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 Novartis AG
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Represented by
Ms Gladys of M/s Daniel & Gladys,

..... Applicant

M/s Cipla Ltd., 289, Bellalis Road,
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Represented by Dr. Gopakumar G.Nair
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..... Opponent

Dr. Bindu Jacob Examiner of Patents & Designs

I. History of the proceedings

1. M/s Novartis AG a Swiss Company, hereinafter referred as 'applicant', have filed an application for patent for their invention titled 'DISPERSIBLE TABLETS COMPRISING DEFERACIROX' on 11th April 2005 through their

agent M/s De Penning and De Penning and it was numbered as 593/CHENP/2005 for the International application number PCT/EP03/11351 filed on 14th October 2003 having priority of UK application number 0223978.8 filed on 15th October, 2002.

2. The agent filed a request for examination of application for patent on 16th September 2005 and the application was published under section 11(A) of the Patents (Amendment) Act, 2005, herein after referred as 'Act' in the Patent Journal dated 24th August 2007.

3. The application was taken up for the examination and the First Examination Report (FER) was issued on 11th May 2006.

4. M/s Cipla Ltd., hereinafter referred as 'opponent' has filed a pre-grant opposition through their Attorney M/s Gopakumar Nair Associates hereinafter referred as 'Attorney for the opponent' under section 25 (1) of the Act within the stipulated time limit. In response to the pre-grant opposition the applicant filed a reply statement and evidence through their Counsel M/s Daniel & Gladys hereinafter referred as 'Counsel for the Applicant'.

5. The opponent filed pre-grant representation under various grounds, but during the hearing the attorney for the opponent argued on the grounds as filed and relied on section 25(1) (e), 25(1) (f) and 25(1) (h). However the arguments made during the hearing are discussed in the decision.

II. Novelty

6. The attorney for the opponent argued that deferacirox in free acid form, pharmaceutically acceptable salt, crystalline form and all conventional pharmaceutical dosage forms including dispersible tablet along with list of well known suitable carriers or excipients are disclosed in WO/1997/49395 (WO'395). Further argued that Examples A and D describes tablet and oral

suspension powder respectively, incorporating the range of dosage and necessary excipients as well as the pharmacopoeial limitation for dispersible tablets 3 minutes for dispersion. The attorney submitted that the claims of the present invention are anticipated with the teachings of WO'395.

7. The counsel for the applicant replied that the prior art WO'395 taught the preparation of tablets, sugar-coated tablets, hard gelatin capsules and oral suspension powders with suitable carriers which depends on the nature of the active ingredient and their preparation, but it did not disclose the preparation of dispersible tablets containing deferacirox. The counsel further submitted that the examples A to D of WO'395 described the preparation of tablets of active ingredient in Example A, coated tablets in Example B, hard gelatin capsules in Example C and oral suspension powders in Example D, where as it did not specifically disclose the preparation of dispersible tablets of deferacirox.

8. It is concluded that the prior art document WO'395 cited by the attorney for the applicant have not been disclosed explicitly or implicitly the inventive features of the claimed invention. The cited document disclosed deferacirox as a product and compositions containing deferacirox such as tablets, coated tablets, capsules and oral suspensions. Another document ICL670A:Preclinical profile filed on 12.1.11 along with the additional evidence Annexure H(III), in page 200, para 2 of the said document disclosed the pharmacokinetic study of diferocirox with three oral formulations in which two dispersible tablets and a sachet form, but there was no detailed information pertaining to the composition of the present invention. The said preclinical profile document is not a valid document because there no details relating to the publication. All the components of the present invention are not specifically disclosed in the prior art documents. Therefore claims of the claimed inventions are novel over the cited prior art. I refuse the opposition filed under section 25(1) (b) of the Act.

III. Inventive Step

9. The attorney for the opponent submitted that dispersible tablet formulation comprising deferacirox in a concentration from 0.1-50% (page 10, para 1) with excipients such as fillers like, lactose, sucrose and mannitol, disintegrants such as starches, binders such as polyvinylpyrrolidone, lubricants such as magnesium stearate, glidants, and surfactants (page 9, para 3; page 8, para 2) to treat iron overload as iron chelator disclosed in WO'395. Further submitted that US5698221 (US'221) disclosed a dispersible tablet comprising compounds useful for the treatment of Alzheimer's disorders, wherein the active compound is present in a concentration from 15-50% of the tablet, or i.e., in an amount from 50-800 mg with fillers from 30-50% (column 7, line. 25-28), disintegrants up to 30% (column 5, line 55-60), binders from 1-5% (column 6, line 39-42), at least one surfactant from 0.05-1 % (column 7, line 45-50), glidants from 0.2-0.5% (column 7, line 55-58) and a lubricant such as magnesium stearate in a concentration from 0.25-1 % (column 7, line 29-30); mixing the components together, wet granulating them together, along with lubricants, and compressing the dried mixture into tablets (column 8, line 19-column 9, line 15) for preparing dispersible tablet. US/2002/0061333 (US'333) disclosed a dispersible macrolide compound and methods for producing the dispersible macrolide compound, in which the active ingredient is between 20% and 60% of the total weight of the tablet. In claim 13, the proportion of magnesium stearate as lubricant is disclosed between 0.5% and 3% and in claim 17, the method of preparing the dispersible tablet is provided with all possible steps such as mixing the active ingredient with disintegrant, wet granulating the resulting mixture with at least one surfactant, drying of the granules and dry addition of other excipients (lubricants, glidants, diluents etc) and compression of the resulting mixture.

10. The attorney submitted that it would have been obvious to combine the specific range of excipients disclosed in US'221 and US'333 replacing the

active ingredient with deferacirox as disclosed in WO'395 to arrive at a dispersible formulation of the impugned invention which disperse within 2 to 5 minutes. The ranges of excipients claimed in the alleged application fall within the ranges of the excipients disclosed in US'221.

11. Further argued that the disclosures in the prior art documents, the teaching of Remington's The Science and Practice of Pharmacy, European Pharmacopoeia and other relevant prior art documents on dispersible tablet clearly and categorically lead to prior knowledge, which meets the TSM test for obviousness in KSR v Teleflex. There are two phases described in the description namely inner phase and outer phase, wherein adding outer phase into an inner phase is by blending is a routine technique followed in the formulation industry. The problem encountered by the inventors are poor flowability and to its sticking tendency which may be due to the low density of the active ingredient, to its electrostatic characteristics, but the applicant did not provided any solution to this problem.

12. The attorney submitted that the dosage form of the active ingredient as disclosed in the impugned invention has already been disclosed in WO'395 page 9, para 3, where daily oral administration are between 10 and approximately 120 mg/kg, in particular 20 and approximately 80 mg/kg, and for a warm-blooded animal having a body weight of approximately 40 kg, preferably between approximately 400 mg and approximately 4,800 mg, in particular approximately 800 mg to 3.200 mg, which is expediently divided into 2 to 12 individual doses. Further submitted that the alleged patent application deserves to be rejected on this ground of obviousness under Sec 25(I) (e) of The Patents Act, 1970.

13. The counsel for the applicant submitted that the opponent reiterated the use of silica (highly disperse) in Example A of WO'395 is a teaching for making dispersible tablets, whereas the role of silica in pharmaceutical preparation is

to ease the powder flow when tablets are formed and it teaches the formulation of a tablet comprising 68% of the active ingredient but not the dispersible tablet with the active ingredient of about 5-40% in weight based on the total weight of the dispersible tablet. Further, tablets and dispersible tablets are different from each other and the percentages of active ingredient, 68% and 5-40% are far away from each other. Hence, a person skilled in the art has no incentive to prepare a dispersible tablet with this particular range of active ingredient from the teachings of the said prior art document WO'395. Macrolides of US'333 and Compound I of the present invention differ greatly in their chemical structures and properties and also not relevant because the formulation of tablets may vary based on the chemical and physical properties of the active ingredient, route of administration, the manufacturing process to be employed and the method by which the tablet is to be used. Hence, the formulation of one active ingredient is not applicable to the other. A person skilled in the art could not arrive with the present invention by a hindsight view from the teachings of the prior art documents without any inventive step.

14. The counsel further submitted that the disclosure of the prior art must be complete in itself without taking account of what a skilled worker might achieve the results by trial and error. Hence the cited documents can not be taken as a disclosure of the prior art for the subject patent application. The Applicant has optimized the amount of drug available to the body with high drug load having enhanced drug dissolution the maximum of 90% in accordance with the US Pharmacopoeia. The percentage of dissolution of the drug substance has to be superior within a minimum period of time.

15. The counsel submitted that the inventors were encountered two problems while working with Deferacirox, (i) the substance is basically water insoluble and (ii) the substance becomes easily electrostatically charged, but they had overcome these difficulties with the active ingredient and has prepared a dispersible tablet comprising Deferacirox for the treatment of patients with

iron overload. Claim 1 describes about a dispersible tablet comprising Compound I and pharmaceutically acceptable salts thereof in an amount of 5-40% whereas Claim 2 describes two components for the preparation of dispersible tablets namely Compound I and their pharmaceutically acceptable salts thereof along with suitable excipients. Hence, the two Claims are different independent claims that satisfy the criteria of patentability and thus the present invention is a patentable subject matter.

16. The counsel further submitted that page 157 of the Annexure H (I) - H (III) filed by the Opponent are the pages of the Journal "Remington-Practice of the Science and Pharmacy" which describes the lubricants used in the formulation of tablets. The Applicant submits that the pages in the Journal itself mention that "the primary problem in the preparation of water-soluble tablet is the selection of a satisfactory lubricant and it includes a wide range of lubricants used in the formulations. It also mentions that magnesium stearate is the widely used lubricant but it also has hydrophobic properties that retard disintegration and dissolution. The type and amount of lubricant has chosen based on the properties of active ingredient for the formulation of Dispersible tablet containing Deferacirox. The choice of suitable excipients depends on the nature of the active ingredient and the process of tablet formulation. Further, the Applicant submits that the type and quantity of excipients are based on the active ingredient composition and properties. Invention as a whole shall be considered. In other words, it is not sufficient to draw the conclusion that a claimed invention is obvious merely because individual parts of the claim taken separately are known or might be found to be obvious.

17. It is concluded that the process for the preparation of the dispersible tablets according the applicant, involving two steps (a) granulating an inner phase, (b) mixing it with one or more pharmaceutically acceptable excipients and adding it to the inner phase followed by compressing under spray lubricating

conditions vide para 5, page 8 and para 1, page 10, which contradicts to the four phases (Phase I to IV) provided in Examples 1 and 2, page 14 and 15 respectively. There is no detailed method for the preparation of the dispersible tablet with four phases. Total weight of the tablet and proportion of the active pharmaceutical ingredient (API) including all possible excipients incorporated with phase wise ingredients for four phases i.e., phase I to IV in Examples 1 7 2, but method making four phases is not clearly described in the specification. It appears that the applicant is not clear on the phases involved in the method of preparation of dispersible tablet. Moreover there are no specific teachings pertaining to process parameters for preparing phase I and adding the phase II onto the phase I provided in the description. Further, all the steps involved in the preparation of dispersible tablet of the present invention are conventional and routine in the pharmaceutical formulation industry, but there are no specific improvement with specific details provided in the description.

18. The problem encountered by the inventors are poor flowability and to its sticking tendency vide page 7, para 4, but there is no data relating to the improvement in the flowability and sticking tendency provided in the specification. Solution for the problem and object of the invention is substantially not provided in the complete specification. The API i.e., deferocirox is known in the art as a iron chelator for the treatment of iron overload in transfusion dependent anemias, sickle cell disease to reduce the iron-related morbidity and mortality. Intended pharmaceutical preparations along with the possible excipients are also disclosed in para 2 and 3 of page 7 WO'395, more particularly the information relating to high loading as a dispersible tablet in para 2 of page 8, the contents reproduced below:

> *"Dispersible tablets are tablets which rapidly disintegrate in a comparatively small amount of liquid, e.g. water, and which, if desired, contain flavourings or substances for masking the taste of the active ingredient. They can advantageously be employed for the oral administration of large individual doses, in which* ***the amount of active***

ingredient to be administered is so large *that on administration as a tablet which is to be swallowed in undivided form or without chewing that it can no longer be conveniently ingested, in particular by children."*

19. The dosage of dispersible tablet of the present invention is 'a daily dose of 5 to 40 mg/kg of body weight, preferably between 350 and 2800 mg of deferacirox are administered to patients of 70 kg body weight', whereas the dosage disclosed in para 3, page 9 of WO'395 as follows:

"The doses to be administered daily in the case of oral administration are between 10 and approximately 120 mg/kg, in particular 20 and approximately 80 mg/kg, and for a warm-blooded animal having a body weight of approximately 40 kg, preferably between approximately 400 mg and approximately 4,800 mg, in particular approximately 800 mg to 3.200 mg, which is expediently divided into 2 to 12 individual doses."

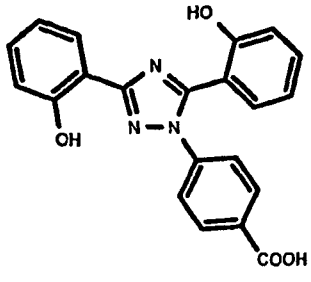
Thus the dosage of the present invention is fall within the range/limit of the prior art WO'395. Altering the dose and dosage regimen within the range of the prior art can not be considered to be inventive. A man skilled in the art can design the dose and dosage regimen according to the need and necessity.

20. The pharmaceutically acceptable excipients used in the present invention are known in the art. Selection of the required excipients for the specific drug delivery system and manipulating the range of the excipients is a routine work in the pharmaceutical formulation industry. Mere selection or choice of the excipient which is available in the art and manipulating the range of the excipient to suit the API for preparing dispersible tablet is routine experiment and it is not inventive. The applicant claimed filler, disintegrant, binder, surfactant, glidant and lubricant as excipients in claim 10, but there is no specific excipient claimed in the said claim or any other claims other than lubricant as magnesium stearate. Claim 10 as follows:

'The dispersible tablet according to any one of claims 2 to 9 wherein the pharmaceutically acceptable excipients comprise: (i) at least one filler in a total amount of about 35 to 55 % in weight based on the total weight of the tablet, (ii) at least one disintegrant in a total amount of about 10% to 35% in weight based on the total weight of the tablet (iii) at least one binder in a total amount of about 1. 5% to 5% in weight based on the total weight of the tablet, (iv) at least one surfactant in a total amount of about 0. 2% to 1% in weight based on the total weight of the tablet, (v) at least one glidant in a total amount of about 0.1% to 0.5% in weight based on the total weight of the tablet, and/or (vi) at least one lubricant in a total amount of less than about 0.4% in weight based on the total weight of the tablet.'

21. Claiming excipients generically for preparing dispersible tablet of defercirox do not involve any inventive merit. All the essential ingredients present in the composition shall be incorporated with proportion in the principal claim of any composition application for patent. The applicant in the present application failed to incorporate the essential specific excipients in claim 10. In claim 1, the applicant claimed only the dosage range (5% to 40%) of the API and in claim 2, the said dosage range along with 'at least one pharmaceutically acceptable excipient'. Claims 1 and 2 of the present case as follows:

1) A *dispersible tablet comprising compound I of the formula:*



or a pharmaceutically acceptable salt thereof present in an amount of from 5% to 40% in weight based on the total weight of the table.

2) *A dispersible tablet comprising (a) Compound I or a pharmaceutically acceptable salt thereof, and (b) at least one pharmaceutically acceptable excipient suitable for the preparation of tablets, wherein Compound I or a pharmaceutically acceptable salt*

thereof is present in an amount of from 5% to 40% in weight based on the total weight of the tablet.

22. Claim 1 directed to a dispersible tablet with 5% to 40% of the API. There is no inventiveness involved in claim 1 because dispersible tablet as one of the choice of medicament and the dosage range is also disclosed in WO'395. The only difference between the prior art (WO'395) and claim 1 of present invention is combining the dispersible tablet and dosage range together, which is described in different places of WO'395. A skilled can easily combine many features disclosed in different places of the prior art according to the need and requirement. Claim 2 is directed to a dispersible tablet with API in a range 5% to 40% and at least one pharmaceutically acceptable excipient. Addition of pharmaceutically acceptable excipient to the subject matter of claim 1 is the present independent claim 2. The API, dose and intended pharmaceutical preparations are known in the prior art, but selecting the API, dose and specific drug delivery system without giving any specific excipient can not be considered as inventive over the prior art. The term 'at least' means 'not less than one' and open ended, which is not definitive in nature. There are two important requirement for any composition patent application, (1) it is mandatory to disclose the API and all the excipients specifically with proportion in any composition or new drug delivery system for known drug; (2) support pertaining to unforeseen effect of the composition or new drug delivery system for known drug with closest prior art shall be provided in the specification. The applicant failed to adhere any of the two requirements stated above. There is a teaching in page 7 and 8 of WO'395 pertaining to free acid form, crystalline form, dispersible tablet, dosage range and excipients. Consequently, I am in an opinion that claims 1, 2 and claims dependent to claims 1 & 2 do not involve any inventive feature to consider as an invention.

23. The details provided in Examples 3-7 such as tablet shape, appearance, dissolution rate, disintegration time, mass uniformity, content of uniformity,

determination of degradation products are regulatory or pharmacopoeial requirements, but those details can not be considered as support for an invention. There is no specific data or teaching or solution provided for the problem addressed in the specification and it is not clear how the applicant has overcome such problems (i) solubility of the substance in water and (ii) the substance electrostatically charged.

24. The range of excipients generically claimed in the present application has already been specifically disclosed in column 5–8 and method of preparing the dispersible tablet in column 10-11 of US'221. The API, dose, use and intended pharmaceutical preparations are known from WO'395. A man skilled in the art can easily be motivated to combine the teachings of WO'395 and US'221 together with Remington-Practice of the Science and Pharmacy to arrive at a conclusion to optimize the proportion of excipients for the API (deferocirox) with the methods available in the art for preparing dispersible tablet. Unless there is a surprising achievement of an improved technical advance as compared to the existing knowledge of the particular composition over WO'395 and US'221 is shown, such solution cannot be considered as involving an inventive step, but as providing equivalent alternatives of composition which are obvious to a person exclusively relying on known properties of known compounds. Thus, claims 1, 2 & 13 and claims dependent to 1, 2 & 13 do not involve and inventive step under the provisions of the Act. I allow the opposition filed under section 25(1) (e) of the Act.

IV. Not an invention

25. The attorney for the opponent submitted that there is total absence of any "Surprising Effect" in the alleged invention. Therefore Claims 1 to 14 in the alleged patent application are not patentable under Section 3 of the Patents Act, 1970. Claim 1 to 4 and subsequent dependent claims are for 'crystalline form' of Deferacirox. The Applicants have themselves on page 8, para 4 have admitted that Deferacirox used for the dispersible tablet in the impugned

invention, is crystalline form obtained from the preparation described in Ex. 5 of WO'395. Further, Free Acid and Crystalline form of free acid as claimed in Claim 4 and Claim 5 are admittedly prior art in Page 3 of the impugned application.

26. The attorney reiterated that 'known' crystalline form of a known substance is not patentable under Sec.3 (d) of The Patents Act, 1970. The Applicants have failed to provide any data in relation to 'enhanced efficacy' of the deferacirox dispersible tablet, in the body of the specification. Deferacirox in crystalline form as dispersible tablet, having been known and in public domain through WO'395, compositions comprising crystalline form of Deferacirox in the impugned invention and in the absence of any proved 'enhanced therapeutic efficacy'. As such, the impugned invention is liable to be rejected for grant under Section 25(I) (f) of the Patents Act, 1970.

27. The Counsel for the applicant submitted that the present invention relates to a novel pharmaceutical composition and not a new use or new derivative of a known substance. Therefore, the subject matter of the present invention does not fall within the scope of Section 3 (d) of the Patents Act, 1970. Hence the present invention can not be opposed under section 25(1) (f) of the Patents Act, 1970.

28. I am in an opinion that the following requirements are mandatory in case of composition patent application;

(i). All the components of the invention shall be incorporated in the principal claim to make invention novel and inventive.

(ii). All the necessary ingredients including the API and excipients shall be incorporated with proportion of each ingredient in the principal claim.

(iii). Support relating to unexpected synergistic effect shall be incorporated in the specification.

29. Even though the applicant claimed the present subject matter as an application for composition, they failed to follow any of the above minimum requirements (a) to (c) to consider as application for composition. Filler, disintegrant, binder, surfactant and glidant are generically claimed in claim 10 and generally claimed in claim 2 as excipient(s). Generic can not be allowed in claims, because nature and function of specific substances vary among themselves in a particular generic, for example, all the specific substances such as maize, starch, microcrystalline cellulose, cross-linked polyvinylpyrrolidine etc., in a generic 'disintegrant' do not behave identically/similarly with different API in different drug delivery system . Therefore, specific substance with proportion shall vary depend upon the API and drug delivery system. Therefore it is mandatory to provide specific substances (ingredients) with proportion in claim 1. Even subject matters of claims 1, 2 & 10 have combined together to form a composition claim, it is still considered to be a mere admixture, because each of the ingredient present in the composition functioning as per intended purpose, the total effect is an additive effect. There is no unforeseen synergistic effect with support provided in the specification. Therefore, the claims of the present invention for patent are not an invention under the provision of the Act and the opposition filed u/s 25(1) (f) is allowed.

V. Information and undertaking regarding foreign applications

30. The attorney submitted that that the impugned patent application is liable to be rejected under Section 25(i)(h) of the Patents Act, 1970, because the applicant have failed to disclose information or furnishing false information relating to parallel proceedings of corresponding foreign patent applications. The Applicants are duty bound to submit the documents relating to Annexure H (I), Annexure H (II) and Annexure H (III) to the Patent Office as per the requirements of Section 8 (Information and undertaking regarding foreign applications) in Form 3.

31. The counsel submitted that the applicant filed Form - 3 along with the complete specification and Annexure to Form -3 with the Reply to the First Examination Report dated 02/02/2007. Therefore the applicant met the requirement under section 8 of the Act.

32. The applicant met the entire requirement as per section 8 of the Act. Therefore opposition filed under section 25(1) (h) of the Act is rejected.

VI. Order

33. In view of the discussion in the preceding paragraphs, considering the relevant oral and written submissions made by both the parties and all the circumstances of the case, the pre-grant opposition filed by the opponent under section 25(1) (e) and 25(1) (f) of the Act is accordingly allowed and refusing the grant of patent without any order as to costs.

Dated this 17th day of June, 2011.

(Dr. S.P.SUBRAMANIYAN)
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