Public assessment report for pharmaceutical medicinal product
Reagila® (Cariprazine hydrochloride)
27th March 2019, Division of Health Product Enterprise Services,
Thai Food and Drug Administration

Name of product	Cariprazine, Reagila®
Active Substance(s) **(ATC code)**	INN: Cariprazine (N05AX15)
Pharmaceutical form	Hard capsule
Strength	Cariprazine capsule 1.5, 3, 4.5 and 6 mg
Route(s) of administration	Oral administration
Therapeutic indication(s)	**Indication as stated in SmPC:** Reagila® is indicated for the treatment of schizophrenia in adult patients. **Indications as stated in the patient information leaflet (PIL):** ใช้เพื่อรักษาโรคจิตเภทในผู้ใหญ่
Submitted number and date of submission	1C 15075/61 (N), 1C 15076/61 (N), 1C 15077/61 (N), 1C 15078/61 (N) 20 August 2018
E-Identifier Number	E6100033

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Public assessment report for Cariprazine hydrochloride 1.5, 3, 4.5 and 6 mg

Submitted number: 1C 15075/61 (N), 1C 15076/61 (N),

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Part 1: Introduction and summary review

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. People with schizophrenia may seem like they have lost touch with reality. Although schizophrenia is not as common as other mental disorders, the symptoms can be very disabling. Symptoms of schizophrenia usually start between ages 16 and 30.[1]

Pathology of schizophrenia including ; overactivity of the mesolimbic pathway may trigger positive symptoms (hallucinations, delusions), the dopamine theory of negative and cognitive symptoms suggests that there is a hypofunction of dopaminergic neurotransmission in the mesocortical pathway.

The symptoms of schizophrenia fall into three categories : positive (hallucinations, delusions, thought disorders, movement disorders), negative (reduced expression of emotions via facial expression or voice tone), and cognitive (poor executive functioning, trouble focusing or paying attention, problems with working memory).[2]

Antipsychotic drugs have been marketed in Thailand by several MAHs such as first generation of antipsychotics have common feature of D2 antagonist and have problems of extrapyramidal AEs (e.g. Parkinsonism, akathisia, dyskinesia), current guidelines recommend atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole) which has dual mode of action (D2 antagonist plus 5-HT antagonist) as first-line treatment but efficacy in negative or cognitive symptoms are limited (up to 40% of patients do not respond at all).

Reagila or cariprazine hydrochloride is the new generation antipsychotic and displays high-affinity for dopamine D3 receptor and lower affinity for D2 receptor. The manufacturing site of drug substance and drug product is Gedeon Richter PLC.,Hungary. It was approved in US FDA and EMA. The clinical trial data showed Cariprazine hydrochloride has efficacy to treat schizophrenia in adult patients.

Part 2: Summary of the dossier

2.1 Type of marketing authorization application

Product type: New chemical entity

Application type: Stand alone application

Review method: Abbreviated assessment; un-redacted evaluation report from EMA

2.2 Administrative data

2.2.1 Product

Name of Product: Invented name	Cariprazine, Reagila®
Active Substance(s)	Cariprazine hydrochloride
Strength	Cariprazine capsule 1.5, 3, 4.5 and 6 mg
Therapeutic class **(ATC Code)**	Other antipsychotics (N05AX15)
Pharmaceutical form	Hard capsule
Route of administration	Oral administration
Drug Characteristics	White to yellowish white powder.
Packaging	Primary packaging Transparent hard PVC/PE/PVDC blister heat-sealed with hard aluminium foil backing. Secondary packaging The blisters are packed into folded carton with a patient leaflet.
Package size(s)	Each blister contains 7 capsules and 4 blisters is delivered in each box .

2.2.2 Source

- Name and address of the applicant for importation

Mitsubishi Tanabe Pharma (THAILAND) CO. LTD, 63 Athenee Tower Room No. 1203, 12th Floor, Soi Ruamrudee, Wireless Road, Lumpini, Pathumwan, Bangkok 10330, Thailand

- Name and address of the manufacturer(s) of the dosage form

Gedeon Richter Plc. , Budapest, Hungary

- Name and address of the packaging and the secondary packaging

The same as stated in the name and address of the manufacturer

- Name and address of the manufacturer(s) which take responsibility on inspection before release

The same as stated in the name and address of the manufacturer

Evaluation results

Gedeon Richter Plc. , was licensed as manufacturer for modern medicine used in human. The manufacturer has been permitted both in sterile products and non-sterile products. The manufacturer has been certified GMP compliance by National Institute of Pharmacy, Hungary; membered of PIC/s.

Market authorization holder, Mitsubishi Tanabe Pharma (THAILAND) Co., Ltd, also attached GMP clearance certificate approved by Bureau of drug control, Thai FDA. It performs manufacturer has standard manufacturing process which is equivalent standard control in Thailand.

Part 3: Analytical Physico-Chemical, Biological and Microbiological Documentation

3.1 Drug substance

3.1.1 General information

3.1.1.1 Nomenclature:

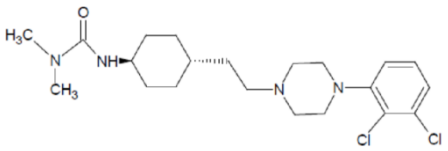
INN name: Cariprazine

Chemical names: trans-N-{4-[2-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-N',N'-dimethylurea hydrochloride

3.1.1.2 Structure

Structural formula:

Molecular



formula: $C_{21}H_{32}Cl_2N_4O$. HCL (463.87 g/mol)

3.1.1.3 General Properties

Physical appearance: White or almost white crystalline powder

Melting point: Degradation occurs before melting

Solubility :

Solvent	Solubility class

Iso-Propanol	Practically insoluble
N,N-Dimethylformamide	
Acetone	Very slightly soluble
Acetonitrile	
Water	
Dichloromethane	Slightly soluble
Ethanol	
Methanol	Freely soluble

Hygroscopicity : Cariprazine hydrochloride is non-hygroscopic**.**

3.1.2 Manufacture

3.1.2.1 Manufacturer(s)

The Manufacturer is in Hungary, where has worked in manufacturing process and process controls.

3.1.2.2 Description of Manufacturing Process and Controls

The synthesis of the active substance is described in five stages, which comprise three synthetic steps.

Evaluation results

Cariprazine hydrochloride was manufactured in Hungary. The manufacturer has valid GMP certified by National Institute of Pharmacy and Nutrition, Hungary. Manufacturing process and quality control is suitable by identification of critical steps in process and control including process validation, so all of documents confirm that drug substance manufacturing processes are reliable suitable and acceptable.

3.1.4 Control of drug substance

Manufacturer defined specification of cariprazine drug substance and analytical method and also validation of analytical procedures.

Validation of Analytical Procedures

The manufacturer reported the validation parameter of cariprazine hydrochloride as below:

1. Particle size distribution
2. Identification
3. Metal residue
4. Related substance
5. Residual solvents
6. Microbiological purity
7. Assay

Batch analysis

The results from COAs of commercial batches shows the results are met all of the specification criteria described in “Test and specifications”

Evaluation result

Specification, analytical method of drug substance were followed by European Pharmacopeia and in-house method were also evaluated by method validation on suitable parameters. In addition, manufacturer tested consistency on 3 batches the results shows all batches were consistency. Then all can summarized that manufacturing process, analytical method and process validation of drug substance was reliable, suitable and acceptable.

3.1.5 Container closure system

The container closure system for drug substance was stated in stability data. The packaging of drug substance is a double polyethylene bags closed with plastic bands. The suitability of these packaging materials is verified by stability testing**.**

Evaluation result

Drug substance contained in standard container is suitable, reliable and acceptable**.**

3.1.7 Stability

Stability data on 10 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package, double PE bag and cardboard box, for up to 60 months under long term conditions at 25°C ± 2°C/60% ± 5% RH and for up to 6 months under accelerated conditions at 40°C± 2°C / 75%± 5% RH according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch.

The following parameters were tested : characters, loss on drying, related substances, and assay. Supplementary tests as microbiological purity and polymorphic testing are performed at the start and after 60 months (long-term conditions). The analytical methods used were the same as for release and are stability indicating.

Evaluation results

Number of batch, condition, duration and parameters followed by ICH guideline are suitable**.** The stability results indicate that the active substance manufactured by the proposed suppliers sufficiently stable in the proposed container**.**

3.2 Drug product

3.2.1 Manufacture

The manufacturer of the drug product is Gedeon Richter Plc., Budapest (Hungary). The GMP certificate issued by the competent authority of Hungary.

Table shows Address and responsibility of the manufacturer

Address	Responsibility
Gedeon Richter Plc. Gyomroi ut 19-21, Budapest H-1103	Manufacture Cariprazine hard capsules, Analytical testing, Batch release, Primary

Postal address : Budapest. P.O.B.27, H 1475 Hungary	and secondary packaging, Storage and distribution

Batch Formula

Components	Quality Standard Reference
Cariprazine hydrochloride	In-house
Starch, pregelatinised (maize)	EP 9.0
Magnesium stearate	EP 9.0

Evaluation result

Gedeon Richter Plc. is suitable and acceptable manufacturer. They show valid certificate of GMP compliance of a manufacturer from competent authority of Hungary. The process is considered to be a standard manufacturing process. The in-process controls are adequate for controlling these steps. Major steps of manufacturing process have been validated. It has been demonstrated that the manufacturing process is capable of producing the drug product of intended quality in a reproducible manner.

3.2.2 Description and Composition of the drug product

The drug product is presented in size 4 (1.5 mg, 3 mg and 4.5 mg) or size 3 (6 mg) hard capsules filled with a white to yellowish white powder mixture. It is available in blister made of transparent hard PVC/PE/PVDC blister foil heat-sealed with hard aluminium foil backing.

Components	Quality Standard Reference	Function
Cariprazine* hydrochloride	In-house specification	Active ingredient
Starch, pregelatinised (maize)	Ph.Eur 9.0	Diluent, disintegrant
Magnesium stearate	Ph.Eur 9.0	Lubricant

*Expressed as cariprazine hydrochloride salt equivalent to 1.5 mg, 3 mg, 4.5 mg, 6 mg free-base.

Evaluation results

The formulation including active ingredient and excipients is complied with Ph.Eur and in-house specification that show formulation has standard and acceptable. Moreover they have no use of novel excipients in the formulation.

3.2.3 Control of drug product

Drug product has quality control by specification, analytical method and validation method. Moreover, the quality control of drug product has analytical method and validation method to assure their qualities in each lots

There are 3 batches in each dose of the drug product (Cariprazine 1.5 mg, 3 mg, 4.5 mg, 6 mg) for process validation. All results comply with specifications.

Evaluation results

There are specifications, analytical method and process validation. All of them conducted by acceptable standard. Manufacturing process of drug product follow Ph.Eur and in-house verified by analytical validation. Moreover, Manufacturer identify in process control in each steps for consistency. Overall we can summarise that manufacturing process of drug product is suitable, reliable, consistent and acceptable.

3.2.4 Container closure system

The primary packaging consists of double polyethylene bags. The specification of polyethylene bags complied by European Pharmacopoeia current edition. The polyethylene bag is provided by Gedeon Richter and certified.

Evaluation result

Quality of container closure system of drug product comply with European Pharmacopoeia. MAH attached certificate of analysis data for considering, All results comply with the proposed specification. Then we can summarize that container closure of drug product is suitable and acceptable.

3.2.5 Stability

The stability study was started to test the quality of the drug product under the following conditions.

Test	Condition	Packaging	Batch size (Capsules)	No. of batch	Time (month)
Long term storage	30 ± 2°C , 75 ± 5%RH	Transparent PVC/PE/PVDC//Al blister	200,000	3 batches	0,3,6,9,12,18,24,36,48, 60 months
Accelerated	40 ± 2°C , 75 ± 5%RH	Transparent PVC/PE/PVDC//Al blister	200,000	3 batches	0, 3, 6 months
Photostability	25 ± 2°C , Ambient RH	Transparent PVC/PE/PVDC//Al blister	979,000	1 batch	1.2 mil.Lux.hr

At the 36-month and at last 60-month stability point of the long-term stability study all three batches of four strengths were tested for all parameters prescribed in the protocol.

Evaluation results

Stability test of drug product including number of batch, condition, duration and parameters is suitable. Drug product stability protocol conforms with ASEAN Guideline. So, the proposed shelf-life of 36 months keeping the blister in the outer carton in order to protect from light, do not store above 30°C is acceptable.

Assessor's conclusions on Quality

The evaluating result of un-redacted assessment report from EMA and analyzing in Thai-Asian environment and regulation can summarize that the critical points involving efficacy and safety had been clarified already. Moreover, the expert committee meeting on 27th March 2019 summarized in the similarly results. Then overall in the quality data on manufacturing and quality control of drug substances and drug product is acceptable.

Part 4: Non-clinical documentation

4.1 Pharmacology

4.1.1 *Primary pharmacodynamics studies*

The mechanism of action of cariprazine, as with other medicines having efficacy in schizophrenia, is not fully understood. However, the therapeutic effect of cariprazine may be mediated through a combination of partial agonist activity at dopamine D3, D2L and D2S receptors and serotonin 5-HT1A receptors, and antagonist activity at serotonin.

4.1.2 *Safety Pharmacology*

Cariprazine is no significant effects on QT or other ECG parameters and no major effects on the respiratory, renal, or gastrointestinal systems.

4.2 Pharmacokinetic

Absorption

Cariprazine is rapidly and extensively absorbed in rats and dogs. The oral bioavailability is approximately 52-63 **%** in rats and 64-80**%** in dogs, indicating some first pass effect during the oral absorption of Cariprazine. No food effect is observed.

Distribution

Cariprazine can readily enter CNS (brain-to-plasma AUC ratio 7.6-10.9). In vitro plasma protein binding in human, dog, and rat plasma is approximately 96**%** over a wide range of concentrations without an apparent concentration-dependent effect.

Metabolism

CYP3A4 and CYP2D6 are enzymes involved in the metabolism of Cariprazine and its major active metabolites (DCAR and DDCAR). Cariprazine has weak inhibitory effect on CYP2D6 enzymes, and metabolites have no inhibitory effect on them. Cariprazine and

metabolites have no significant induction effects on CYP1A2, CYP2D6 and 3A4.

Excretion

The primary elimination route of cariprazine and its metabolites is biliary (app. 77% in rats and 62% in dogs).

4.3 Toxicology

4.3.1 *Single dose*

The minimal lethal oral dose in mice and female rats was 100 mg/kg and male rats was 200 mg/kg. Drug-related clinical findings preceding death in both mice and rats included lethargy, ataxia, hunched posture, decreased activity, palpebral closure and hypothermia.

4.3.2 *Repeated dose*

Cariprazine has been evaluated in repeat-dose toxicity studies in mice, Wistar rats and beagle dogs. Clinical signs in the repeat-dose toxicity studies were mainly neurologic in nature and included tremor, disorientation, abnormal gait, decreased motor activity, flat body posture, limb abduction, lower lip retraction, increased or decreased muscle tone, back muscle contraction, hunched posture, lethargy, piloerection, brown/yellow fur staining, and chromodacryorrhea. The main toxic changes are phospholipidosis, decrease in body weight, appearance of CNS clinical signs.

4.3.3 *Genotoxicity*

Cariprazine was not mutagenic in the bacterial reverse mutation or in the human lymphocyte chromosomal aberrations assays in vitro. In vivo mouse micronucleus assay is also negative.

4.3.4 *Carcinogenicity*

The carcinogenic potential of cariprazine was evaluated in a 28-week study in mice and 2-year carcinogenicity study in Wistar rats. In the 28-week study, there were no significant increase in neoplastic changes due to cariprazine treatment. In the 2-year rat study, there were no statistically significant increases in the incidence of tumor.

4.3.5 *Reproductive and developmental*

There are study in female rats and male rats for fertility and early embryonic development, rat and rabbit study for embryo-fetal development and pre/post –natal development study was conducted only in pregnant rat.

The results of fertility were lower fertility and conception indices in female. No effect was observed in male rats. The results of embryo-fetal development met malformations and variations in rats, in rabbits there were no teratogenic effect. The results of pre/post –natal development met toxicities such as total litter loss, reduced viability and weight, absence of milk in stomuch of early decedents.

Assessor's conclusions on Non-clinical

Non-clinical data could summarize that study design, number of laboratory animals

were suitable and the results were reliable. Toxicity study followed by good laboratory practice and unmet unexpected toxicity. The expert committee meeting on 27th March 2019 summarized in the similarly results as un-redacted assessment report from EMA that overall in non-clinical data was suitable and acceptable.

Part 5: Clinical Study Reports

The Proposed indication of Cariprazine hydrochloride is indicated for the treatment of schizophrenia in adult patients. The clinical data can be summarized as below table

Table : Summary of efficacy results from the main studies supporting the present application

No.	Study	Subjective/ Primary Objective	Study design	Intervention	Result
1. RGH-MD-04	A double-blind, Placebo and active-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia	Schizophrenia/ Reduction of PANSS total score	Multicenter, multinational, randomized, double-blind, placebo and active-controlled, parallel group, fixed-dose study in adult patients who had a primary diagnosis of schizophrenia	Group 1: cariprazine 3 mg Group 2: cariprazine 6 mg Group 3: Aripiprazole 10 mg Group 4: Placebo Duration 6 weeks	PANSS-T change from baseline to endpoint (6 weeks) 1. Cariprazine 3 mg : -20.2 (p-value 0.0044) 2. Cariprazine 6 mg : -23.0 (p-value < 0.0001) 3. Placebo : -14.3 4. Aripriprazole : -21.2 (p-value 0.0008)
2.RGH-MD-05	A double-blind, Placebo -controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia	Schizophrenia/ Reduction of PANSS total score	Multicenter, multinational, randomized, double-blind, placebo -controlled, parallel group, fixed/flexible-dose study in adult patients who had a primary diagnosis of	Group 1: cariprazine 3-6 mg/day Group 2: cariprazine 6-9 mg/day Group 3: Placebo Duration 6 weeks	PANSS-T change from baseline to endpoint (6 weeks) 1. Cariprazine 3-6 mg : -20.2 (p-value 0.0044) 2. Cariprazine 6 mg : -23.0 (p-value < 0.0001) 3. Placebo : -14.3

			schizophrenia		4. Aripriprazole : -21.2 (p-value 0.0008)
3. RGH MD-16	Evaluation of the safety and efficacy of RGH-188 in acute exacerbation of schizophrenia	Schizophrenia/ Reduction of PANSS total score	Multicenter, multinational, randomized, double-blind, placebo and active-controlled, parallel group, fixed-dose study in adult patients who had a primary diagnosis of schizophrenia	Group 1: cariprazine 1.5 mg Group 2: cariprazine 3 mg Group 3: cariprazine 4.5 mg Group 4: risperidone 4 mg Duration 6 weeks	PANSS-T change from baseline to endpoint (6 weeks) 1 cariprazine 1.5 mg : -17.3 2 cariprazine 3 mg : -18.7 3 cariprazine 4.5 mg : -20.2 4 risperidone 4 mg : -25.3 5. Placebo : -9.5
4. RGH-MD-06	A Randomized, double-blind, Placebo-controlled, Parallel-group study of cariprazine in the Prevention of relapse in patients with schizophrenia	Schizophrenia/ Time to relapse	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible- and fixed-dose study evaluating time to relapse in adult patients who had a primary diagnosis of schizophrenia and had received cariprazine in the open-label phase (OLP) of the study. Patients were allowed to progress from run-in to stabilisation and from stabilisation to double-blind only if	Group 1: cariprazine 3-9 mg/day Group 2: Placebo Duration 26-72 weeks	p-value for superiority of cariprazine vs placebo using logrank test = 0.001

			responders and tolerators.		
5. RGH-188-005	A Randomized, double-blind, parallel-group study to investigate the efficacy, safety, and tolerability of cariprazine in patients with predominant negative symptoms of schizophrenia	Schizophrenia / Reduction of PANSS total score	Multicenter, randomized, double-blind, active-controlled, parallel-group, fixed/flexible dose, 26-week study in adults with a primary diagnosis of schizophrenia and with predominant negative symptoms	Group 1: cariprazine (4.5 mg, range 3-6) Group 2: risperidone (4 mg, range 3-6) Duration 26 weeks	PANSS Factor Score for Negative Symptoms change from Baseline to endpoint 1. cariprazine : -8.9 ± 0.3 2. risperidone : -7.4 ± 0.4 p-value for superiority of cariprazine vs risperidone = 0.002

Clinical studies are divided in 3 parts

1. Clinical Pharmacokinetic

Absorption

Administration of a high-fat breakfast delayed the absorption of cariprazine. The effect of food on the exposure of DCAR and DDCAR metabolites was also minimal but had no significant effect on the drug exposure .

Distribution

Cariprazine is highly bound to plasma proteins with an unbound fraction of 0.04. The metabolites DCAR and DDACR have unbound fractions of 0.05 and 0.07, respectively.

Elimination

The half-life of cariprazine is between 1 and 3 days. The metabolites DCAR has a half-life of 1 to 2 days and DDCAR half-life is ranging between 2 to 3 weeks. Based on population PK analysis, the effective half-life leading to steady state is about 1 to 1.5 day for cariprazine and DCAR and 6 to 9 days for DDCAR. Approximately 90**%** of steady state is reached in about 4 to 5 days for cariprazine and DCAR and 21 to 31 days for DDCAR.

Excretion

The overall average daily excretion of cariprazine and its metabolites in urine was 21% of the daily dose. Approximately 1.2% of the daily dose was excreted in urine as unchanged cariprazine. The major metabolite excreted in urine was DDCPPC acid and it accounted for approximately 6.6% of the daily dose. Approximately 4.0 and 0.4% of the daily dose were excreted as the DDCAR and DCAR metabolites in urine, respectively.

2. Clinical efficacy

To support proposed indication, treatment of schizophrenia in adult patient, clinical efficacy studies are divided in 3 main parts including study in acute schizophrenia, study in predominant negative schizophrenia (PNS) and study in maintainance schizophrenia.

2.1 ***Study in acute schizophrenia*** *(**RGH-MD-04, RGH-MD-05 and RGH-MD-16**)*

2.1.1 RGH-MD-04 : A double-blind, placebo and active-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia.

Objectives : The objective of this study was to evaluate the efficacy, safety, and tolerability of cariprazine relative to placebo in patients with acute exacerbation of schizophrenia.

Outcomes/endpoints : The primary efficacy variable was change from baseline in the PANSS total score at week 6.

The results : Change form baseline to week 6 in PANSS total score (MMRM) -ITT population

	Placebo (N = 149)	*Cariprazine, mg/day*		*Aripiprazole 10.0 mg/day (N = 150)*
		3.0 (N = 151)	*6.0 (N = 154)*	
Baseline PANSS total score, mean ± SD	96.5 ± 9.1	96.1 ± 8.7	95.7 ± 9.4	95.6 ± 9.0
Change at Week 6				
LS mean (SE)	−14.3 (1.5)	−20.2 (1.5)	−23.0 (1.5)	−21.2 (1.4)
LSMD (95% CI) versus placebo	—	−6.0 (−10.1, −1.9)	−8.8 (−12.9, −4.7)	−7.0 (−11.0, −2.9)
p–value[a]	—	0.0044	< 0.0001	0.0008
Adjusted p–value[b]	—	0.0044	< 0.0001	—

a P-values are from an MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and baseline value and baseline-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within–patient scores.

b Adjusted P-values = adjusted by matched parallel gatekeeping procedure.

CI = confidence interval; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; N = number of patients in the Intent-to-Treat Population; PANSS = Positive and Negative Syndrome Scale.

2.1.2 RGH-MD-05 : A double-blind placebo-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia.

Objective : The objective of this study was to evaluate the safety, efficacy and tolerability of cariprazine relative to placebo in patients with acute exacerbation of schizophrenia.

Outcomes/endpoints : The primary efficacy variable was change from baseline in the PANSS total score at week 6.

The results : Change form baseline to week 6 in PANSS total score (MMRM) -ITT population

	Placebo (N = 145)	*Cariprazine 3-6 mg/day (N = 147)*	*Cariprazine 6-9 mg/day (N = 147)*
Baseline PANSS total score, Mean ± SD	96.6 ± 9.3	96.3 ± 9.3	96.3 ± 9.0
Change at Week 6			
LS mean (SE)	−16.0 (1.6)	−22.8 (1.6)	−25.9 (1.7)
LSMD vs placebo (95% CI)	—	−6.8 (−11.3, −2.4)	−9.9 (−14.5, −5.3)
p-value[a]	—	0.0029	< 0.0001
Adjusted p-value[b]	—	0.0029	< 0.0001

a P-values are from an MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and baseline value and baseline-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within–patient scores.

b Adjusted p-values = adjusted by matched parallel gatekeeping procedure.

CI = confidence interval; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; N = number of patients in the Intent-to-Treat Population; PANSS = Positive and Negative Syndrome Scale; SE = standard error of the LS mean.

2.1.3 RGH-MD-16 : Evaluation of the safety and efficacy of RGH-188 in the acute

exacerbation of schizophrenia.

Objective : The objective of this study was to evaluate the safety, efficacy and tolerability of RGh-188 (cariprazine) relative to placebo in patients with acute exacerbation of schizophrenia.

Outcomes/endpoints : The primary efficacy variable was change from baseline in the PANSS total score at week 6.

The results : Change from baseline to week 6 in the PANSS-T score (LOCF)-ITT population:

	Placebo (N = 148)	*Cariprazine, mg/day*			*Risperidone 4.0 mg/day N = 138)*	*p-Value[a]*
		1.5 (N = 140)	*3.0 (N = 140)*	*4.5 (N = 145)*		
Baseline, mean ± SEM	97.3 ± 0.8	97.1 ± 0.8	97.2 ± 0.7	96.7 ± 0.8	98.1 ± 0.8	
Change at Week 6, mean ± SEM	–9.5 ± 1.6	–17.3 ± 1.7	–18.7 ± 1.8	–20.2 ± 1.6	–25.3 ± 1.7	< 0.0001
LSMD (95% CI)[b]	—	–7.5 (–11.8, –3.3)	–8.8 (–13.1, –4.6)	–10.4 (–14.6, –6.2)	–15.0 (–19.4, –10.8)	
p-Value[b]	—	0.0005	< 0.0001	< 0.0001	< 0.0001	

Note: p-Values were based on an ANCOVA model for change from baseline, with treatment group and pooled study center as factors and the baseline value as a covariate.

a p-Value for the comparison of the average effect of cariprazine 3.0 mg/day and cariprazine 4.5 mg/day with that of placebo.

b Comparison of the corresponding treatment group to placebo.

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LSMD = least squares mean difference; PANSS = Positive and Negative Syndrome Scale.

Summary (RGH-MD-04, RGH-MD-04 and RGH-MD-16) : Cariprazine change PANSS total from baseline significantly when compare placebo (P<0.01)

2.2 *Study in* predominant negative schizophrenia (RGH-188-005)

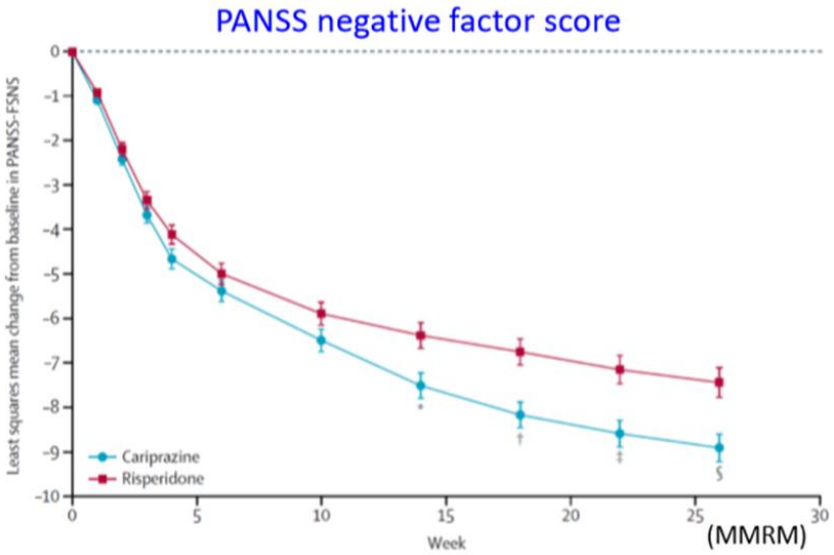
2.2.1 RGH-188-005 : A randomized, double-blind, parallel-group study to investigate the efficacy, safety, and tolerability of cariprazine in patients with predominant negative symptoms of schizophrenia.

Objectives : The objective of this study was to evaluate the efficacy, safety, and tolerability of cariprazine for the treatment of patients with schizophrenia having predominant negative symptoms.

Outcomes/endpoints : The primary efficacy parameter was the change from baseline to endpoint in the PANSS factor score for negative symptoms.

The results : Change from baseline in the PANSS factor score for negative symptoms ITT-population

Summary (RGH-188-005): Mean change from baseline in PANSS-NFS and PSP in cariprazine



group is more than risperidone group significantly.

2.3 *Study in maintainance (RGH-MD-06)*

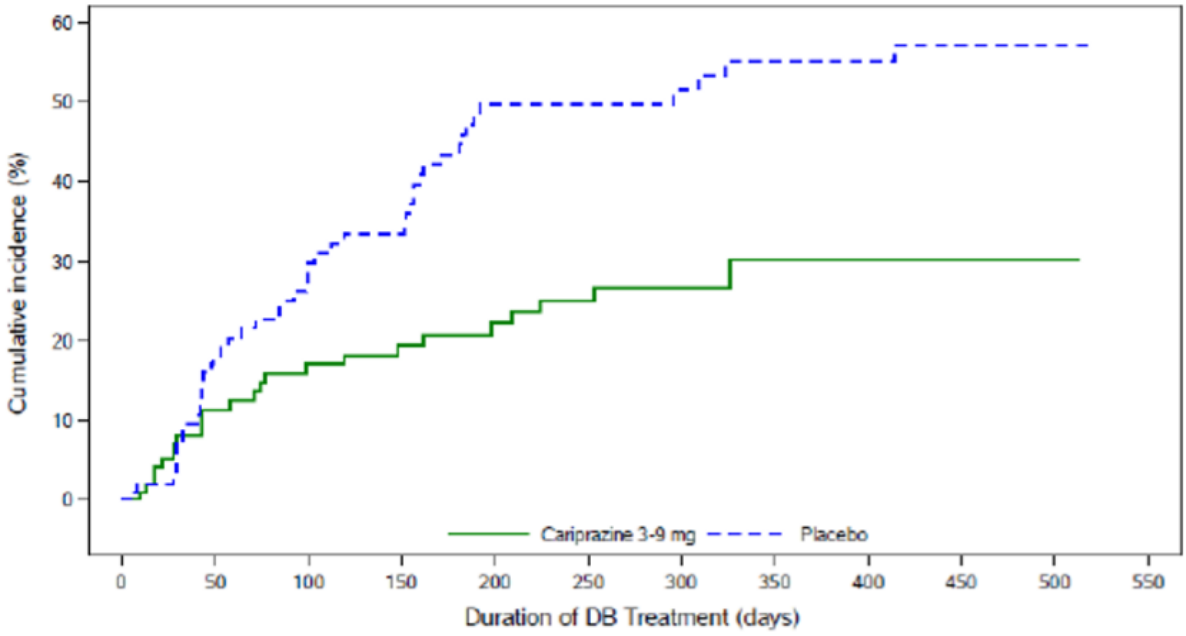
2.3.1 RGH-MD-06 : A randomized, double-blind, placebo –controlled, parallel-group study of cariprazine (RGH-188) in the prevention of relapse in patients with schizophrenia

Objectives : The objective of this study was to evaluate the efficacy and safety of cariprazine (RGH-188) relative to placebo in the prevention of relapse of symptoms in patients with schizophrenia.

Outcomes/endpoints : The primary efficacy parameter was time to first relapse during the DBP.

The results : Primary efficacy analysis **:** survival analysis summary of time to first relapse during the double-blind treatment period-double blind intent to treat population

Kaplan-Meier curves of the cumulative rate of relapse :



DB = double-blind.

b P-value is based on the log-rank test.

c Hazard ratio (cariprazine 3-9 mg vs placebo) is based on Cox proportional hazards regression model, with treatment group as an explanatory variable.

CI = confidence interval.

Summary (**RGH-MD-06**) **:** Incidence of cariprazine group is less than placebo group significantly**.**

3. Clinical safety

3**.**1 The most frequency TEAEs (defined as occurring in more than 10**%** of patient) were Akathisia, Insomnia, Headache and EPS as below table

Table show incidence of adverse event in each Cariprazine group and placebo group

Preferred term (PT)	*Placebo N=683 n (%)*	*Cariprazine 1.5–6 mg N=2048 n (%)*	*Cariprazine 9–12 mg N=741 n (%)*	*Cariprazine overall N=2728 n (%)*
Patients with at least one AE	**467 (68.4)**	**1569 (76.6)**	**610 (82.3)**	**2137 (78.3)**
Gastrointestinal disorders				
Nausea	31 (4.5)	141 (6.9)	40 (5.4)	181 (6.6)
Constipation	32 (4.7)	113 (5.5)	48 (6.5)	161 (5.9)
Dyspepsia	21 (3.1)	100 (4.9)	35 (4.7)	135 (4.9)
Vomiting	24 (3.5)	91 (4.4)	30 (4.0)	121 (4.4)
Diarrhoea	23 (3.4)	72 (3.5)	34 (4.6)	106 (3.9)
Toothache	22 (3.2)	61 (3.0)	33 (4.5)	94 (3.4)
Abdominal discomfort	16 (2.3)	41 (2.0)	24 (3.2)	65 (2.4)
Infections and infestations				
Nasopharyngitis	10 (1.5)	49 (2.4)	23 (3.1)	71 (2.6)
Investigations				
Weight increased	10 (1.5)	104 (5.1)	50 (6.7)	154 (5.6)
Blood creatine phosphokinase increased	11 (1.6)	54 (2.6)	33 (4.5)	87 (3.2)
Metabolism and nutrition disorders				
Decreased appetite	13 (1.9)	52 (2.5)	17 (2.3)	69 (2.5)
Musculoskeletal and connective tissue disorders				
Back pain	14 (2.0)	65 (3.2)	12 (1.6)	77 (2.8)
Pain in extremity	16 (2.3)	42 (2.1)	23 (3.1)	65 (2.4)
Nervous system disorders				
Akathisia	23 (3.4)	299 (14.6)	107 (14.4)	404 (14.8)
Headache	81 (11.9)	247 (12.1)	94 (12.7)	340 (12.5)
Extrapyramidal disorder	22 (3.2)	143 (7.0)	58 (7.8)	198 (7.3)
Somnolence	13 (1.9)	63 (3.1)	26 (3.5)	89 (3.3)
Psychiatric disorders				
Insomnia	69 (10.1)	287 (14.0)	94 (12.7)	379 (13.9)
Restlessness	20 (2.9)	126 (6.2)	53 (7.2)	178 (6.5)
Anxiety	27 (4.0)	141 (6.9)	32 (4.3)	172 (6.3)
Schizophrenia	60 (8.8)	101 (4.9)	41 (5.5)	142 (5.2)
Agitation	27 (4.0)	78 (3.8)	18 (2.4)	95 (3.5)
Psychotic disorder	19 (2.8)	44 (2.1)	22 (3.0)	66 (2.4)

3.2 Incidence of Extrapyramidal side effect and akathisia in each clinical trial as below table

Study	Population	Study Duration, wk	Treatment Group	Extrapyramidal Symptoms vs Extrapyramidal Disorder, n (%)	Akathisia, n (%)
Schizophrenia					
Durgam et al[4] (2014)	Acute exacerbation of schizophrenia	9	Placebo	7 (4.6)	12 (7.9)
			Cariprazine 1.5 mg/d	15 (10.3)	16 (11.0)
			Cariprazine 3 mg/d	12 (8.2)	22 (15.1)
			Cariprazine 4.5 mg/d	12 (8.2)	19 (12.9)
			Risperidone 4 mg/d	14 (10.0)	14 (10.0)
Kane et al[5] (2015)	Acute exacerbation of schizophrenia	9	Placebo	3 (2.0)	5 (3.4)
			Cariprazine 3 to 6 mg/d	8 (5.3)	24 (15.9)
			Cariprazine 6 to 9 mg/d	15 (10.1)	25 (16.9)
Durgam et al[6] (2015)	Acute exacerbation of schizophrenia	9	Placebo	...	7 (4.6)
			Cariprazine 3 mg/d	...	11 (7.1)
			Cariprazine 6 mg/d	...	23 (14.6)
			Aripiprazole 10 mg/d	...	11 (7.2)
Durgam et al[7] (2016)	Acute exacerbation of schizophrenia	6	Placebo	6 (4.7)	1 (0.8)
			Cariprazine 1.5 to 4.5 mg/d	8 (6.3)	13 (10.2)
			Cariprazine 6 to 12 mg/d	13 (9.8)	12 (9.0)
Durgam et al[8] (2016)	Relapse prevention in patients with schizophrenia	97	Open-label phase: cariprazine 3 to 9 mg/d	56 (7.3)	147 (19.2)
			Double-blind phase: placebo	3 (3.0)	3 (3.0)
			Double-blind phase: cariprazine 3 to 9 mg/d	6 (5.9)	5 (5.0)

3.3 Ocular effect

Bilateral cataract and cystic degeneration of the retina were observed in the nonclinical program. The most commonly reported ocular AE was blurred vision, for which there was an apparent dose-response relationship with cariprazine. Post-marketing experience.

As of 05 Apr 2018 , no cases were received related to ocular changes (lenticular changes and cataracts)

Summary

1. The most frequently reported ADRs with cariprazine in the dose range (1.5-6 mg) were akathisia (19%) and parkinsonism (17.5%). Most events were mild to moderate in severity.

2. Extrapyramidal side effect and akathisia was reported for the first time within the first 6 weeks of treatment.

3. Dose dependency was seen for akathisia.

Assessor's conclusions on clinical

As the information of pharmacokinetic, efficacy and safety clinical data is acceptable. The study design, population and duration is suitable for proposed indication. Regarding, the safety data, no unexpected pattern of adverse event was reported. The most common are akathisia and parkinsonism. The evaluation is consistency with assessment report from EMA. Cariprazine is quite safe in adult patient.

Part 6: Risk Management Plan

The information of RMP is valid and suitable due to the risk management had been conducted in summary of product characteristic and patient leaflet already.

Label evaluation

Registered label from Mitsubishi Tanabe Pharma (THAILAND) CO. LTD is Unit carton label and inner label following Thai FDA 2009 ANNEX 3 Package insert and labeling rule.

UNIT CARTON

No.	Topic	Available	Appropriate
1	Product name	✓	✓
2	Dosage form	✓	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date	✓	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition	✓	✓
10	Country's Registration Number	✓	✓
11	Name and address of Marketing Authorization Holder	✓	✓
12	Name and address of manufacturer	✓	✓
13	Special labeling	✓	✓
14	Recommended Daily Allowance (Vitamins and minerals)	n/a	n/a
15	Warning	✓	✓
16	Pack sizes	✓	✓

✓ Available or appropiate

n/a not available

Blister/Strips

No	Topic	Available	Appropiate
1	Product name	✓	✓
2	Name of Active Ingredients	✓	✓
3	Strength of Active Ingredients	✓	✓
4	Batch Number	✓	✓
5	Expiration date	✓	✓
6	Country specific	✓	✓
7	Country's Registration Number	X	✓

✓ Available or appropriate

n/a not available

Patient information leaflet (PIL) evaluation

Patient information leaflet of Cariprazine is adapted from SmPC and the originator SmPC. The information in Patient information leaflet is accurate, complete, and consistency with SmPC, quality data, non-clinical data and clinical data. The important information for patient is summarized in this PIL, however, user testing in Thais is required 12 months after receiving registered paper.

Summary of product characteristics (SmPC) evaluation

Summary of product characteristics conform to quality, non-clinical and clinical supporting data. The important information for healthcare professional is summarized in this SmPC, promotes rational drug use.

Overall Benefit/risk assessment

As evaluation results, The reviewers evaluated the documents submitted to support the quality, efficacy and safety of Cariprazine. It concluded that quality of cariprazine is acceptable and pass the standard criteria, non-clinical and clinical data supported proposed indication and no serious adverse event reported during study through post-marketing. The evaluation results of un-redacted assessment report from EMA and Thai advisory expert committee on 27th March 2019 are consistency, overall benefit/risk assessment is positive, so all can summarized Reagila capsule 1.5 mg, 3 mg, 4.5 mg and 6 mg registered indication below is acceptable; Treatment of schizophrenia in adult patient.

Cariprazine registered in new chemical medicine. MAHs have to follow up adverse event closely and comply with risk management plan. Then we should approve Cariprazine in special control medicine and the overall benefit/risk assessment supports approval of Cariprazine, under the following 4 requirements

1) This medicine will only be prescribed in hospitals and clinics.

2) Follow the adverse event in post-marketing conducted by SMP protocol submitted in eCTD.

3) Submit the complete version of PIL after the user testing passes the criteria (user testing result should be submitted to Thai FDA within 12 months after the marketing authorization approval).

4. Submit data and follow by proposed risk management plan in 1.8.2 Risk management system on eCTD , as attached file

Reference

1. Schizophrenia [Internet]. National institute of mental health.Mental health information [cited Feb 22, 2019]. Available from: https://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml

2. Ranna Parekh, M.D., M.P.H., Schizophrenia. The American Psychiatric Association (APA). [cited Feb 22, 2019]. Available from: https://www.psychiatry.org/patients-families/schizophrenia/what-is-schizophrenia

Appendix 1

(Risk management plan)

Appendix 1

Risk Management Plan (RMP)) for Reagila, can conclude as;

Risk	Management	
	Pharmacovigilance activities (Routine and additional)	**Risk Minimization Measures (RMM)**
Important identified risk		
Extrapyramidal symptoms including tardive dyskinesia	Routine pharmacovigilance As per EU regulations Additional Pharmacovigilance None	Routine RMM : Appropriate labeling (SmPC and PIL). It is mentioned in SmPC section 4.4, 4.6 and 4.8 Additional RMM : None
Weight gain	Routine pharmacovigilance As per EU regulations Additional Pharmacovigilance None	Routine RMM : Appropriate labeling (SmPC and PIL). It is mentioned in SmPC section 4.4 and 4.8 Additional RMM : None
Important potential risk		
Neuroleptic malignant syndrome	Routine pharmacovigilance As per EU regulations Additional Pharmacovigilance None	Routine RMM : Appropriate labeling (SmPC and PIL). It is mentioned in SmPC section 4.4 and 4.8 Additional RMM : None
Metabolic changes (Hyperglycemia, Dyslipidaemia)	Routine pharmacovigilance As per EU regulations Additional Pharmacovigilance None	Routine RMM : Appropriate labeling (SmPC and PIL). It is mentioned in SmPC section 4.4 and 4.8 Additional RMM : None
Ocular changes (lenticular changes and cataracts)	Routine pharmacovigilance - As per EU regulations - Including targeted follow-up of post-marketing reports using a specific questionnaire - Including half yearly trend analysis Additional Pharmacovigilance	Routine RMM : Appropriate labeling (SmPC and PIL). It is mentioned in SmPC section 4.4, 4.8 and 5.3 Additional RMM : None

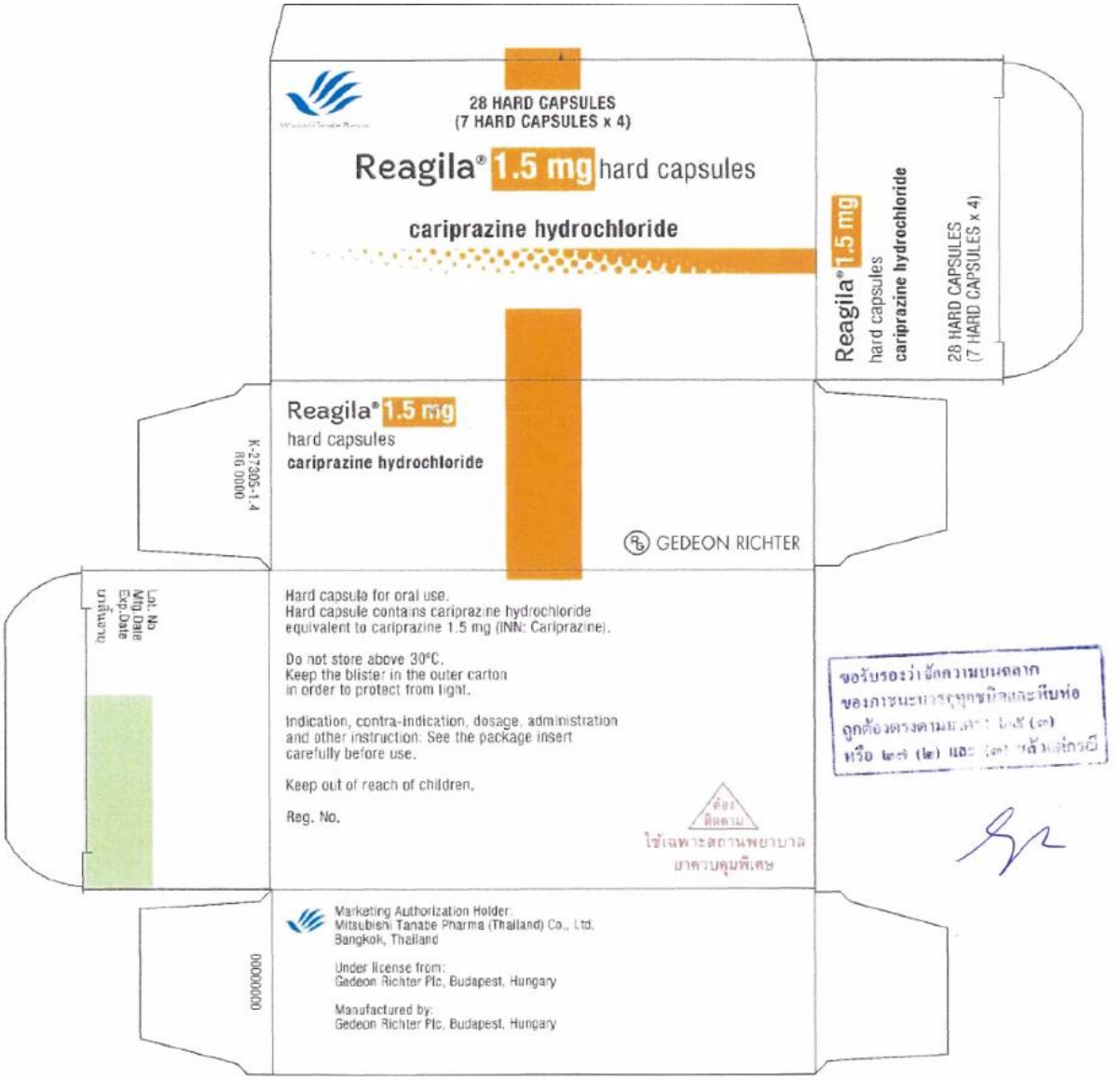
	- PASS study : A randomized, open-label, ophthalmologist-masked study in approximately 1000 schizophrenic patients to compare lens opacity changes during long-term treatment with cariprazine versus risperidone. The study duration will be 2 years and special lens opacity scale such as the modified Age- Related Eye Disease Study (AREDS) Clinical Lens Grading System for classifying cataracts will be applied	
Suicidal ideation and behaviour	Routine pharmacovigilance As per EU regulations Additional Pharmacovigilance None	Routine RMM : Appropriate labeling (SmPC and PIL). It is mentioned in SmPC section 4.4 and 4.8 Additional RMM : None
Rhabdomyolysis	Routine pharmacovigilance As per EU regulations Additional Pharmacovigilance None	Routine RMM : Appropriate labeling (SmPC and PIL). It is mentioned in SmPC section 4.4 and 4.8 Additional RMM : None
Interaction with CYP3A4 inhibitors and inducer toxicity	Routine pharmacovigilance As per EU regulations Additional Pharmacovigilance - Clinical study to investigate the effect of cariprazine on the pharmacokinetics of combined oral contraceptive (COC) (Ethinyl Estradiol and Levonorgestrel) - Clinical study to investigate the interaction between cariprazine and a moderate CYP3A4 inhibitor (erythromycin) in patients with different CYP2D6 genotypes.	Routine RMM : Appropriate labeling (SmPC and PIL). It is mentioned in SmPC section 4.3 and 4.5 Additional RMM : None
Developmental and reproductive toxicity	Routine pharmacovigilance As per EU regulations Additional Pharmacovigilance None	Routine RMM : Appropriate labeling (SmPC and PIL). It is mentioned in SmPC section 4.4,4.5,4.6 and 5.3) Additional RMM : None

Missing information		
Use during lactation	Routine pharmacovigilance As per EU regulations Additional Pharmacovigilance None	Routine RMM : Appropriate labeling (SmPC and PIL) Additional RMM : None
Use in patients > 65 years	Routine pharmacovigilance - As per EU regulations - Targeted follow-up of post-marketing reports using a specific questionnaire Additional Pharmacovigilance None	Routine RMM : Appropriate labeling (SmPC and PIL). It is mentioned in SmPC section 4.2 and 4.4 Additional RMM : None
Use in patients with severe renal or hepatic impairment	Routine pharmacovigilance - As per EU regulations Additional Pharmacovigilance None	Routine RMM : Appropriate labeling (SmPC and PIL). It is mentioned in SmPC section 4.2 and 5.2 Additional RMM : None

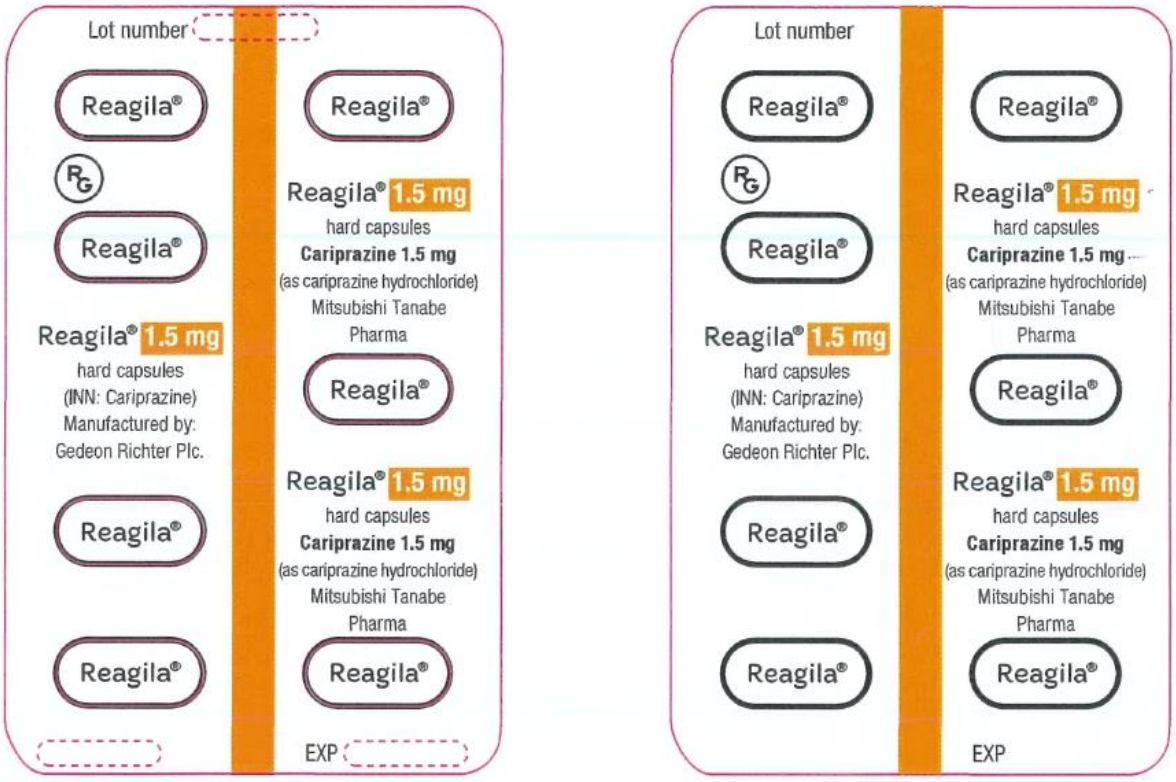
Appendix 2

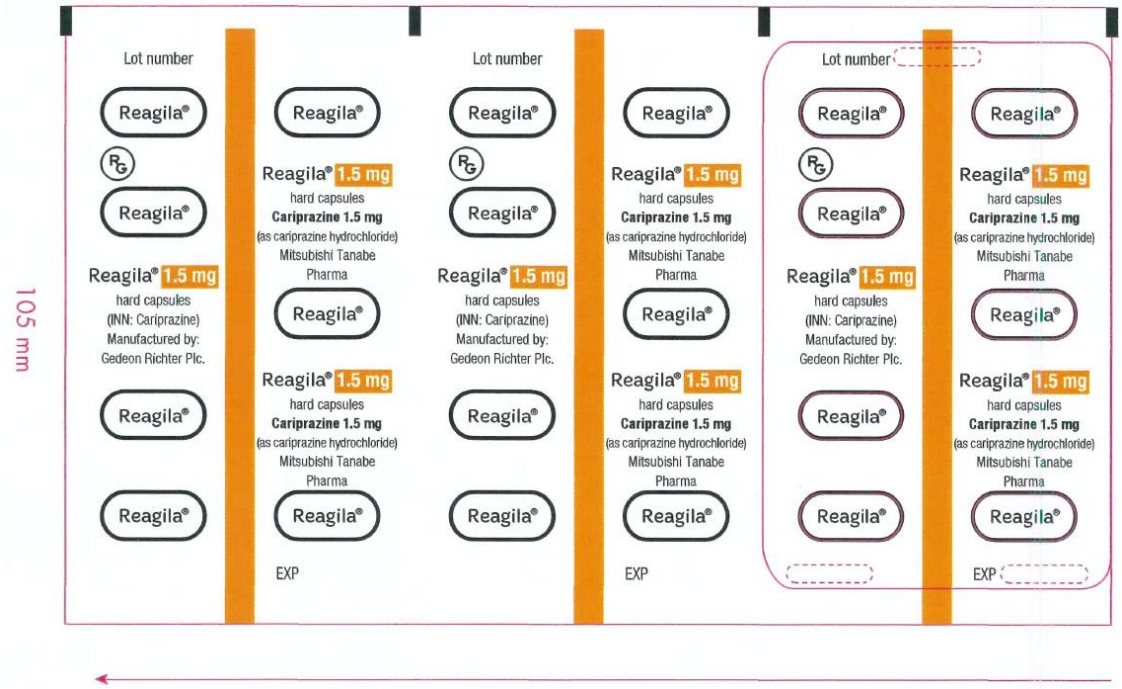
(Labeling)

Unit carton label “1.5 mg hard capsule”

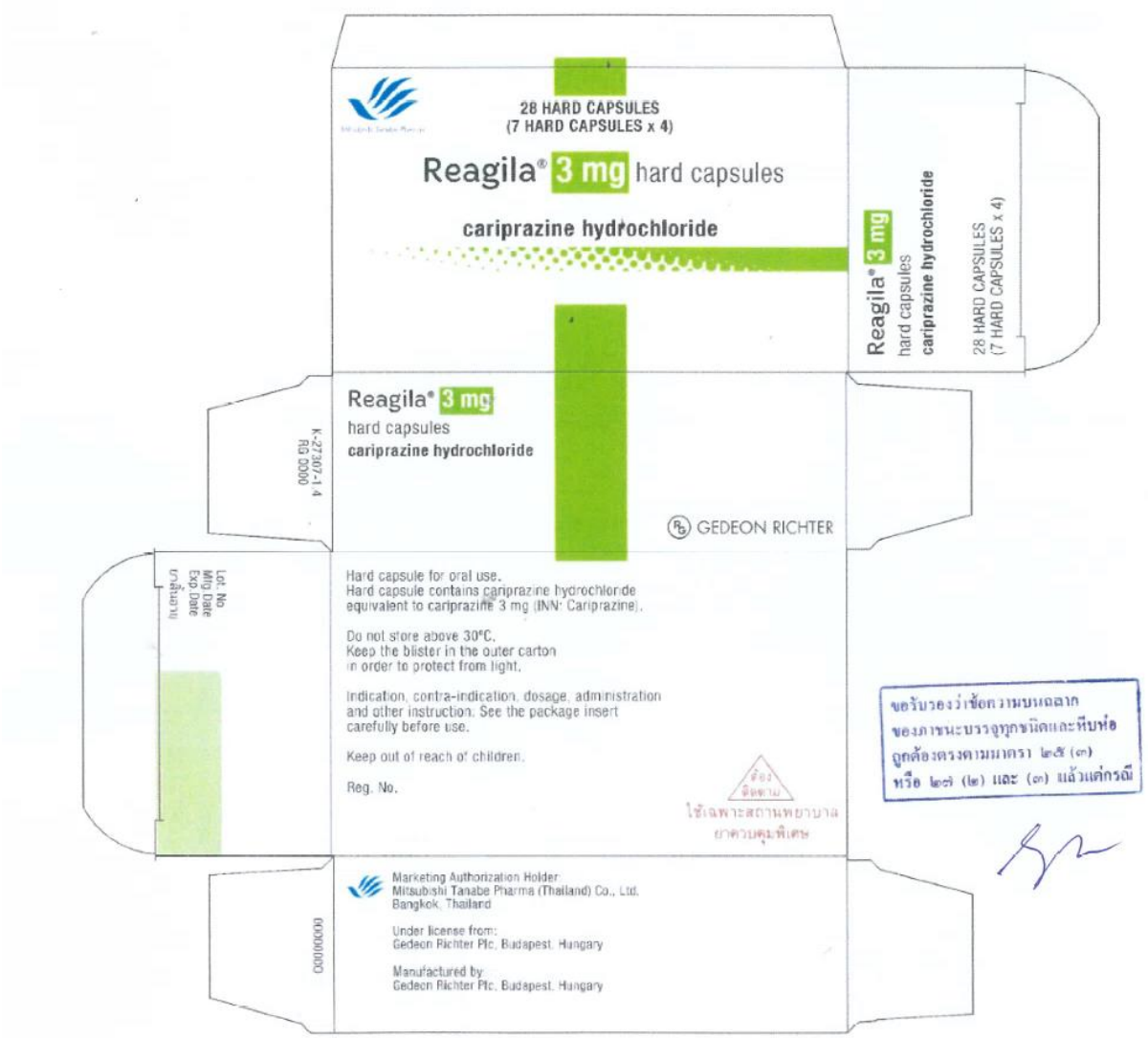


Blister/Strip “1.5 mg hard capsule”

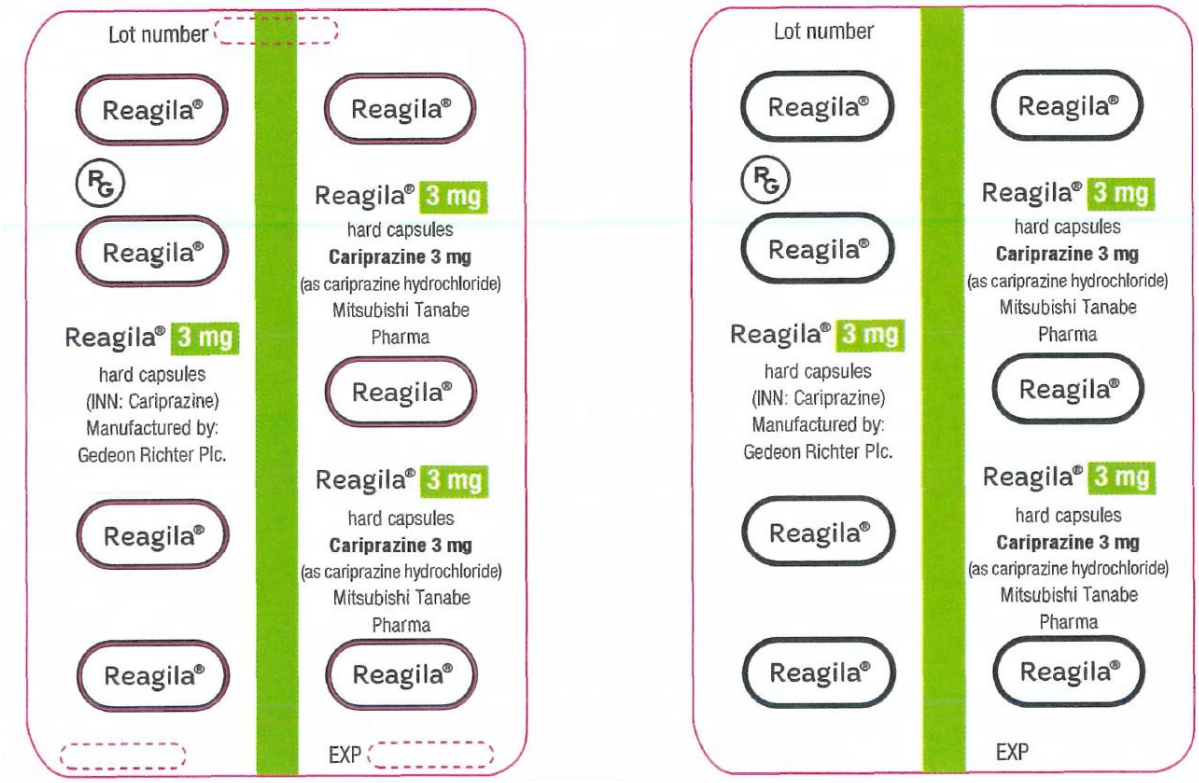


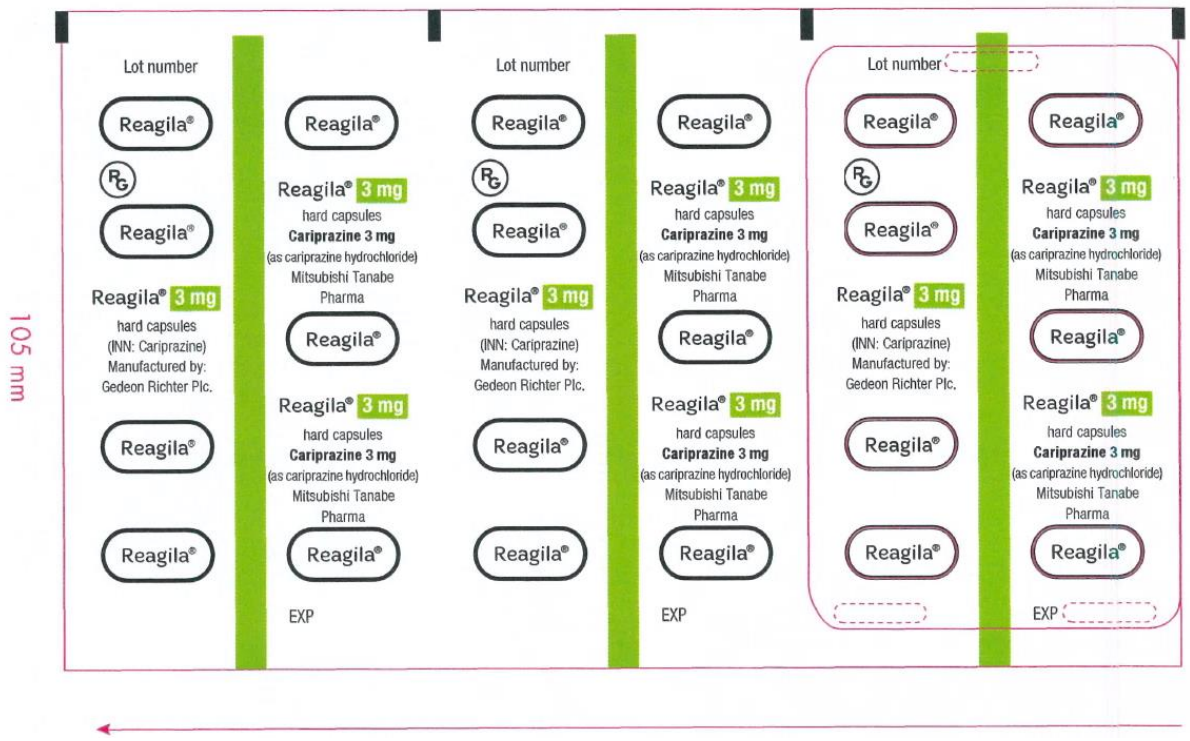


Unit carton label “3 mg hard capsule”

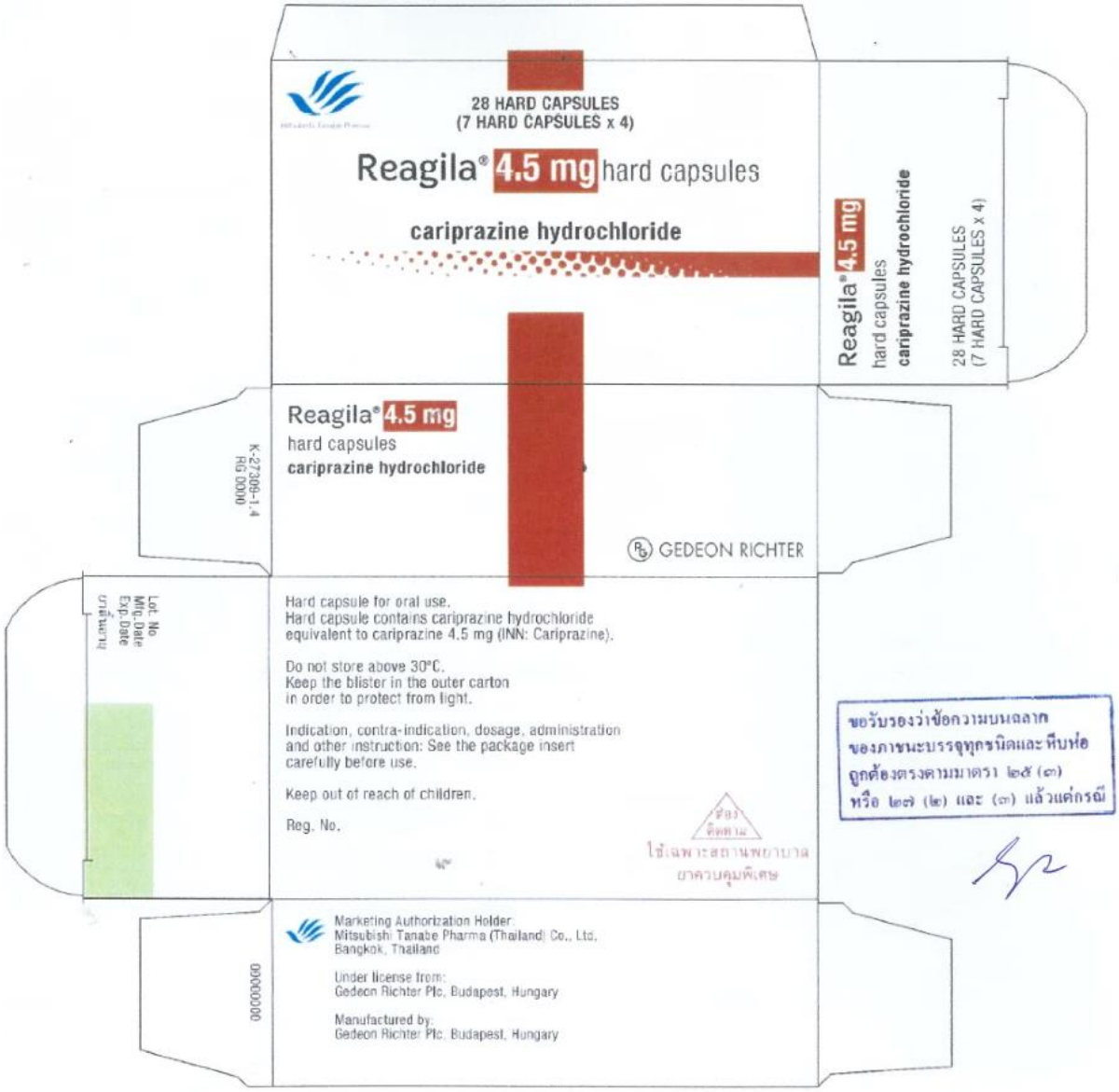


Blister/Strip “3 mg hard capsule”



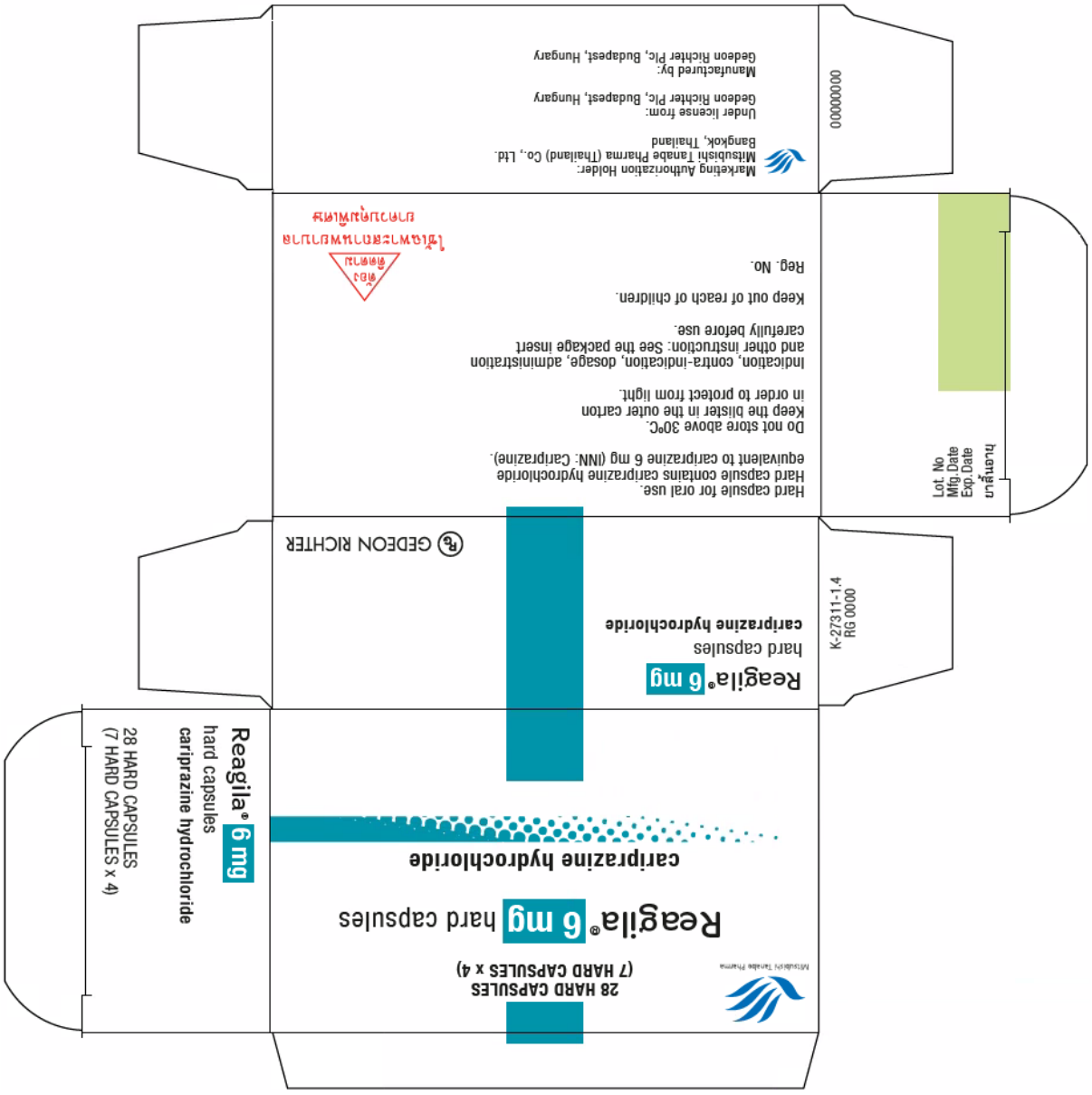


Unit carton label “4.5 mg hard capsule”



Blister/Strip “4.5 mg hard capsule”

Unit carton label “6 mg hard capsule”



Blister/Strip “6 mg hard capsule”