter the systemic circulation at a detectable concentration without any reference to endoxifen.

Documents E40-E51 were relied upon by the appellant to confirm that 4-OH-Tam was widely known to be metabolically inactivated following oral administration

and that 4-OH-Tam had been successfully developed in a different direction, namely for transcutaneous administration. Document E54 and the post-published document E55 also focus on the administration of 4-OH-Tam. As explained above in section 1.3.3 in relation to documents E8 and E30, the Board does not consider that the unsuitability of 4-OH-Tam for oral administration demonstrates the existence of a prejudice against oral administration of endoxifen.

Document E52 confirms the susceptibility of endoxifen to glucuronidation by liver enzymes (see page 2013, right column, last paragraph). However, as explained above in section 1.3.3 in relation to document E31 the Board does not consider that the susceptibility of endoxifen to glucuronidation demonstrates a prejudice against its suitability for oral administration.

The passages from document E53 (pages 52, 54, 60 and 80) relied upon by the appellant in the letter of 26 May 2021 relate to droloxifene, raloxifene and 4-OH-Tam without specific reference to endoxifen. Moreover, document E53 was published in 2013, which is well after the filing date for the patent.

Document E56 (see abstract) discusses differences in the metabolic sulfation of raloxifene and 4-OH-Tam without reference to endoxifen.

Documents E57 and E58 (see abstracts) discuss the consequences of enterohepatic recirculation (EHC) on the exposure to drugs without reference to endoxifen. Moreover, these documents were published after the filing date for the patent.

Documents E59 and E60 (see abstracts) report on the influence of the position of the hydroxyl groups on the glucuronidation of flavones without reference to endoxifen. Moreover, document E60 was published after the filing date for the patent.

Document E61 reports the more rapid elimination of droloxifene as compared to tamoxifen without reference to endoxifen.

Document E62 was cited by the appellant to merely point out that tamoxifen is glucuronidated after its conversion to endoxifen.

The Board therefore considers that documents E39-E62 are not suitable to address the issues that lead to the decision under appeal. The Board therefore decided not to admit documents E39-E52 under Article 12(4) RPBA and not to admit documents E53-E62 under Article 13(1) RPBA.

1.3.5 Accordingly, the Board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step.

2. Auxiliary request 1 - inventive step

The appellant argued that the formulation of endoxifen in tablets or capsules with an enteric coating allowed for the further protection of orally administered endoxifen against degradation in the acid environment of the stomach.

As pointed out in the decision under appeal and not contested by the appellant, tablets and capsules with an enteric coating represent conventional formulations

for oral administration of active agents, including tamoxifen. It is common knowledge that in such formulations the enteric coating protects the active agents against the acid environment of the stomach.

The skilled person would therefore consider the formulation of endoxifen in a tablet or capsule with an enteric coating obvious as solution to the problem of providing a suitable and convenient administration form for endoxifen in the treatment of cancer, which allows protection of the endoxifen against degradation in the stomach.

Accordingly the Board concludes that the subject-matter of claim 1 of auxiliary request 1 does not involve an inventive step.

3. Auxiliary requests 2 and 3 - admittance

The claims of auxiliary requests 2 and 3 require with respect to the claims of the main request and auxiliary request 1 the presence a lipid in the defined composition. The required presence of a lipid had not been defined in any of the requests on which the decision under appeal was based and thus represents an amendment to the appellant's case in accordance with Article 12(4) RPBA.

The appellant did not rely on any particular effect that would be associated with the presence of a lipid in the defined compositions in support of an inventive step. The amendment of the appellant's case in auxiliary requests 2 and 3 is therefore considered unsuitable to address the finding in the decision under appeal, that claimed invention lacked an inventive step.

Accordingly, the Board decided not to admit auxiliary requests 2 and 3 under Article 12(4) RPBA.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated