

THE PATENTS ACT, 1970  
(39 of 1970)  
as amended by  
THE PATENTS (AMENDMENT) ACT, 2005  
(15 of 2005)  
(with effect from 1-1-2005)

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THE PATENTS RULES, 2003  
as amended by  
THE PATENTS (AMENDMENT) RULES, 2006  
(with effect from 5-5-2006)

M/s BAYER SCHERING PHARMA AG,  
D-13342, Berlin,  
Germany.

Represented by

Ms. Ranjana Mehta Dutt of Remfry & Sagar

..... Applicant

1. M/s Cipla Ltd., 289, Bellalis Road,  
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Represented by Mr. Gopakumar Nair  
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2. M/s Natco Pharma Ltd.,  
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Represented by S.Majumdar,  
M/s S.Majumdar & Co.,

..... Opponents

K. Varaprasad, Examiner of Patents & Designs

## **1. History of the proceedings**

1. M/s M/s BAYER SCHERING PHARMA AG, D-13342, Berlin, Germany, hereinafter referred as 'applicant', have filed an national phase application for patent for their invention titled 'PHARMACEUTICAL COMBINATION OF ETHINYLESTRADIOL AND DROSPIRENONE FOR USE AS A CONTRACEPTIVE' on 18<sup>th</sup> February 2002 through their agent M/s De Penning and De Penning and it was numbered as IN/PCT/2002/410/CHE for the International application number PCT/IB00/01213 filed on 21<sup>st</sup> August 2000. The application was prosecuted by M/s Remfry & Sagar, hereinafter referred as 'Attorney for the Applicant'.
2. M/s Cipla Ltd., and M/s Natco Pharma, hereinafter referred as 'opponents', have filed a pre-grant opposition through their attorneys Gopakumar Nair Associates, herein after referred as 'counsel for the Cipla' and S.Majumdar & Co., herein after referred as 'counsel for the Natco' respectively, under section 25 (1) of the Act within the time limit.

## **2. Grounds of opposition**

3. The Grounds of opposition filed under section 25(1) (a) to 25(1) (g).

## **3. Subject matter of the invention**

4. A pharmaceutical composition comprising drospirenone in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, ethinylestradiol in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients.

5. Claims of the present invention which was amended during prosecution of the patent application as follows:

- 1) *A pharmaceutical composition comprising 66, 7p; 15 (3, 16 [3-dimethylene- 3-oxo-17a-pregn-4-ene-21, 17-carboiactone (Drospirenone) in an amount of from about 2 mg to about 4 mg, and 17a-ethinylestradiol 17a-ethinylestradiol (Ethinylestradiol) in an amount of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients wherein said Drospirenone is in micronized form or sprayed form a solution onto particles of an inert carrier.*
- 2) *The composition as claimed in claim 1 wherein the drospirenone is in micronized form.*
- 3) *The composition as claimed in claim 2, wherein the drospirenone has a surface area of more than 10,000 cm<sup>2</sup>/g.*
- 4) *The composition as claimed in any of the preceding claims comprising drospirenone in an amount of from 2.5 mg to about 3.5 mg.*
- 5) *The composition as claimed in claim 4, wherein drospirenone in an amount of about 3 mg.*
- 6) *The composition as claimed in any of the preceding claims, wherein said ethinylestradiol is in micronized form or sprayed form a solution onto particles of an inert carrier.*
- 7) *The composition as claimed in any of the preceding claims comprising ethinylestradiol in an amount of from 0.015 mg to about 0.04 mg.*

- 8) *The composition as claimed in claim 7, comprising ethinylestradiol in an amount of from 0.02 mg to 0.03 mg.*
  - 9) *The composition as claimed in any of claims 1-3 comprising Drospirenone in an amount of from 3.0 to 3.5 mg and ethinylestradiol in an amount of from 0.015 to 0.03 mg.*
  - 10) *The composition as claimed in claim 9 comprising drospirenone in an amount of about 3 mg and ethinylestradiol in an amount of about 0.03 mg.*
  - 11) *The composition as claimed in any of the preceding claims, wherein said composition is in the form of an oral dosage form.*
  - 12) *The composition as claimed in claim 11, wherein said oral dosage form is in the form of a tablet, pill or capsule.*
6. The counsels for the opponents submitted that the Ld. Controller is at the liberty to take any documents on record submitted during the pre-grant proceedings, which are already in public domain and any person can access these documents through internet, Journals etc. Hence, the additional documents submitted cannot be considered as new evidence, as the opponents, are only bringing the accessible documents which are already in public domain for assessing the patentability. Further argued that the complete specification of the instant application is the intrinsic evidence, whereas test reports, affidavits and any other documents filed during the proceeding are extrinsic evidence and such extrinsic evidences shall be considered as evidence/support.

#### **4. Wrongful obtaining**

7. Counsel for Cipla submitted that the idea and the knowledge to perform the alleged invention have been obtained by the alleged inventor from the prior disclosures which is apparent from the documents submitted in Annexures along with written submission and therefore the invention is wrongfully obtained by the alleged applicant from the prior inventors.
  
8. It is concluded that almost 80% of the inventions filed in the Patent Office are incremental inventions, which are extension of research work of the earlier inventions and generally accepted fact. Therefore there is no restriction for doing any research work and thereafter protecting their interests in any form. The evidences submitted by the counsel are not relevant to this ground, because there is no substantial proof submitted for 'wrongful obtaining'. The origin of the invention and how it is wrongfully obtained must be proved with certain documentary evidence. The provision 25 (1) (a) in the Act is applicable where any invention is fraudulently obtained, unlawfully obtained, stealing the information relating to the invention and such similar situations from the opponent or any person, more specifically the knowledge, know-how and/or *modus operandi* of any invention acquired wrongfully. It is concluded that this ground of opposition is not valid.

#### **5. Novelty**

9. The counsel for Cipla submitted that the US5569652 disclosed the combination of Drospirenone (0.5-50 mg per day) and Ethinylestradiol (0.02-0.04 mg) and the said patent is an orange book listed patent in USFDA for the combination of Drospirenone (0.5-50 mg per day) and Ethinylestradiol. US5922349 disclosed the pharmaceutical compositions comprising an estrogen such as ethinyl estradiol and mestranol, estradiol and their esters and progestogen which can be employed are micronized

progesterone, norethisterone acetate, norgestrel, levonorgestrel, gestodene, CPA, chlormadinone acetate, Drospirenone (1-3 mg) and 3-ketodesogestrel. Further argued that the phrase "are micronized" is used in '349 applicable to the entire ingredients, which follows the phrase "are micronized". US publication 20050282790 discloses combination of Drospirenone 0.5 mg to less than 5 mg and Ethinylestradiol 0.010 to 0.05 mg daily for treatment of premenstrual dysphoric disorder (PMDD), wherein the corresponding DE19654609 published on 25/06/1998, which is prior to the priority date of the alleged application. A monophasic contraceptive and a kit comprising a progestin and estrogen disclosed in WO 98/04269 wherein a progestin is selected from trimegestone, dienogest or Drospirenone (250µg – 4mg) and an estrogen is ethinyl estradiol (10-20 µg) for 23-25 days beginning on day 1 of the menstrual cycle. Further Wolfgang K.H. Oelkers, Steroids, 1996, vol.61, p166 – 171 is described combined use of ethinyl estradiol and drospirenone slightly lowers body weight and blood pressure and also stated it is an ideal oral contraceptive combination. W.Oelkers et. al., J. Clin. Endocrinol. Metab., reported that the combination of drospirenone 3mg with ethinylestradiol 15 – 30µg as an oral contraceptive proved remarkable ability to slightly lower body weight and blood pressure. The counsel further argued that documents submitted during the proceeding US 5897539, WO/98/04268, US 5,824,667, US 5888543, US 6479475, and US 5583129 along with the prior arts cited in the ISR are also disclosing the combination of drospirenone and ethinylestradiol which adversely impacts the novelty of the alleged invention and the amount of drospirenone 0.5mg – 5mg and ethinylestradiol 10 – 50µg is disclosed in various documented cited above.

10. The attorney for the applicant submitted that during international phase the claims are amended to include the limitation to 'drospirenone is micronized form' and the ISR addressed novelty after convinced with the amendment carried out in the claim. Further stated that none of the

documents cited in the representation are of any relevance with regard to novelty of subject invention.

11. The attorney contended that WO 97/11680 equivalent to US5922349 merely teaches "micronized progesterone" but not "micronized drospirenone", since only the natural progesterone, is further characterised by the term "micronized". The word "micronized" refers to what immediately follows it, namely the term progesterone, and not the subsequently listed progestins. The declaration submitted by Dr. Jörg Elliesen who is an inventor of the subject-matter described in WO 97/11680 to the USPTO has clarified that the micronized form is restricted to progesterone i.e. the term "micronized progesterone" was recognized as a standard phrase in the art and the Examiner in-charge of US application no. 09/757,688 subsequently confirmed that micronized drospirenone was not taught by WO 97/11680. The attorney submitted that WO 97/11680 does not teach micronization of drospirenone, but only micronization of progesterone. Micronization as a tool to improve the oral bioavailability of steroid hormones was only described for acid-stable hormones, such as spironolactone and progesterone but none of the prior art documents suggests using drospirenone in micronized form and therefore the claimed invention is novel over the documents submitted by the opponents.

12. It is concluded that the prior art documents submitted by the opponent explicitly and implicitly disclosed the composition, dosage dosage regimen and intended use of drospirenone and ethinylestradiol, which is the subject matter of the present invention. There are few prior art documents including WO 98/04267, WO 98/ 04269, US'129, US'667, US'652, DE'609, Oelkar's articles and US5756490 disclosed the combination of drospirenone and ethinylestradiol for oral delivery. But the only difference between the said prior art documents and the present invention is

'micronized form of drospirenone'. Physical form can not be considered for assessing novelty of any given substance, because there is improvement only in physical properties such as solubility, particle surface area etc, but the activity of said substance remains same. It may be convenient to manufacture the composition as a medicament in dosage form and improved dissolution with such a physical form i.e., micronized (smaller particle size), but it can not be considered as novel since the substance is already known in other form i.e., larger particle size. Making smaller particle size from larger particle or any other such form may give many advantages, which are considered as discovery but not considered to be a novel substance, because the active substance remains same whereas the change is only in the nature/appearance of the substance. The medicament may be in any form of delivery system, but the representation and proportion of active ingredients in the composition of such a delivery system is the inventive feature. Even changing the form i.e., micronized of any one or all the active ingredients in the formulation shall not be considered as novel because the active ingredients and proportion of each ingredient are same with the prior art documents. Novelty should reside in the compound itself but not in the physical form of the compound.

Drospirenone is known compound and combination with ethinylestradiol in particular combination is also known in the art. Micronized form of drospirenone is only novel aspect in the present composition shown by the applicant's counsel. Making small particle/crystalline size of the known compound drospirenone can not become novel substance. In this connection, it is noteworthy to mention that sea salt and powdered sea salt are one and the same but there is a difference in the crystalline size. The powder salt is convenient in many ways but it is not a different matter with respect to sea salt and it is considered to be other form of the matter. In both cases chemical substance is same. Changing the particle size for better physical property is mere change in the physical form and therefore the claimed invention is not novel.

## 6. Invention is prior claimed in India

13. The counsel for Cipla submitted that the Indian Patent Application No. 2211/DEL/1996 titled "hormone replacement therapy method and hormone dispenser". In page 17 of the said specification the phrase "are micronized" is applicable to the entire ingredients, which follows the phrase "are micronized" and Claim 17 of the said application discloses;

*"17. A dispenser according to claim 14, wherein the estrogen is ethinyl estradiol or estradiol or an ester thereof, estrone, estrone sulphate or conjugated estrogens and the progestogen is micronized progesterone, norethindrone or esters thereof, norgestrel, chlormadinone acetate, cyproterone acetate, desogestrel, 3-ketodesogestrel, drospirenone, norgestimate, levo-norgestrel or gestodene."*

14. The attorney for the applicant submitted that the word "micronized" refers to what immediately follows it, namely the term progesterone, and not the subsequently listed progestins. Further stated that the declaration submitted by Dr. Jörg Elliesen who is an inventor of the subject-matter described in US'349 to the USPTO has clarified that the micronized form is restricted to progesterone i.e. the term "micronized progesterone" was recognized as a standard phrase in the art.

15. It is concluded that the 2211/DEL/1996 did not disclose the subject matter of the claimed invention explicitly. The active ingredients ethinylestradiol and drospirenone present in the combination of the present invention is disclosed in 2211/DEL/1996 as one of the few estrogens and progestogens, but not claimed the said specific active ingredients ethinylestradiol and drospirenone in the combination exclusively in claim 17. Thus the ground of opposition filed u/s 25(1)(c) is not valid.

## 7. Inventive step

16. The counsel for the Cipla submitted that a micronization method for improving the digestive absorption and bioavailability of poorly soluble drugs such as griseofulvin, progesterone, spironolactone and diosmin was reported by Chaumeil, J.C. *Methods Find Exp Clin Pharmacol* 1998, 20(3): 211-215. The bioavailability of micronized tablets of spironolactone was significantly higher than that of standard tablets was disclosed by McInnes et. al., *J Clin Pharmacol*. 1982 Aug-Sep;22(8-9):410-417. Further the counsel argued that Krause I determined plasma levels of spirorenone and one of its metabolites by High-Performance Liquid Chromatography where plasma levels of drug and metabolite have been measured after oral doses of 10 and 40 mg, respectively, administered to two male volunteers. On Page 41 line 25 has clearly mentioned that spirorenone and its 1,2-dihydro derivative are unstable towards acid catalyzed lactone ring isomerization. However, 80 % of both the compounds on incubation got converted into alpha form at about 400 minutes after beginning. The lactone rearrangement product of spirorenone was not detectable in the plasma suggesting that the absorption process was much faster than the acid catalysed isomerization of the drug. The metabolite of spirorenone, however, chromatographically characterized as 1, 2-dihydro- spirorenone, could be measured in the plasma of the test subjects, on page 43 of Krause I and it was detectable only after at least 1.5 h after drug administration, suggesting a relatively low rate of formation. Its concentration then constantly rose up to the end of the study period concluding the formation of drospirenone and not the formation of inactive metabolite of Spirorenone. The counsel argued further that one can easily be concluded that the Drospirenone and Spirorenone are molecules closely relating to each other in their chemical structure and chemical behaviour but differing in their therapeutic application. Spirorenone is a diuretic and drospirenone is diuretic as well as contraceptive.

17. The counsel for the Cipla submitted that Krause II reported the isolation and identification of spirorenone metabolites from the Monkey (*Macaca Fascicularis*), in which the presence of inactive isomers of spirorenone was not detected in the blood plasma of *Macaca Fascicularis* monkeys, but the metabolite detected was 1, 2-dihydro- spirorenone as the same got absorbed *in vivo*.
18. The counsel for the Cipla argued that Krause III disclosed the pharmacokinetics of the spirorenone in Healthy Volunteers after single dose and repeated daily doses and found that there was no accumulation of spirorenone in plasma where the active metabolite, 1,2-dihydrospirorenone, accounts for 16% of the AUC of spirorenone, after 14 doses the ratio had increased to 52%. Krause I and III studies as above identified the problem of lactone ring isomerization with spirorenone as well as drospirenone under acidic conditions in *in vitro* studies and also further confirmed that the same have been absent *in vivo* in humans and monkeys confirming that the process of absorption is much faster than acid catalyzed isomerization. From the above one can envisage that as such there is no problem of isomerization with Drospirenone under acidic conditions at gastric pH as the process of absorption is much faster than acid catalyzed isomerization. Thus, the counsel submitted that since drospirenone being fraternal twin of spirorenone, the motivation available for spirorenone can easily be extended to drospirenone with exercising the inventive skills.
19. The attorney for the applicant replied that spirorenone is used for all Krause I to III studies but not the drospirenone and referred the EPO application number 019000579.2, title 'pharmaceutical combination of micronized drospirenone and an estrogen for hormone replacement therapy' which is similar type of invention where patent is granted and

subsequently revocation for the patent has also been filed before the EPO. The opposition division of EPO observed the following;

“ spirorinone and drospirenone (DRSP) are two different compounds: DRSP is a progestin, spirorinone is a mineral corticoid, an aldosterone antagonist, a diuretic and not a sexual hormone. Therefore, even if both compound do isomerize in acidic medium in vitro, they indeed have different pharmacological properties”.

Kruase II page 84 in the 'Results' para 2,

“In the HPLC chromatograms a metabolite with the same retention time as 1,2-dihydrospirorenone could be observed.”

20. The attorney submitted that spirorenone used in higher doses and also can not be used as a contraceptive. Therefore, Krause I to III is not at all relevant to this subject matter.

21. The counsel for Cipla argued that US'349 disclosed the pharmaceutical compositions comprising an estrogen such as ethinyl estradiol and mestranol, estradiol and their esters and progestogen which can be employed are micronized progesterone, norethisterone acetate, norgestrel, levonorgestrel, gestodene, CPA, chlormadinone acetate, drospirorenone (1-3 mg) and 3-ketodesogestrel, wherein the phrase "are micronized" used is applicable to the entire ingredients that follows the phrase "are micronized". Further the counsel submitted that embodiment disclosed in summary of the present invention is to identify a preferred minimum dosage of drospirenone is identified for reliable contraceptive activity and daily dosage of drospirenone and ethinylestradiol is also achieved. The alleged claims of dosage are known and there is no reduction as such in the dosage as against the statement made by the applicants in the summary of invention.

22. The counsel submitted that the amounts of both the active ingredients in the dosage forms claimed in the alleged claims are already available through the state of art from articles by Oelkar's which discloses 3 mg of drospirenone and 15-30 µg of ethinylestradiol. The combination of drospirenone in an amount of 2 to 4 mg and ethinylestradiol in an amount of 0.01 to 0.05 mg for inhibition of ovulation is known from WO 98/04267, WO 98/ 04269, US'129, US'667, US'652 and DE'609.
23. The counsel relied upon the above cited documents and submitted that combination of the subject matter is known and the combination was conveniently and effectively administered prior to the impugned application with the teachings and conclusions drawn from Krause I to III studies, the use of micronized drospirenone in the alleged invention is nothing but pursuance of known options within his or her technical grasp without exercising inventive skills, that led to anticipated success in the current case. The counsel submitted that composition comprising drospirenone and ethinylestradiol is obvious to a person skilled in the art to improve the bioavailability using the known technique called micronization, accordingly, the pending claims currently on record should be rejected.
24. The attorney for the applicant submitted that the Krause papers, ("Krause I, Krause II and Krause III"), described the behaviour in the gastrointestinal tract is related to spirorenone but not to drospirenone. Although having a similar chemical structures these are two different compounds with very different dosage regimens and pharmacological effects. The spirorenone dosages investigated in Krause I-III are 2.5-20 times higher than the claimed drospirenone dosages.
25. The counsel for Natco submitted that US'652 disclosed a method for simultaneously achieving, during menopause or premenopause, a

contraceptive effect, an anti- androgenic effect, and an anti-aldosterone effect in a female patient by administering effective amount of 0.05 to 50 mg per day and effective amount of ethynylestradiol in the range of 0.02 mg to 0.04 mg. US 5756490 disclosed a combination comprising effective amounts of ethynylestradiol and drospirenone to be used in the combination lies in the range of 0.015 mg to 0.025 mg and 1 to 3 mg respectively. US 5583129 disclosed a method of inducing contraception in a female by administering a composition comprising 0.015 mg to 0.02 mg of ethynylestradiol and 0.1 to 0.3 mg of drospirenone. US'667 also disclosed a combination for oral contraception wherein the components are 2 mg to 6 mg of 17 $\beta$ -estradiol and 0.02 mg of ethynylestradiol and a gestagen selected from 0.25 to 30 mg of drospirenone and 0.1 to 0.2 mg of cyproterone acetate. WO 1998/004267 disclosed an effective amounts of ethynylestradiol and drospirenone ranges between 0.05 to 0.15 mg and from 0.5mg to 3 mg respectively for use as a contraceptive. WO1997/011680 and RU2101013 taught micronization of steroids including progesterone and other natural and synthetic estrogen, which have low solubility. The counsel further submitted that micronization was abundantly used well before the priority date for precisely the same problem of low solubility and it is an obvious technique, which would occur naturally to any person skilled in the art to counter the problem of low solubility.

26. The counsel further submitted that applicant's representative present at the hearing explained the inventiveness of the present invention in a simplified manner as below, where micronized drospirenone without enteric coated could not be accepted in view of the prior art knowledge available at the time of the invention.

	Micronization	Non micronization
Enteric coated	Accepted	Accepted
Non-enteric coated	not accepted	Accepted to a certain extent

27. The counsel further submitted that it would be evident from the US district court and the CAFC judgment where micronization of acid sensitive spironolactone, also a steroid and related to drospirenone was known before the priority date of the present invention. Therefore teaching away with respect to penicillin G and erythromycin does not amount to an absolute teaching away as exceptions were known to exist at the time of the invention with respect to related steroids. In view of spironolactone a person skilled in the art will be motivated to try micronization on drospirenone in order to achieve desired solubility. Further submitted that correlation of in vitro, in vivo is required to predict the activity of a formulation in vivo. Moreover in vitro testing is not the sole basis upon which a drug dose formulation decision is made. Therefore in vitro tests are not blindly followed and a careful formulator will verify such tests by in vivo tests. However in the present case, the applicant has not carried out such in vivo tests and has placed entire reliance on the in vitro test data, which apparently taught away from the present invention. The counsel submitted that the micronization of drospirenone despite its susceptibility to acid was obvious as evident from the foregoing submissions.

28. The attorney for the applicant replied that drospirenone was sparingly soluble in water as well as rather unstable in an acidic environment in and isomerises into a therapeutically inactive isomer, which was verified experimentally by Nickisch et al. It is also explained on page 4, lines 6-7, of the present application and as discussed in detail by Nickisch et al, that

drospirenone is rearranged into an inactive isomer under acidic conditions, such as those prevailing in the stomach. Further submitted that the instability of drospirenone in an acidic environment has also been described in WO 98/06738 and therefore oral drug compositions containing drospirenone are problematic in terms of getting an effective amount of drospirenone dissolved in the (acidic) gastric fluid without losing the active form of drospirenone due to the isomerism pathway. The attorney further submitted that drospirenone in micronized form has the (expected) effect where the molecule is dissolved from its composition significantly faster than non-micronized form and exposed to the hydrochloric acid present in the stomach almost immediately after being administered.

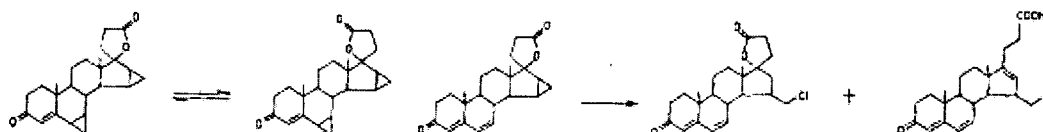
29. The attorney submitted that a too fast dissolution of compounds, which are not stable under the (acidic) conditions prevailing in the stomach, is not desirable as this would, in most situations, lead to a lowered bioavailability. This is taught in the textbook "Pharmazeutische Technologie" by Bauer et al., 1993. A similar teaching can be found in the textbook "Pharmaceutics: The Science of Dosage Form Design" by Aulton, 1988 "Certain drugs such as penicillin G and erythromycin are unstable in gastric fluids. Thus chemical degradation will be minimized if such a drug does not dissolve readily in gastric fluids. Hence particle size reduction would not only produce an increased rate of drug dissolution in gastric fluid but also an increase in the extent of drug degradation. This would result in a decrease in the amount of intact drug available for absorption from the small intestine." Thus, although micronization, in general, was indeed available to the skilled person at the priority date of the present application, the skilled person would not have considered this technique as being suitable in the case of drospirenone.

30. The attorney submitted that two prior art documents (Nickisch et al. and WO 98/06738) have described the acid-labile nature of drospirenone and also common general knowledge from the textbooks by Bauer et al. and Aulton at the priority date of the subject application, the fast dissolution of an orally administered drug should be avoided when the drug in question is not stable under the conditions prevailing in the stomach. Further, previously micronized hormones were all perfectly stable in acid and, therefore, acid-dependent degradation of these molecules was not a problem and dissuade the skilled person from micronizing drospirenone.
31. The attorney argued that preformulation may be described as a stage of development during which the physical pharmacist characterizes the physical-chemical properties of the drug substance in question which are considered important in the formulation of a stable, effective and safe dosage form and such parameters as crystal size and shape, pH-solubility profile, pH-stability profile, polymorphism, partitioning effect, drug permeability and dissolution behaviour are evaluated." (emphasis added).
32. The attorney submitted that the *in vitro* experiments clearly shows the pH conditions in the stomach and the small intestine, elucidates the deleterious effect of micronization on the stability of drospirenone in an acidic environment and therefore the skilled person would conclude that significantly more (about twice as much) drospirenone would eventually be available for absorption in the intestinal system if drospirenone is provided in non-micronized form as compared to drospirenone provided in micronized form. Based on such data, the skilled person would certainly not be motivated to develop an oral dosage form containing micronized drospirenone.
33. Further the attorney submitted that it is quite contrary to the expectations of the skilled person, the present inventors found that the bioavailability of

micronized drospirenone turned out to be high when administered orally, which is clear from Example 4 of the present application and from the pharmacokinetic study by Hartmut Blode. The affidavit of Hartmut Blode shows the results from a pharmacokinetic study in healthy women, wherein the plasma levels of therapeutically active drospirenone was followed for 7 days following single oral administration of a tablet formulation containing micronized drospirenone versus a similar tablet formulation containing non-micronized drospirenone, significantly greater amount of active drospirenone is absorbed and present in the plasma following oral administration of drospirenone in micronized form as compared to oral administration of drospirenone in non-micronized form.

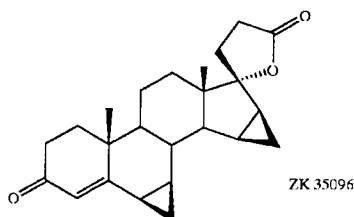
34. The attorney submitted that micronized drospirenone is superior to non-micronized drospirenone where much larger amount of drospirenone is transferred to the blood stream when using the micronized substance as opposed to the non-micronized substance. More particularly, about 30% higher dose of non-micronized drospirenone as compared to micronized drospirenone is required to achieve an equivalent therapeutic effect. Eventhough drospirenone has been known since the late 1970s and the possibility of micronizing drospirenone was available for about twenty years, nobody actually did it.

35. It is concluded that Nickisch et. al., published acid catalyzed rearrangements of 15, 16-substituted 17 $\alpha$ -pregnene-21,17-carbolactone derivatives.

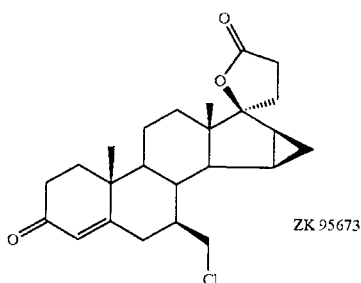


The products formed are due to the catalytic rearrangement and purely it is a synthetic method. It can not be considered as equivalent to an in vivo method for devising the dosage forms, because the reaction condition and object of Nickisch research is entirely different. In WO 98/06738, the authors disclosed a process for producing drospirenone and intermediate products formed during synthesis. It is yet again a synthetic method which is not equivalent to in vivo test. The intermediate formed are impurities in that particular process. Comparing the production method with in vivo tests has no logic. The skilled man never considers those documents as relevant documents. Laboratory synthetic environment and gastric fluid in the body are different subject matters. The information provided in WO 98/06738 is reproduced hereunder:

“From some tests, it is known that in the case of acidic action, drospirenone can be decomposed with acidic action via two reaction routes. For one thing, under acidic conditions, the drospirenone is easily converted into epimeric isolactone ZK 35096.



The second product is produced by an HCl attack on the 6,7-methylene group, which results in ring opening product ZK 95672”.



It is concluded from the statement of the inventors of WO 98/06738, the two impurities formed from unknown methods and unknown conditions. The statement is unbelievable because there is no reference or any process parameters to support the findings. Therefore it is a mere statement without any evidence. It is concluded that the composition containing drospirenone is problematic in terms of getting an effective amount of drospirenone dissolved in the (acidic) gastric fluid loose the active form of drospirenone due to the isomerism pathway, is no more than a hypothesis. Strength of the acid (concentrated or diluted) together reaction condition gives the desired product in the laboratory. Both in vivo and in vitro, pH is playing a major role wherein the behavior of the drug in the particular pH may be differing in the biological fluid and laboratory condition. The behaviors of the drug in the biological fluid not only depend upon pH also depend on drug-drug interaction, various other excipients present in the dosage form. Therefore it may not be the only factor that decides the acid catalyzed isomerism of drospirenone inside the body, but various other factors also involved. Therefore, the skilled man in the art in no way looked for the irrelevant documents Nickisch et. al and WO 98/06738.

36. Progesterone is a progestogen and drospirenone also a progestogen. Progesterone is naturally occurring steroid and the problem encountered was absorption and bioavailability due to poor solubility. To improve the absorption and bioavailability Chaumeil, McInnes et. al and US'349 micronized progesterone. Since drospirenone is also from the same group and used for similar ailment, skilled man obviously try to micronize drospirenone for better absorption and bioavailability.
37. It is concluded that Krause I to III studied the pharmacokinetics of spirorenone, an aldosterone antagonist and one of its metabolite in plasma, from the Monkey Macaco Fascicularis and human volunteers.

Spirorinone and drospirenone are two different compounds and used for different ailments, but the metabolite of spirorenone identified and characterized from Krause is 1, 2-dihydro- spirorenone, nothing but drospirenone. From Krause studies it is well known to person skilled in the art that spirorenone converts into a major single metabolite drospirenone whenever administered into the system and there was no lactone rearrangement product of spirorenone was detectable in the plasma, but the absorption process was much faster than the acid catalysed isomerization of the drug. Even though the drug used in the study of Krause is spirorenone, the substance absorbed is drospirenone (1,2-dihydrospirorenone). In the same acidic medium the metabolite of spirorenone i.e., drospirenone is generated and absorbed without further degradation/isomerism. Therefore absorption of drospirenone whether in micronised or non-micronised form behave as same in the biological fluid and absorbed without any further degradation.

38. It appears that the way in which the phrase 'are micronized' is represented in US'349, column 10, line 16-28 as 'Examples of progestogen which can be employed to this invention are micronized progesterone, norethisterone acetate, norgestrel, levonorgestrel, gestodene, CPA, chlormadinone acetate, drospirorenone and 3-ketodesogestrel which applicable to all the progestogens. But in claim 11 of the same document claimed as 'is micronized' in place of 'are micronized' which reproduced hereunder:

"A method according to claim 1, wherein the estrogen is ethinyl estradiol or estradiol or an ester thereof, estrone, estrone sulfate or conjugated estrogens and the progestogen is micronized progesterone, norethindrone or ester thereof, norgestrel, chlormadione acetate, cyproterone acetate, desogestrel, 3-ketodesogestrel, drospirenone, norethindrone, norgestimate, levonorgestrel or gestodene."

Since claim is an important part in the patent specification which protect the interests of the patentee throughout the monopoly period 20 years, the patentee of US'349 would have claimed as 'are micronized', if all the active ingredients in the group are needed to be protected for micronized form. Therefore it is concluded that micronized form is restricted to only the naturally occurring, poorly soluble progesterone, but not applicable to all progestogens.

39. Penicillin G and erythromycin are antibiotics with different physical and therapeutic activity. Particle size reduction of penicillin G and erythromycin may not be produced an increased rate of drug dissolution in gastric fluid with an increase in the extent of drug degradation. Comparing drospirenone, a steroid drug with antibiotics having different structure, physico-chemical property and pharmacokinetic activity have no relevance.
40. It is concluded that many prior art documents including WO 98/04267, WO 98/ 04269, US'129, US'667, US'652, DE'609, Oelkar's articles and US5756490 disclosed the combination of drospirenone and ethinylestradiol, dosage with the dosage regimen. Even many of the above cited prior art compositions of drospirenone and ethinylestradiol have been successfully treated patients; it is really a surprising fact to note how the inventors of the present invention faced the acid catalysed isomerism of drospirenone for the same combination. In this regard, there was no single prior art document submitted in support of said acid catalysed isomerism of drospirenone in combination with ethinylestradiol by the applicant.
41. It is concluded that in vivo and in vitro tests are distinct because in vitro tests are conducted in chemical environment whereas in vivo tests are conducted in biological environment. The mechanism of action in vivo is

absorption but in vitro it is dissolution. Dissolution is only depending on solubility i.e., physical property, but absorption depends not only on the solubility but also relied on many factors, precisely, several other host factors in the system influence the results of the in vivo test. Tests of in vivo provide the standard method to determine drug sensitivity or resistance. With in vivo test one can assess the safety and efficacy of the drug, but with in vitro it is not possible to assess the same. Therefore, in vitro study of drospirenone cannot be considered as final result and it cannot be expected to be same in vivo.

42. It is concluded that micronization is a technique routinely used in the formulation industry to increase the dissolution rate of a poorly soluble drug through increasing the surface area, in other words making large crystals into small crystals so as to increase the solubility. There is no comparative study details pertaining to micronized and non-micronized drospirenone is provided in the specification and how the micronized form overcome the acidic decomposition in the acidic environment of the body i.e., in vivo. Moreover, there is no scientific reasoning is given to support the surprising increased absorption of drospirenone when administered orally. In general, activity of drug in vivo is different from in vitro. It is common general knowledge that the large crystals dissolve slowly than the smaller crystals that dissolve freely in a given medium. The representative of the applicant who attended the hearing explained that the micronised form of drospirenone is only suitable when the tablet of the composition is enteric coated with a desired polymer whereas it is not suitable for non-enteric-coated tablets. It is concluded that the enteric coated layer protects the micronised drospirenone from acidic environment and release the drug in the desired place where it will not be prone to isomerism.

43. It is concluded that the composition of the present invention is known in the art from the publications including WO 98/04267, WO 98/ 04269, US'129, US'667, US'652, DE'609, Oelkar's articles and US5756490 with the proportion of active ingredients in the combination of drospirenone and ethinylestradiol and dosage regimen, micronisation for poorly soluble similar drugs such as progesterone and spironolactone are also known from Chameil and McInnes, Kauase I to III suggesting that the absorption process of the metabolite (1,2-dihydrospirorenone) generated was much faster than the acid catalyzed isomerism of the drug decomposition, wherein the substance generated and absorbed is drospirenone from the acid catalysed isomerism of spirorenone and the said metabolite is readily absorbed without further degradation/isomerism. Therefore, it is obvious to a skilled person in the art to conceive the teachings available in the above cited prior arts at that point of time for preparing the composition of the present invention. The claimed invention does not involve an inventive step in view of the preceding observations.

#### **8. Not an invention**

44. The counsel for Cipla submitted that opponents submitted that there is only one double bond difference between Spirorenone and Drospirenone and their chemical structure and chemical behaviour are closely related to each other but differing in their therapeutic application. Spirorenone is a diuretic and Drospirenone is diuretic as well as contraceptive. Further the counsel submitted that drospirenone is metabolite of Spirorenone and 1,2 dihydrospirorenone is as per Sec 3(d) the same substances as spirorenone which has only undergone hydrogenation. The use of the drospirenone and ethinylestradiol is known and modifying any one of the ingredient as micronized considered to be the same active ingredient falls within the ambit of Section 3(d).

45. The counsel for Cipla argued that the combination of the present invention is disclosed 3 mg of Drospirenone and 15-30 ng of Ethinylestradiol in Krause I, II and III, Articles by Oelkars, WO 98/04267, WO 98/ 04269, US'129, US'667, US'652 and DE'609 and therefore the alleged invention is mere admixture without any synergy or surprising result.
46. The counsel for Natco submitted that the specification fails to demonstrate the synergistic activity of the presence composition over prior art examples 2, 3 and 4 demonstrate the dissolution of drospirenone and ethinylestradiol from the tablet prepared according to example 1 and bioavailability of drospirenone and ethinylestradiol. Example 5 illustrates the contraceptive efficacy of the formulation with 2mg and 3mg drospirenone, however no reference is made to ethinylestradiol. Further the counsel stated that the applicant did not provide comparative data over the previously known compositions to substantiate the superiority of the present composition.
47. The attorney for the applicant strongly resisted the opponent's attorney's arguments and submitted that applicant's invention relates to a novel, inventive and synergistic composition and Section 3(d) is not applicable. Further submitted that the enhanced efficacy as micronizing drospirenone in the composition had pronounced effects on the in vivo efficacy of the drug as established by the data in Affidavit of Hartmut Blode where it is observed about 30% increase in oral bioavailability was achieved as compared to administration of a composition containing drospirenone in non-micronized form. The attorney submitted that significant improvement in bioavailability of the claimed composition establishes that the claimed subject-matter does not fall under the exclusions mentioned in Section 3(d).

48. The applicant's attorney denied the statement of the opponents counsel and submitted that the composition of the present invention is not a mere admixture but a synergistic mixture having improved properties. In this regard, the attorney referred page 6 of the specification wherein it has been mentioned that 'since drospirenone is an aldosterone antagonist, it has diuretic properties and is therefore suitable for counteracting the water-retentive properties of ethinyl estradiol' and Example 4 of the specification with regard to the increased bioavailability of drospirenone.

49. It is concluded that there is no comparative efficacy data for the present composition with the similar composition in the art provided in the specification to support the improvement, whereas there is unclear efficacy information only for the composition of the present invention in example 5 that cannot be considered to be an improvement in efficacy over the similar compositions in the prior art. In the absence of the comparative efficacy data the object and inventiveness of the invention is defeated. The active ingredients in the composition which produce the desired effect are drospirenone and ethinylestradiol, but both are known in the art. Therefore, combination of drospirenone and ethinylestradiol, dosage and dosage regimen is known in the art, but only improvement shown is micronisation of drospirenone. Micronisation of the known substance considered to be the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance. Moreover drospirenone (1,2-dihydrospirorenone) is a metabolite of spirorenone which is evident from Kruase I to III research publication. Thus claiming micronised form of a known metabolite is considered as not an invention under the provision of the Act.

50. It is a basic requirement for a combination when any two or more known substances are present in any invention for patent, it should possess unexpected synergistic effect, otherwise it is considered to be a mere

admixture. Combination of drospirenone and ethinylestradiol, dosage, dosage regimen and intended use is already known in the art. As per the argument of the attorney for the applicant the combination of the invention with micronised form of drospirenone is the inventiveness in this present patent application. To support the inventiveness there was no data relating to synergistic effect of the combination is provided in the specification. The study of the Hartmut Blode is pertaining to micronised and non-micronised drospirenone alone, but not for the combination of drospirenone and ethinylestradiol. The bioavailability data of Hartmut Blode can not be considered for the purpose of determining the total bioavailability of the combination of the present invention. It is concluded that the combination of the present invention is a mere admixture resulting only in the aggregation of the properties of the components thereof.

#### **9. Insufficient Disclosure**

51. The counsel for Cipla submitted that the alleged patent application and specification does not fulfill the enablement requirements of written description as the specification does not describe a single example wherein the surface area of the active ingredients is more than  $10,000\text{cm}^2/\text{g}$  and also devoid of embodiment to substantiate the claim in the specification.
52. The attorney for the applicant replied that Example 1 of the specification clearly discloses the preparation of a tablet formulation containing the components of the composition claimed in claim 1 and enhanced bioavailability of the components is described Example 4.
53. It is concluded that the complete specification described the particle size, surface area of the micronised drospirenone and ingredients of the composition. Therefore, the complete specification fully and particularly

describe the invention and its operation or use and the method by which it is to be performed and disclose the best method of performing the invention which is known to the applicant and for which he is entitled to claim protection.

#### **10. Section 8 particulars**

54. The counsel for Cipla submitted that applicant has failed to disclose the mandatory information u/s 8 of Indian Patents Act, 1970. The attorney for the applicant replied that the applicant had submitted the details with respect to foreign filing along with requisite petition. It is concluded that the applicant fulfilled the requirement during prosecution of the application.

#### **11. Decision**

55. In view of the discussion in the preceding paragraphs, considering the relevant written submissions made by the parties and all the circumstances of the case, the pre-grant opposition filed by the opponents under section 25(1)(a) to 25(1)(g) of the Act is accordingly accepting the representation and refusing the grant of patent without any order as to costs.

Dated this 2<sup>nd</sup> day of December, 2010.



**(Dr. S.P.SUBRAMANIYAN)**

Assistant Controller of Patents & Designs

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