(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 December 2018 (20.12.2018)

W!P O | PCT

(10) International Publication Number
WO 2018/229794 Al

(51) International Patent Classification:
C07D 295/135 (2006.01) *A61K 31/495* (2006.01)
A61P 25/18 (2006.01)

(21) International Application Number:
PCT/IN2018/050385

(22) International Filing Date:
12 June 2018 (12.06.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201721020643 13 June 2017 (13.06.2017) IN

(71) Applicant: **CIPLA LIMITED** [IN/IN]; Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra 400013 (IN).

(72) Inventors: **VERGHESE, Annie;** Flat No-A-603, Tulsi, Harmony, Sector- 1, Near, Saraswat Bank, Khanda colony, Panvel, Mumbai, Maharashtra 410206 (IN). **MALHOTRA, Geena;** 3403 Springs, Island City Centre, Next to Wadala Telephone Exchange, G. D Ambekar Marg, Dadar (East), Mumbai, Maharashtra 400014 (IN).

(74) Agent: **NAIR, Gopakumar G.;** Gopakumar Nair Associates 'ShivmangaP, 3rd Floor, Near Big Bazaar, Akurli Road, Kandivali (East), Mumbai, Maharashtra 400101 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Hi))*

Published:
— *with international search report (Art. 21(3))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

WO 2018/229794 A1

(54) Title: AMORPHOUS FORM OF CARIPRAZINE

(57) Abstract: The present invention discloses amorphous form of Cariprazine, method of manufacturing; premix of amorphous Cariprazine and pharmaceutical compositions thereof.

AMORPHOUS FORM OF CARIPRAZINE

Technical field of the Invention:

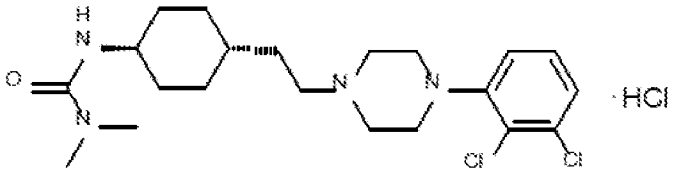
The present invention relates to polymorphic forms of Cariprazine and its pharmaceutically acceptable salts, method of manufacturing and pharmaceutical compositions thereof. More particularly, the present invention relates to amorphous form of Cariprazine, method of manufacturing; premix of amorphous Cariprazine and pharmaceutical compositions thereof.

Background of the invention:

Cariprazine (Vraylar) is an antipsychotic drug. It acts as a **D 2** and D 3 receptor partial agonist, with high selectivity towards the D 3 receptor.

The chemical name of Cariprazine is trans-4- (2-[4-(2,3-dichlorophenyl)-piperazin- 1 -yl]-ethyl} -N, N-dimethylcarbamoyl-cyclohexylamine.

Cariprazine HC1 has the following structural Formula I:



Formula I

Vraylar is used in the treatment of primary negative symptoms of schizophrenia and/or predominantly negative symptoms of schizophrenia.

Cariprazine is specifically and generically disclosed in WO2005/012266.

US7943621B2 discloses monohydrochloride, dihydrochloride, monohydrobromide, maleate and methanesulphonate salts of trans 4-{2-[4-(2,3-dichlorophenyl)-piperazine-l-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine and process of preparing them.

A new polymorph of a compound possesses physical properties that differs from, and is advantageous over, other crystalline or amorphous forms and exhibit different physical properties such as melting point, X-ray diffraction patterns, density, stability, and solubility.

There remains an unmet need for additional solid state forms of Cariprazine having good physiochemical properties, desirable bioavailability, and advantageous pharmaceutical parameters.

Objectives of the invention:

An object of the invention is to provide amorphous form of Cariprazine.

Another object of the invention is to provide process for the preparation of amorphous form of Cariprazine.

Yet another object of the invention is to provide premix of Cariprazine with the pharmaceutically acceptable excipients.

Yet another object of the invention is to provide the process for the preparation of premix of Cariprazine with the pharmaceutically acceptable excipients.

Summary of the invention:

One aspect of the present invention provided herein is amorphous form of Cariprazine.

According to another aspect of the present invention there is provided amorphous form of Cariprazine which is characterized by XRD, DSC , TGA and IR.

According to yet another aspect of the present invention there is provided a process for the preparation of amorphous form of Cariprazine comprising:

a) dissolving Cariprazine in a solvent;

b) evaporating the solvent; and

c) isolating amorphous Cariprazine.

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising amorphous form of Cariprazine together with one or more pharmaceutically acceptable carriers, excipients or diluents.

According to another aspect of the present invention there is provided the use of amorphous form of Cariprazine in the treatment of primary negative symptoms of schizophrenia and/or predominantly negative symptoms of schizophrenia.

According to another aspect of the present invention there is provided premix of Cariprazine with the pharmaceutically acceptable excipients.

According to another aspect, provided herein is a process for preparing premix of Cariprazine with the pharmaceutically acceptable excipients, which may be carried out by the following steps:

a. dissolving Cariprazine and pharmaceutically acceptable excipients/premixing agent in a suitable solvent;
b. removing the solvent from the solution obtained in step (a) to obtain premix; and
c. drying the premix of Cariprazine.

Another aspect of the present invention is to provide a composition comprising the said premix of Cariprazine which can be easily processed into pharmaceutical formulations.

Detailed description of the invention:

In accordance with the above aspects, the invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

Many pharmaceutical solids can exist in different physical forms. Polymorphism is often characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystalline lattice.

Polymorphic forms of a compound can be distinguished in the laboratory by analytical methods such as X-ray diffraction (XRD), Differential Scanning Calorimetry (DSC) and Infrared spectrometry (IR).

Cariprazine exist in different polymorphic forms, which may differ from each other in terms of stability, physical properties, spectral data and methods of preparation.

The present invention is directed to new polymorphic forms of Cariprazine and its pharmaceutically acceptable salts.

Cariprazine includes Cariprazine and its salts, hydrates, solvates, anhydrates and premix.

In an embodiment, provided herein is novel amorphous form of Cariprazine.

According to another aspect of the present invention there is provided amorphous form of Cariprazine characterized by XRD, DSC, IR, TGA.

According to another embodiment, the process for preparation of amorphous form of Cariprazine comprises the following steps;

a) dissolving Cariprazine in a solvent;
b) evaporating the solvent; and
c) isolating amorphous Cariprazine.

The solvent may be selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol, acetone, water, formic acid, dimethyl

sulfoxide, dimethylformamide, dimethylacetamide, 2-methyl tetrahydrofuran, N-methyl-2- pyrrolidone, and mixtures thereof.

Optionally the amorphous form may be obtained by the addition of anti- solvent. The anti-solvent may be selected from the group consisting of water, dichloromethane, and mixtures thereof.

The addition of the anti-solvent may result in the formation of a precipitate.

The isolating step of amorphous Cariprazine by this method may be achieved by filtering and drying the precipitate, distillation, spray drying, lyophilization, or agitated thin film drying.

The Cariprazine used in step (a) is selected from Cariprazine or its polymorphic forms known in the prior art.

The amorphous form of Cariprazine obtained according to the process of the present invention can be formulated into various pharmaceutical compositions like powder, granules, capsules, tablets, pellets etc.

According to another aspect of the present invention there is provided the use of amorphous form of Cariprazine in the treatment of primary negative symptoms of schizophrenia and/or predominantly negative symptoms of schizophrenia.

According to another embodiment, of the present invention is to provide premix of Cariprazine with the pharmaceutically acceptable excipients.

The premix according to the process of the present invention may be obtained as crystalline or amorphous.
Premixes are characterized by a variety of associated properties such as stability, flow, and solubility.

Although there are a variety of premixes, there is a continual search in this field of art for premixes that exhibit an improved property.

The term "premix" used herein is to describe combinations of Cariprazine and at least one pharmaceutically acceptable excipient/premixing agent.

In an embodiment, the present invention provides a Cariprazine premix having enhanced stability, dissolution properties that can be easily formulated into pharmaceutical composition.

The premix of the present invention is prepared by combining Cariprazine with suitable pharmaceutically acceptable excipients.

In an embodiment, the process for preparation of premix of Cariprazine comprising steps of;

a. dissolving Cariprazine and pharmaceutically acceptable excipients/premixing agents in an suitable solvent;

b. removing the solvent from the solution obtained in step (a) to obtain premix; and

c. drying the premix of Cariprazine.

The pharmaceutically acceptable excipient/ premixing agents used in step (a) include, but are not limited to polyvinylpyrrolidone (also called povidone), co-polymers of PVP and vinyl acetate such as copovidone (e.g. Kollidon VA 64 polyvinyl alcohol, polyethylene glycol, polyol (Mannitol), sodium starch glycolate, colloidal silicon dioxide (aerosil), hydroxypropyl methylcellulose, low substituted hydroxypropylcellulose, hydroxypropylcellulose, methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethylcellulose, polyvinyl

acetate, Eudragit, cyclodextrins, gelatins, hypromellose phthalate, sugars, and combinations comprising one or more of the foregoing agents.

In an embodiment the weight ratio of Cariprazine and premixing agent may range from 1:10 to 10: 1.

The process for preparing the Cariprazine premix comprises of dissolving Cariprazine in a solvent system selected from a group of polar solvents such as Cl-C4 alcohols; chlorinated organic solvents such as chloroform, dichloromethane, ethylene dichloride alone or in combination.

In an embodiment the dissolution temperatures may range from about 10°C to about reflux temperature of the solvent, depending on the solvent used for dissolution.

In an embodiment, solvent may be removed by known techniques such a distillation, evaporation, spray drying, spray coating, lyophilisation. sublimation (typically under vacuum) and desorption or freeze drying.

The premix of Cariprazine is characterized by XRD, DSC, IR and TGA.

The Cariprazine using in step (a) is selected from the polymorphic forms of Cariprazine known in prior art.

The premix can be formulated using suitable excipients into various pharmaceutical compositions like powder, granules, capsules, tablets, pellets etc using the methods known in the art.

The present invention includes administration of an effective amount of stable amorphous Cariprazine premix (either alone or as the active component of a pharmaceutical composition) used in the treatment of primary negative symptoms of schizophrenia and/or predominantly negative symptoms of schizophrenia.

In yet another embodiment, the present invention provides a complex of Cariprazine and cyclodextrin.

In yet another embodiment, the present invention provides a composition comprising the said complex of Cariprazine and cyclodextrin which can be easily processed into pharmaceutical formulations.

As used herein, "a cyclodextrin" refers to the natural cyclodextrins, a- cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, and their respective derivatives.

The following examples, which include preferred embodiments, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of examples and for purpose of illustrative discussion of preferred embodiments of the invention.

Examples:-

Example 1

Amorphous pre-mix of Cariprazine hydrochloride and Eudragit

Charged 5.0 g of Cariprazine hydrochloride, 5.0 g Eudragit E PO, 25 ml ethanol and 25 ml MDC. The reaction mixture was stirred at 25-30°C to get a clear solution. The solvent was removed under reduced pressure at 40-45°C to get solid premix.
Yield- 10 g
The X-ray analysis of the residue gave featureless diffractogram showing the residue was amorphous.

Example 2

Amorphous pre-mix of Cariprazine hydrochloride and Eudragit

Charged 5.0 g of Cariprazine hydrochloride, 5.0 g Eudragit E PO, 25 ml ethanol and 25 ml MDC. The reaction mixture was stirred at 25-30°C to get a clear solution. The solvent was removed under reduced pressure at 30°C to get solid premix.
Yield -10 g.

The X-ray analysis of the residue gave featureless diffractogram showing the residue was amorphous.

Example 3

Amorphous pre- mix of Cariprazine hydrochloride and Eudragit

Charged 5.0 g of Cariprazine hydrochloride, 5.0 g Eudragit E PO, 25 ml dimethylacetamide and 25 ml MDC. The reaction mixture was stirred at 25-30°C to get a clear solution. The solvent was removed under reduced pressure at 30°C to get solid premix.

Yield -10 g.

The X-ray analysis of the residue gave featureless diffractogram showing the residue was amorphous.

Example 4

Amorphous Cariprazine hydrochloride

Cariprazine hydrochloride (5.0 grams) was dissolved in water (200 ml) and filtered. The clear solution was then freeze dried (lyophilized) to get amorphous Cariprazine hydrochloride.

The X-ray analysis of the residue gave featureless diffractogram showing the residue was amorphous.

Example 5

Amorphous pre-mix of Cariprazine hydrochloride and Lactose

Cariprazine hydrochloride (2.5 grams) and lactose monohydrate (2.5 grams) were stirred in a 1:1 water/ethanol mixture (100 ml) in a round bottom flask until complete dissolution was achieved. The solution was then spray-dried, producing a residue to obtain a co-precipitate of the Cariprazine hydrochloride and the lactose.

The X-ray analysis of the residue gave featureless diffractogram showing the residue was amorphous.

Example 6

Preparation of Amorphous Form of Cariprazine hydrochloride

Cariprazine hydrochloride (1.0 g) and acetone (160 mL) were charged in to a round-bottom flask at 25-35° C. The contents were heated to 40-53°C and stirred to dissolve Cariprazine hydrochloride completely. The resulting solution was evaporated completely at 40-45°C under reduced pressure to afford Amorphous Form of Cariprazine hydrochloride.

Yield -900 mg.

The X-ray analysis of the residue gave featureless diffractogram showing the residue was amorphous.

Example 7

Preparation of a Solid Dispersion of Amorphous Cariprazine hydrochloride with Povidone (1:1)

Cariprazine hydrochloride (7.0 g), Povidone K-90 (7.0 g) and ethanol (700 mL) were charged in to a round-bottom flask at 27°C. The contents were stirred at 27°C to obtain clear solution. The resulting solution was evaporated completely at 50-55°C under reduced pressure to afford solid dispersion of Amorphous Cariprazine hydrochloride.

Yield -12.0 g

The X-ray analysis of the residue gave featureless diffractogram showing the residue was amorphous.

We claim,

1. Amorphous form of Cariprazine hydrochloride.

2. A process for preparation of amorphous form of Cariprazine hydrochloride comprises the following steps;
   a) dissolving Cariprazine hydrochloride in a solvent;
   b) evaporating the solvent; and
   c) isolating amorphous Cariprazine hydrochloride.

3. The process as claimed in claim 2, wherein, the solvent is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol, acetone, water, formic acid, dimethyl sulfoxide, dimethylformamide, dimethylacetamide, 2-methyl tetrahydrofuran, N-methyl-2- pyrrolidone, and mixtures thereof.

4. The process as claimed in claim 2, wherein, the amorphous Cariprazine hydrochloride is optionally obtained by the addition of anti-solvent.

5. The process as claimed in claim 4, wherein, the anti-solvent is selected from the group consisting of water, dichloromethane and mixtures thereof.

6. The process as claimed in claim 2, wherein, the isolation of amorphous Cariprazine hydrochloride is achieved by filtering and drying the precipitate, distillation, spray drying, lyophilization, or agitated thin film drying.

7. The process as claimed in claim 2, wherein, the Cariprazine hydrochloride used in step (a) is selected from Cariprazine hydrochloride or its known polymorphic forms.

8. Amorphous Cariprazine hydrochloride premix comprising Cariprazine hydrochloride and one or more pharmaceutically acceptable premixing agents.

9. The Cariprazine hydrochloride premix as claimed in claim 8, wherein, the pharmaceutical premixing agents are selected from the group consisting of polyvinylpyrrolidone (also called povidone), co-polymers of PVP and vinyl acetate such as copovidone (e.g. Kollidon VA 64 polyvinyl alcohol, polyethylene glycol, polyol (Mannitol), sodium starch glycolate, colloidal silicon dioxide(aerosil), hydroxypropyl methylcellulose, low substituted hydroxypropylcellulose, hydroxypropylcellulose, methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethylcellulose, polyvinyl acetate, Eudragit, cyclodextrins, gelatins, hypromellose phthalate, sugars, and combinations thereof.

10. The amorphous Cariprazine hydrochloride premix as claimed in claim 9, wherein, the weight ratio of Cariprazine and premixing agent may range from 1:10 to 10: 1.

11. A process for preparation of premix of amorphous Cariprazine hydrochloride comprising steps of;
    a) dissolving Cariprazine hydrochloride and pharmaceutically acceptable excipients in a suitable solvent;
    b) removing the solvent from the solution obtained in step (a) to obtain premix; and
    c) drying the premix of Cariprazine hydrochloride.

12. The process as claimed in claim 11, wherein, the solvent is selected from a group consisting of polar solvents such as C1-C4 alcohols; chlorinated organic solvents such as chloroform, dichloromethane, ethylene dichloride alone or in combination.

13. The process as claimed in claim 11, wherein, the dissolution temperatures may range from about 10°C to about reflux temperature of the solvent.

14. The process as claimed in claim 2, wherein solvent is removed by techniques such as distillation, evaporation, spray drying, spray coating, lyophilisation. sublimation (typically under vacuum) and desorption or freeze drying.

15. A pharmaceutical composition comprising amorphous Cariprazine hydrochloride premix as claimed in claim 8 along with one or more pharmaceutical excipients.

16. The pharmaceutical composition as claimed in claim 15, wherein the composition is formulated into various dosage forms selected from powder, granules, capsules, tablets, pellets.

17. A Pharmaceutical complex of Cariprazine hydrochloride and cyclodextrin.

18. The pharmaceutical complex as claimed in claim 17, wherein, the cyclodextrin is selected from the group consisting of a- cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, and their respective derivatives.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2018/05Q385

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D295/135 A61P25/18 A61K31/495
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BRUNO C HANCOCK ET AL: "Characteri sti cs and Si gni f i cance of the Amorphous State i n Pharmaceuti cal Systems" , JOURNAL OF PHARMACEUTICAL SCI ENCES, vol . 86, no. 1, 1 January 1997 (1997-01-01) , pages 1-12, XP055274556, DOI : 10. 1021/J S9601896 the whole document ----- -/ - -	1-18

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2018	21/08/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Papathoma, Sofi a

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2018/05Q385

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2018/05Q385

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Al lergan : "VRAYLAR(TM) (cari prazi ne) capsul es, for oral use" , , 1 June 2015 (2015-06-01) , pages 1-30, XP055497846, Retri eved from the Internet: URLrhttps ://www. accessdata.fda.gov/drugsat fda _docs/l abel /2015/2043701bl .pdf [retri eved on 2018-08-07]	1
Y	the whole document i n parti cular page 19	2-18

Y	W0 2015/056164 Al (CHEM0 RES S L [ES]) 23 Apri l 2015 (2015-04-23) the whole document i n parti cular example 7	2-7

X	W0 2011/073705 Al (RICHTER GEDE0N NYRT [HU] ; CZIBULA LASZL0 [HU] ; JUHASZ BALINT [HU] ; AGA) 23 June 2011 (2011-06-23)	1-3,6,7
Y	the whole document i n parti cular example 5 and 6	2-7

Y	CN 106 560 179 A (CSPC PHARMACEUTICAL ZH0NGQI PHARMACEUTICAL TECH CO LTD) 12 Apri l 2017 (2017-04-12) the whole document	8-16

Y	SUNI L S. JAMBHEKAR ET AL: "Cyclodextrins i n pharmaceuti cal formulations I : structure and physi cochemi cal properti es, formation of compl exes, and types of compl ex" , DRUG DISCOVERY TODAY, vol . 21, no. 2 , 1 February 2016 (2016-02-01) , pages 356-362, XP055497919 , AMSTERDAM, NL ISSN : 1359-6446, D0I : 10. 1016/j .drudi s.2015 .11.017 the whole document	17 , 18

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2018/05Q385

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015056164 A1	23-04-2015	EP 3057942 A1	24-08-2016
		ES 2640137 T3	31-10-2017
		HR P20171172 T1	20-10-2017
		IL 245101 A	31-07-2018
		SI 3057942 T1	30-11-2017
		US 2016257661 A1	08-09-2016
		WO 2015056164 A1	23-04-2015
WO 2011073705 A1	23-06-2011	TW 201144289 A	16-12-2011
		W0 2011073705 A1	23-06-2011
CN 106560179 A	12-04-2017	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-18

Cariprazine hydrochloride in amorphous form, a process for its preparation, a premix thereof, a process for the preparation of said premix and pharmaceutical compositions of said premix and a pharmaceutical complex of Cariprazine hydrochloride and cyclodextrin.

1.1. claims: 2-7(completely); 1 (partially)

Cariprazine hydrochloride in amorphous form and a process for its preparation.

1.2. claims: 8-16(completely); 1(partially)

Cariprazine hydrochloride in amorphous form, premixes thereof, a process for the preparation of said premixes and pharmaceutical compositions of said premixes.

1.3. claims: 17, 18 (completely); 1(partially)

Complexes of Cariprazine hydrochloride and cyclodextrin.
