CANADA

PROVINCE OF QUEBEC
DISTRICT OF MONTREAL

500-06-000831-160

(Class Action)
SUPERIOR COURT

STEVEN SCHEER, domiciled and residing at 801 rue Valiquette, City of Verdun, Province of Quebec, H4H 2E1

Plaintiff / Class Representative

-vs.-

BRISTOL-MYERS SQUIBB CANADA CO., legal person duly constituted, having its head office at 2344 Boul. Alfred-Nobel, City of Saint-Laurent, Province of Quebec, H4S 0A4

and

OTSUKA CANADA PHARMACEUTICAL INC., legal person duly constituted, having its head office at 301-2250 Boul. Alfred-Nobel, City of Saint-Laurent, Province of Quebec, H4S 2C9

Defendants

APPLICATION TO INSTITUTE PROCEEDINGS
(Arts. 141 and following *C.C.P.*)

Consumer Law Group

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TO ONE OF THE HONOURABLE JUSTICES OF THE SUPERIOR COURT, SITTING IN AND FOR THE DISTRICT OF MONTREAL, YOUR PLAINTIFF/ CLASS REPRESENTATIVE STATES AS FOLLOWS:

I. INTRODUCTION

1. The present class action is primarily based on the extra-contractual liability of manufacturers for safety defects in a drug by reason of the lack of sufficient indications as to the risks of dangerous side effects including uncontrollable and irrepressible impulses to engage in harmful impulse control behaviours or addictive disorders, such as pathological gambling/gambling disorder, binge eating, uncontrollable spending or shopping (oniomania), and hypersexual behaviours/addiction (defined as the "Impulse-Control Disorders");

2. "ABILIFY" is the brand name of the atypical antipsychotic [1] medication, aripiprazole, which is prescribed to patients in order to inter alia treat *inter alia* symptoms of schizophrenia, to treat manic or mixed episodes in bipolar I disorder (manic depression), and to treat symptoms of major depressive disorder (in combination with antidepressants);

3. On December 12, 2019, the Superior Court of Quebec authorized (certified) the Plaintiff/ Class Representative to institute a class action against the Defendants on behalf of the group of:

> "All persons residing in Canada who were prescribed and have ingested and/or used the drug, ABILIFY® (aripiprazole) before February 23, 2017 and who developed one or more of the following impulse control behaviours:
>
> - pathological gambling (also known as gambling disorder or compulsive gambling);[2]
> - compulsive eating/ binge eating;
> - uncontrollable or compulsive shopping or spending; and/or
> - hypersexual behaviours / sexual addiction;
>
> (the "Impulse-Control Disorders")[3]

[1] Antipsychotics also known as neuroleptics or major tranquilizers, are a class of psychiatric medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia and bipolar disorder – the word atypical indicates that it is a second-generation antipsychotic developed to produce less side effects that its predecessors.

[2] Gambling disorder is the diagnostic term currently used in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); however, much of the literature still uses the term "pathological gambling". For this reason, the term pathological gambling appears throughout the class action so as not to create confusion.

[3] For consistency, in this application, the defined term "Impulse-Control Disorders" will always contain the dash, whether or not it did so in the judgment authorizing the class action.

and their successors, assigns, family members, and dependants (the "Class" or "Class Members");

4. The Plaintiff, Mr. Steven Scheer, has instituted a class action seeking compensatory and punitive damages against the Defendants on behalf of the Class based on the Defendants' (i) inadequate warning of the risk of developing Impulse-Control Disorders associated with and caused by ABILIFY, (ii) failure to notify of the full scope of risks known to be associated with and caused by ABILIFY, and (iii) safety misrepresentations;

5. The Defendants developed, designed, manufactured, tested, marketed, labelled, packaged, promoted, advertised, imported, distributed, and/or sold ABILIFY as safe and/or effective despite a wealth of existing knowledge that the drug had dangerous side effects including uncontrollable and irrepressible impulses to engage in harmful impulse control behaviours or addictive disorders, such as pathological gambling/gambling disorder, binge eating, uncontrollable spending or shopping, and hypersexual behaviours/addiction;

6. The Plaintiff contends that the Defendants represented to the medical and healthcare community, to Health Canada, and to the Class Members that they had developed, designed, manufactured, and tested ABILIFY and that it had been found to be safe and/or effective for its intended uses. In addition, the Defendants concealed their knowledge of ABILIFY's defects from the medical and healthcare community, Health Canada and from Class Members;

7. In its judgment granting class action status, the Superior Court of Quebec identified the principle issues or issues of fact and law to be treated collectively as the following:

   a) Does ABILIFY cause, exacerbate or contribute to an increased risk of dangerous side effects including having uncontrollable and irrepressible impulses to engage in harmful impulse control behaviours such as:

      i) pathological gambling (also known as gambling disorder or compulsive gambling)

      ii) compulsive eating/ binge eating

      iii) uncontrollable or compulsive shopping or spending, and/or

      iv) hypersexual behaviours / sexual addiction

      (the "Impulse-Control Disorders")?

   b) In the affirmative, did the Defendants know or should they have known about the risks of Impulse-Control Disorders associated with the use of ABILIFY?

c) Did the Defendants breach the applicable standard of care in failing to adequately test ABILIFY both before and/or after placing it on the market?

d) Did the Defendants have a duty to warn Class Members of the risk of Impulse-Control Disorders associated with the use of ABILIFY?

e) Did the Defendants adequately and sufficiently advise/warn the Class Members, Health Canada, and/or their physicians about the risks of experiencing the Impulse-Control Disorders associated with the use of ABILIFY?

f) Are the Defendants, or some of them, liable for conspiracy to promote, market, and distribute ABILIFY in Canada without adequate and timely warnings about the risk of Impulse-Control Disorders and, if so, over what period of time?

g) Can causality be determined on a collective basis and, if so, can Class Members rely on a presumption to establish causation?

h) In the affirmative to any of the above questions, did the Defendants' conduct engage their solidary liability toward some or all of the Class Members?

i) Are the Defendants liable to pay compensatory damages to some or all of the Class Members?

j) In the affirmative, can the compensatory damages payable to the Class Members be determined and recovered on a collective basis?

k) Are the Defendants liable to pay aggravated or punitive damages and, if so, in what amount?

II. THE DEFENDANTS

8. Defendant Bristol-Myers Squibb Canada Co. ("Bristol-Myers") is a Canadian pharmaceutical corporation, with its head office in Saint-Laurent, Quebec. Bristol-Myers is and was at all relevant times involved in the development, design, manufacture, testing, marketing, labelling, packaging, promotion, advertising, importation, distribution, and/or sale of pharmaceutical products including ABILIFY. It does business throughout Canada, including within the province of Quebec, the whole as appears more fully from a copy of an extract from the *Registraire des enterprises* updated to February 29, 2020, from a copy of an extract from the *Registraire des enterprises* updated to September 26, 2016, and from copies of extracts from Defendant Bristol-Myers' websites at www.bms.com/ca and www.bmscanada.ca, produced herein *en liasse* as **Exhibit P-1**;

9. Defendant Otsuka Canada Pharmaceutical Inc. ("Otsuka") is a Canadian pharmaceutical corporation, with its head office in Saint-Laurent, Quebec.

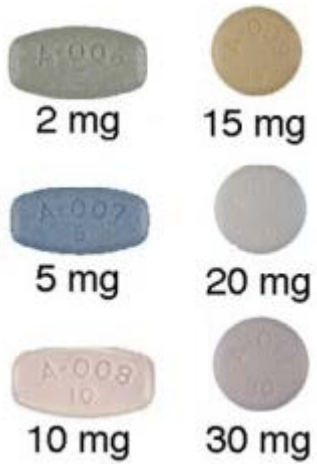
Otsuka is and was at all relevant times involved in the development, design, manufacture, testing, marketing, labelling, packaging, promotion, advertising, importation, distribution, and/or sale of pharmaceutical products including ABILIFY. It does business throughout Canada, including within the province of Quebec, the whole as appears more fully from a copy of an extract from the *Registraire des enterprises* updated to March 2, 2020, from a copy of an extract from the *Registraire des enterprises* updated to September 26, 2016, and from a copy of an extract from Otsuka's website at https://otsukacanada.com, produced herein *en liasse* as **Exhibit P-2**;

10. Defendants Otsuka and Bristol-Myers co-promoted ABILIFY in Canada; as sponsors for ABILIFY in Canada, they were responsible for the Product Monographs, which are the primary source of information for healthcare professionals and patients, setting out the uses, dosage, and risks associated with the drug, the whole as appears more fully from a copy of an extract from Defendant Otsuka's website at www.otsukacanada.com, and from a copy of Defendant Bristol-Myers' News Release entitled "Newest Treatment for Schizophrenia & Related Psychotic Disorders now Available to all Quebecers" dated October 26, 2010, produced herein *en liasse* as **Exhibit P-3**;

11. Both Defendants have either directly or indirectly developed, designed, manufactured, tested, marketed, labelled, packaged, promoted, advertised, imported, distributed, and/or sold ABILIFY to distributors and retailers for resale to or, directly to physicians, hospitals, medical practitioners and to the general public throughout Canada, including within the province of Quebec;

12. Given the close ties between the Defendants and considering the preceding, both Defendants are solidarily liable for the acts and omissions of the other;

III. THE SITUATION



A. What is ABILIFY? What is Dopamine?

13. ABILIFY belongs to a group of medicines called atypical antipsychotics. Atypical antipsychotics (also known as second generation antipsychotics) are a group of antipsychotic drugs used to treat psychiatric conditions. Both generations of medication (typical and atypical antipsychotics) block receptors in the brain's dopamine pathways. Atypicals are less likely to cause extrapyramidal motor control disabilities such as unsteady Parkinson's disease-type movements, body rigidity, and involuntary tremors;

14. Like other atypical antipsychotics, ABILIFY binds to several different neurotransmitter receptors, but unlike others in its class, it doesn't block dopamine receptors [4] (specifically, dopamine D_2 and D_3) or serotonin [5] (specifically, 5-HT_{1A}) receptors. Instead, it's a partial agonist [6] at those receptors – it can activate those receptors, but not to the full biological effect. Aripiprazole is the only antipsychotic that has a dopamine agonistic property; it usually acts as a dopamine antagonist, working clinically as an antipsychotic or antimanic agent, the whole as appears more fully from a copy of the Psychopharmacology article entitled "Unique pharmacological profile of aripiprazole as the phasic component buster" dated January 5, 2007, produced herein as **Exhibit P-4**;

15. In lay terms, ABILIFY can both enhance dopamine and serotonin signaling where those transmitters are deficient, and inhibit signaling where they are in excess;

16. The possible mechanisms related to the occurrence of the Impulse-Control Disorders upon ingesting ABILIFY are the partial agonist properties at dopamine receptors D_2 and D_3, and at serotonin receptor 5 HT_{1A} and the antagonist properties at serotonin receptor 5 HT_{2A} (Exhibits P-52 and P-62). Another hypothesis is that the treatment with drugs having strong dopaminergic antagonist properties prior to the Aripiprazole causes the up-regulation of the dopamine receptors, on which the subsequent addition of the Aripiprazole, can lead to the Impulse-Control Disorders (Exhibit P-56);

17. Because ABILIFY has a high affinity to D_2 receptors, about 90% of D_2 receptors are occupied by it and dopamine transmissions are blocked. However, its intrinsic activity and long half-life adds to the constant dopaminergic tone

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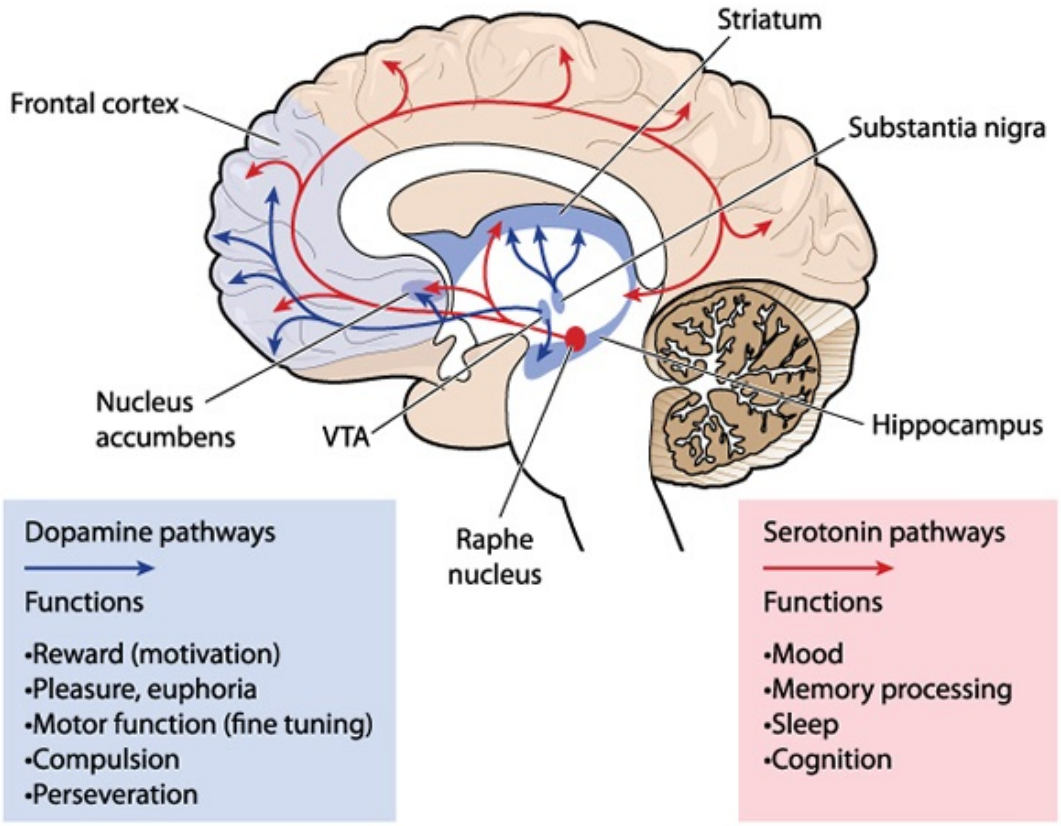
[4] Dopamine is a compound present in the body as a neurotransmitter and a precursor of other substances including epinephrine. *It* helps control the brain's reward and pleasure centers and helps regulate movement and emotional responses, and it enables us not only to see rewards, but to take action to move toward them.

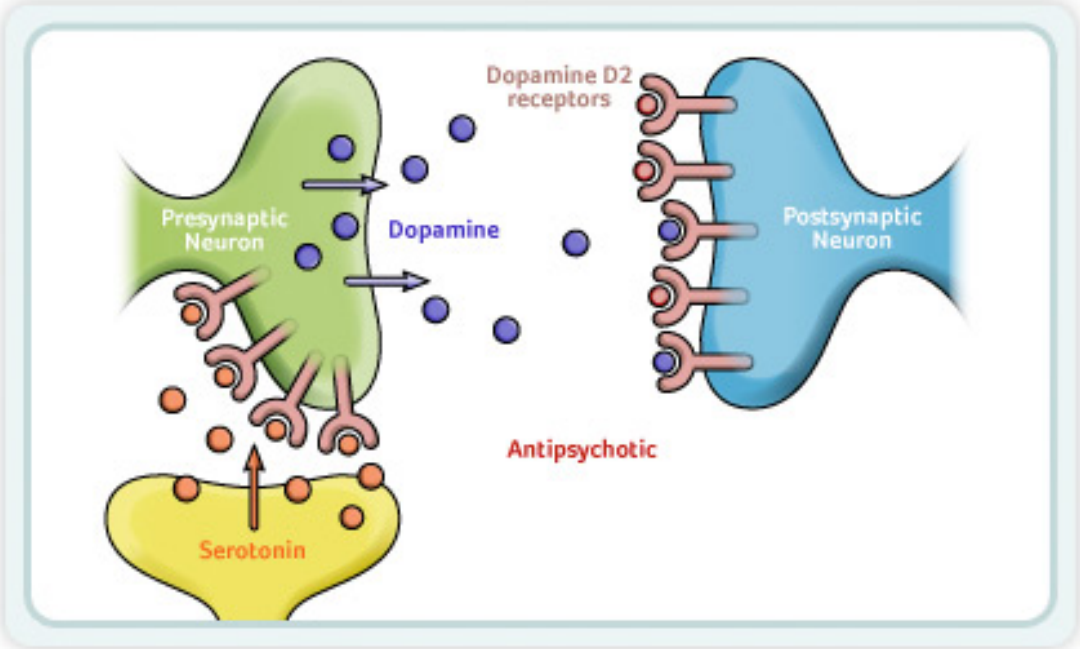
[5] Serotonin is a compound present in blood platelets and serum that constricts the blood vessels and acts as a neurotransmitter. It is thought that *serotonin* can affect mood and social behaviour, appetite and digestion, sleep, memory and sexual desire and function.

[6] In pharmacology, partial agonists are drugs that bind to and activate a given receptor, but have only partial efficacy at the receptor relative to a full agonist.

(Exhibit P-4). The behavioural effects of ABILIFY can also be attributed to the participation of the dopamine D_3 receptor, which is highly enriched in the nucleus accumbens[7] and plays an important role in reward. It has been postulated that dopamine agonists with high D_3 receptor affinity tend to produce impulsive-addictive behavioural abnormality in dopamine dysregulation syndrome (Exhibit P-73);



[7] The nucleus accumbens is a region in the basal forebrain rostral to the preoptic area of the hypothalamus.



18. Dopamine's role in compulsive behaviours is well-known. Dopaminergic reward pathways have frequently been implicated in the etiology of addictive behaviour. Scientific literature has identified dopamine as a potential cause of the Impulse-Control Disorders for years (as will be detailed hereinbelow), the whole as appears more fully from a copy of the Scientific American article entitled "Dopamine Determines Impulsive Behavior" dated July 29, 2010, from a copy of the Current neurology and neuroscience reports article entitled "The Functional Anatomy of Impulse Control Disorders" dated August 21, 2013, from a copy of the Frontiers in Behavioral Science article entitled "How central is dopamine to pathological gambling or gambling disorder?" dated December 23, 2013, from a copy of the Frontiers in Behavioral Science article entitled "What motivates gambling behavior? Insight into dopamine's role" dated December 2, 2013, from a copy of the Scientific American article entitled "How the Brain Gets Addicted to Gambling", from a copy of the Gambling Research Exchange Ontario article entitled "Dopamine release in ventral striatum of pathological gamblers losing money" dated 2010, and from a copy of the Journal of Neuroscience article entitled "Dopamine, Time, and Impulsivity in Humans" dated June 30, 2010, produced herein *en liasse* as **Exhibit P-5**;

19. As was eloquently described by Chief United States District Judge M. Casey Rodgers of the Northern District of Florida in the parallel U.S. litigation in *In Re: Abilify (Aripiprazole) Products Liability Litigation* – Case No. 3:16-md-2734 (which will be described hereinbelow):

> Dopamine is a neurotransmitter in the central nervous system that is believed to play an integral role in a number of physiological processes, including movement, cognition, emotional stability, and,

> relevant to this case, reward-motivated behaviors. It acts on five different receptors—D1, D2, D3, D4, and D5—along four major pathways in the brain—the nigrostriatal pathway, the mesocortical pathway, the mesolimbic pathway, the tuberoinfundibular pathway. This case is primarily concerned with the activity of dopamine in the mesolimbic pathway, which regulates pleasure, reward processing, and motivation. Under normal circumstances, the brain responds to rewarding activities or stimuli by releasing dopamine into the mesolimbic pathway, where it binds with dopamine receptors to produce feelings of pleasure. As dopamine levels subside, so do the feelings of pleasure. If the rewarding activity is repeated, then dopamine is again released, and more feelings of pleasure are produced. The release of dopamine and the resulting pleasurable feelings serve as positive reinforcements that motivate repetition of the pleasure-inducing activity,

The whole as appears more fully from a copy of the Amended Order dated March 15, 2018 in *In Re: Abilify (Aripiprazole) Products Liability Litigation* – Case No. 3:16-md-2734, produced herein as **Exhibit P-6**;

20. In Canada, ABILIFY is available in the oral tablet form in six strengths (2 mg, 5 mg, 10 mg, 20 mg, and 30 mg) usually indicated to be taken on a daily basis for the treatment of certain psychiatric or mood disorders such as schizophrenia, Bipolar I Disorder, and Major Depressive Disorder;

B. Approval of ABILIFY in Canada

21. On July 9, 2009, Defendant Bristol-Myers obtained approval for ABILIFY from Health Canada in the 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg tablet form for the "treatment of schizophrenia and related psychotic disorders" and for the "acute treatment of manic or mixed episodes in Bipolar I Disorder…with lithium or divalproex sodium when there is an insufficient acute response to these agents alone". Thereafter:

    (i) On May 12, 2011, Defendant Bristol-Myers obtained approval from Health Canada to market ABILIFY in Canada "[t]o use as cotherapy with lithium or divalproex sodium for maintaining clinical improvement for up to 1 year in patients with manic or mixed episodes associated with Bipolar I Disorder",

    (ii) On November 21, 2011, Defendant Bristol-Myers obtained approval from Health Canada to market ABILIFY in Canada for the "treatment of schizophrenia in adolescents 15-17 years of age",

    (iii) On March 13, 2012, Defendant Bristol-Myers obtained approval from Health Canada to market ABILIFY in Canada for the "acute treatment of

> manic or mixed episodes in bipolar 1 disorder as monotherapy in adolescent patients 13-17 years of age", and
>
> (iv) On May 29, 2013, Defendant Bristol-Myers obtained approval from Health Canada to market ABILIFY in Canada for the "use as an adjunct to antidepressants for the treatment of Major Depressinve *[sic]* Disorder (MDD) in adult patients who had an inadequate reponse *[sic]* to prior antidepressant treatments during the current episode",

the whole as appears more fully from copies of the five (5) Notices of Compliance obtained from Defendant Bristol-Myers from Health Canada dated July 9, 2009, May 12, 2011, November 21, 2011, March 13, 2012, and May 29, 2013 and from a copy of the Health Canada Summary Basis of Decision (SBD) for ABILIFY dated July 9, 2009, produced herein *en liasse* as **Exhibit P-7**;

22. Accordingly, ABILIFY was launched in Canada on July 9, 2009 in the 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg strengths as a prescription medication;

C. <u>ABILIFY in the United States and in Europe</u>

23. ABILIFY was launched in the United States in or around November of 2002;

24. On October 31, 2001, non-party Otsuka Pharmaceutical Co., Ltd. submitted a New Drug Application to the United States Food and Drug Administration ("U.S. FDA") for ABILIFY. Approval was sought to market ABILIFY in 2, 5, 10, 15, 20 and 30 mg tablets as a treatment for schizophrenia. It was approved on November 15, 2002, the whole as appears more fully from a copy of the Approval Letter – Application 21-436, produced herein as **Exhibit P-8**;

25. The U.S. FDA required that the results of Study 138047 to address the longer-term efficacy of ABILIFY in the treatment of adults with schizophrenia be submitted (Exhibit P-8):

> Submit the results of Study 138047 to address the longer-term efficacy of aripiprazole in the treatment of adults with schizophrenia;

26. On December 3, 2002, non-party Otsuka America Pharmaceutical, Inc., submitted a Supplemental New Drug Application (NDA 21-436/S-001) on the longer-term efficacy of ABILIFY in the treatment of schizophrenia. This application was approved on August 28, 2003, the whole as appears more fully from a copy of the Approval Package Application Number NDA 21-436/S-001 dated August 28, 2003, produced herein as **Exhibit P-9**;

27. In June 2003, non-party Otsuka Maryland Research Institute submitted another Supplemental New Drug Application (NDA 21-436/S-002) for ABILIFY tablets as a treatment for bipolar disorder. This application was approved on September 29, 2004, the whole as appears more fully from a copy of the

Approval Letter and Package for Application Number NDA 21-436/S-002 dated September 29, 2004, produced herein as **Exhibit P-10**;

28. In May 2007, non-party Otsuka Pharmaceutical Development & Commercialization, Inc., submitted another Supplemental New Drug Application (NDA 21-436/S-018) for ABILIFY tablets as an adjunctive treatment for patients with major depressive disorder. This application was approved on November 16, 2007, the whole as appears more fully from a copy of the Approval Letter from the Department of Health & Human Services dated November 16, 2007, produced herein as **Exhibit P-11**;

29. ABILIFY was first authorized in the European Union on June 4, 2004. On December 11, 2008, Otsuka Pharmaceutical Europe Ltd. applied to extend the indication for ABILIFY to treat major depressive episodes and the European Medicines Agency[8] declined to approve ABILIFY as an add-on treatment for depression because of concerns about its efficacy for that indication, the whole as appears more fully from a copy of the European Medicines Agency Press Release entitled "Otsuka Pharmaceutical Europe Ltd withdraws its application for an extension of indication for Abilify (aripiprazole)" dated November 19, 2009, from a copy of the European Medicines Agency Withdrawal Assessment Report for ABILIFY dated January 20, 2010, from a copy of the European Public Assessment Report (EPAR) for ABILIFY, and from a copy of the European Medicines Agency's "Procedural steps taken and scientific information after the authorization" for ABILIFY produced herein *en liasse* as **Exhibit P-12**;

D. <u>The Psychiatric Conditions/ Mood Disorders that ABILIFY is Indicated to Treat</u>

(a) <u>Schizophrenia</u>

30. Schizophrenia is a severe mental disorder characterized by abnormal social behaviour and a failure to comprehend what is real. Common symptoms include false beliefs or suspicions, unclear or confused thinking, hallucinations, delusions, reduced social engagement and emotional expression, and a lack of motivation. People with schizophrenia often have additional mental health problems such as anxiety disorders, major depressive illness, or substance use disorders. Symptoms typically come on gradually, begin in young adulthood, the whole as appears more fully from a copy of the World Health Organization Fact Sheet and from a copy of an extract from the Schizophrenia Society of Canada at <u>www.schizophrenia.ca</u>, produced herein *en liasse* as **Exhibit P-13**;

[8] The European Medicines Agency is an international public health agency charged with the scientific evaluation, supervision and safety monitoring of medicines for the European Union.

31. Schizophrenia affects approximately 1 percent of the Canadian Population, the whole as appears more fully from a copy of an extract from the Public Health Agency of Canada – A Report on Mental Illness in Canada: Chapter 3 Schizophrenia and from a copy of the Statistics Canada publication at Section G – Schizophrenia, produced herein *en liasse* as **Exhibit P-14**;

32. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is the reference manual of the American Psychiatric Association that is widely used in Canada by psychiatrists to diagnose mental health problems. The DSM-5 classifies schizophrenia under "Schizophrenia Spectrum and Other Psychotic Disorders" with the diagnostic criteria *inter alia* as follows:

    A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

        1. Delusions.
        2. Hallucinations.
        3. Disorganized speech (e.g., frequent derailment or incoherence).
        4. Grossly disorganized or catatonic behavior.
        5. Negative symptoms (i.e., diminished emotional expression or avolition).

    B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

    C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

    The whole as appears more fully from a copy of extracts from the DSM-5, produced herein as **Exhibit P-15**;

33. Treatment for schizophrenia is antipsychotic medication (such as ABILIFY) along with counselling, job training and social rehabilitation;

(b) Bipolar I Disorder

34. Bipolar I disorder (previously known as manic depression) is a bio-chemical condition that results in an imbalance of the neurotransmitters in the brain. It is a bipolar spectrum disorder characterized by the occurrence of at least one manic or mixed episode[9]. Most patients also, at other times, have one or more depressive episodes, and all experience a hypomanic stage before progressing to full mania, the whole as appears more fully from a copy of the Psych Central article entitled "The Two Types of Bipolar Disorder", from a copy of an extract from the Canadian Mental Health Association website at www.cmha.ca entitled "Bipolar Disorder", from a copy of the Canadian Mental Health Association brochure for Depression and Bipolar Disorder, dated 2014, and from a copy of the Public Health Agency of Canada article entitled "What Should I Know about Bipolar Disorder (Manic-Depression)?" dated April 23, 2009, produced herein *en liasse* as **Exhibit P-16**;

35. Approximately 1 percent of Canadians aged 15 years and over reported symptoms that met the criteria for bipolar disorder in the previous 12 months. About 1 in 50 adults aged 25-64 years reported symptoms consistent with bipolar disorder at some point in their lifetime;

36. The DSM-5 classifies Bipolar I Disorder under "Bipolar and Related Disorders" with the diagnostic criteria *inter alia* as follows (Exhibit P-15):

> For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.
>
> Manic Episode[10]
>
> A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
>
> B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the

[9] In bipolar disorder, mixed state is a condition during which symptoms of both mania and depression occur simultaneously. Individuals experiencing a mixed state may have manic symptoms such as grandiose thoughts while simultaneously experiencing depressive symptoms such as excessive guilt or feeling suicidal

[10] For our purposes, the diagnostic criteria for a "Hypomanic Episode" basically mirror those of Manic Episode, but instead of the episode lasting at least 1 week, it lasts at least 4 days.

mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

…

Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

(c) Major Depressive Disorder/ Depression

37. Major depressive disorder (MDD), also known simply as depression, is a mental disorder characterized by at least two weeks of low mood that is present across most situations. It is often accompanied by low self-esteem, loss of interest in normally enjoyable activities, low energy, and pain without a clear cause, the whole as appears more fully from a copy of an extract from the National Institute of Mental Health website at www.nimh.gov and from a copy of an extract from the Centre for Addiction and Mental Health website at www.camh.ca, produced herein *en liasse* as **Exhibit P-17**;

38. Depression may come once, twice or many times in a person's life. Or it may be chronic, lasting. There are three major types – major depressive disorder, dysthymia[11] and bipolar disorder, the whole as appears more fully from a copy of an extract from the Ontario Ministry of Health website at www.health.gov.on.ca, produced herein as **Exhibit P-18**;

39. People with major depressive disorder may be constantly sad, hopeless, irritable, and unable to feel pleasure. They may have changes in sleeping and eating habits, and difficulty concentrating or thinking clearly. They often feel guilty and unworthy of love. Some very depressed people might hear imaginary voices confirming their feelings of worthlessness. They start believing bad things about themselves and others, adding to their unhappiness. Some think about dying, or punishing themselves. Some try to kill themselves. This type of depression generally goes away in a few months, especially with proper treatment (Exhibit P-18);

40. The DSM-5 classifies Major Depressive Disorder under "Depressive Disorders" with the diagnostic criteria *inter alia* as follows (Exhibit P-15):

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

[11] Dysthymia (or depressive neurosis) lasts years at a time.

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
   (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

41. According to Statistics Canada's 2012 Canadian Community Health Survey (CCHS) on Mental Health, 5.4% of the Canadian population aged 15 years and over reported symptoms that met the criteria for a mood disorder in the previous 12 months, including 4.7% for major depression and 1.5% for bipolar disorder. Further, almost one in 8 adults (12.6%) identified symptoms that met the criteria for a mood disorder at some point during their lifetime, including 11.3% for depression and 2.6% for bipolar disorder, the whole as appears more fully from a copy of an extract from the Government of Canada website at www.canada.ca, produced herein as **Exhibit P-19**;

E. The Impulse-Control Disorders

42. Broadly defined, Impulse-Control Disorders are a group of psychiatric disorders that involve problems with behavioural self-control resulting in harm to oneself or to others. Core characteristics of Impulse-Control Disorders include: (1) a behaviour that is repetitive or compulsive, despite adverse consequences; (2) an inability to stop the harmful behavior; (3) an urge or craving to engage in the harmful behavior; and (4) a pleasurable ("hedonic")

quality to the harmful behavior. Impulse-Control Disorders are also termed addictive disorders, due to increasing recognition of similarities between Impulse-Control Disorders and alcohol and drug addiction in terms of clinical features, cognitive changes, treatment, and underlying neurobiological processes. For example, people with a gambling disorder exhibit cravings, tolerance through a need to increase betting, euphoric "highs," and even withdrawal symptoms similar to what people with a drug addiction experience, the whole as appears more fully from a copy of the Frontiers in Psychiatry review article entitled "Impulse control disorders: updated review of clinical characteristics and pharmacological management" dated February 21, 2011 and from a copy of the Science Magazine article entitled "'Behavioral' Addictions: Do They Exist?" dated November 2, 2001, produced herein *en liasse* as **Exhibit P-20**;

43. Examples of specific Impulse-Control Disorders include, but are not limited to, pathological gambling (also known as gambling disorder or compulsive gambling), compulsive sexual behaviour (i.e. hypersexuality or sexual addiction), compulsive buying/shopping (i.e. shopping addiction), and compulsive eating (i.e. binge eating). Many psychiatric conditions feature impulsive-compulsive behaviours, such as attention-deficit/hyperactivity disorder, mania, and substance use disorders, although they are not formally labeled as an Impulse-Control Disorder. The classification of a specific disorder as an Impulse-Control Disorder, and the very definition of an Impulse-Control Disorder, is an evolving field of psychiatry, the whole as appears more fully from a copy of the Neuron Review article entitled "Impulsivity, compulsivity, and top-down cognitive control" dated February 24, 2011, produced herein as **Exhibit P-21**;

(a) <u>Pathological Gambling/ Gambling Disorder</u>

44. Pathological gambling is a major psychiatric disorder and is considered to be the most extreme form of "disordered gambling". It may be defined as an addictive urge to gamble continuously despite harmful negative consequences or a desire to stop, the whole as appears more fully from a copy of the Journal of Gambling Studies article entitled "Pathologic Gambling and Impulse Control Disorders" dated March 2005, produced herein as **Exhibit P-22**;

45. Gambling disorder is defined as persistent, repetitive, maladaptive gambling behavior (after mania is ruled out) at least at one point of time in a 12-month period (episodic or persistent), which leads to harmful consequences in personal, social, and occupational life

46. Gambling disorder is described as ongoing and repetitive engagement in gambling activities that leads to significant distress or impairment, the whole as appears more fully from a copy of an extract from the Centre for Addiction and Mental Health website at <u>www.problemgambling.ca</u>, produced herein as **Exhibit P-23**;

47. The DSM-5 classifies Gambling Disorder under "Non-Substance-Related Disorders" with the diagnostic criteria *inter alia* as follows (Exhibit P-15):

> Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period:
>
> 1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
> 2. Is restless or irritable when attempting to cut down or stop gambling.
> 3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling.
> 4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble).
> 5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed).
> 6. After losing money gambling, often returns another day to get even ("chasing" one's losses).
> 7. Lies to conceal the extent of involvement with gambling.
> 8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.
> 9. Relies on others to provide money to relieve desperate financial situations caused by gambling.

The whole as appears more fully from a copy of an extract from American Psychiatric Association website at www.psychiatry.org, produced herein as **Exhibit P-24**;

48. Gambling disorder is classified as a mental health disorder on the World Health Organization's International Classification of Diseases list (ICD-11) and is described as follows:

> Gambling disorder is characterized by a pattern of persistent or recurrent gambling behaviour, which may be online (i.e., over the internet) or offline, manifested by:
>
> 1. impaired control over gambling (e.g., onset, frequency, intensity, duration, termination, context);
> 2. increasing priority given to gambling to the extent that gambling takes precedence over other life interests and daily activities; and
> 3. continuation or escalation of gambling despite the occurrence of negative consequences. The behaviour pattern is of sufficient

> severity to result in significant impairment in personal, family, social, educational, occupational or other important areas of functioning.
>
> The pattern of gambling behaviour may be continuous or episodic and recurrent. The gambling behaviour and other features are normally evident over a period of at least 12 months in order for a diagnosis to be assigned, although the required duration may be shortened if all diagnostic requirements are met and symptoms are severe.

The whole as appears more fully from a copy of the ICD-11 entry for Gambling disorder, produced herein as **Exhibit P-25**;

49. In Canada, there is also the Canadian Problem Gambling Index (CPGI), which is a 31-item measure used for screening purposes to determine whether a person in the general population may have a gambling problem. The CPGI asks questions about an individual's gambling habits from four categories:

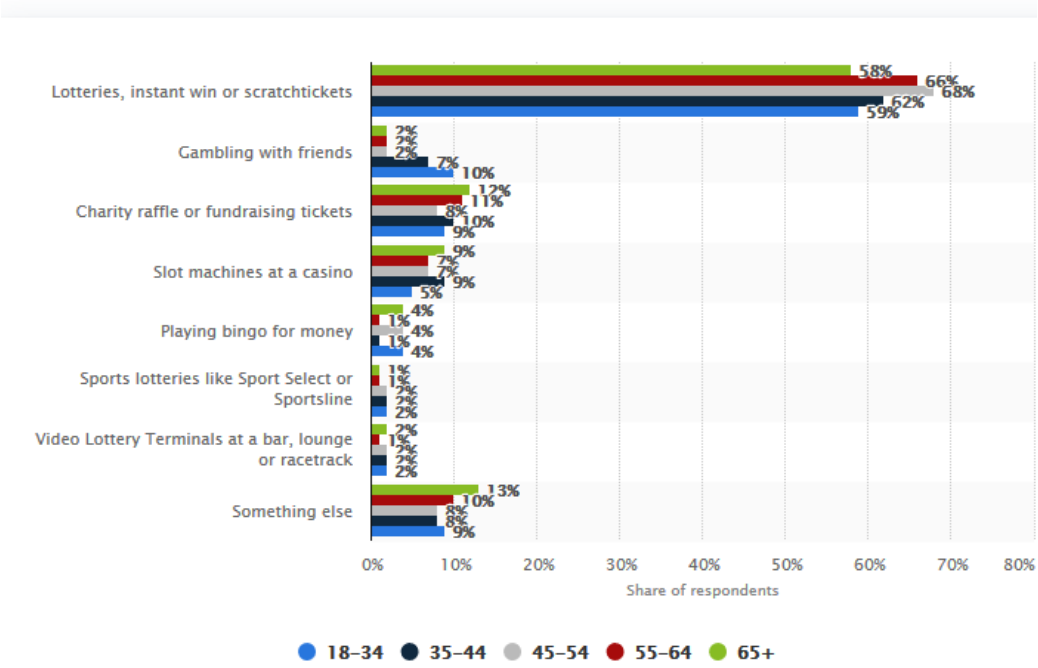
    (i) An individual's involvement in gambling;
    (ii) Problem gambling behaviour;
    (iii) The consequences they (or others) experience as a result of his/her problem gambling; and
    (iv) Correlates of problem gambling,

    The whole as appears more fully from a copy of an extract from the Gambling Research Exchange Ontario website at www.greo.ca, produced herein as **Exhibit P-26**;

50. Risk factors for gambling disorder include (1) temperamental factors (eg, antisocial personality disorder, depressive disorder, bipolar disorder, and substance/alcohol use disorders); and (2) genetic, environmental, and physiological factors. A third risk factor for pathologic gambling is the use of dopamine receptor agonists and partial dopamine agonists (aripiprazole). (Exhibits P-49 and P-51). Aripiprazole can increase impulse-control problems and pathologic gambling as a result of its partial agonistic action on D_3 receptors;

51. Dopamine has been a prime candidate for investigation of neurochemical abnormalities in pathological gamblers, given its established roles in both drug addiction and rewarded behaviour. In patients with Parkinson's disease, sudden onset gambling can be observed, alongside other reward-driven behaviors, including compulsive shopping and hypersexuality, as a side effect of dopamine agonist medications, the whole as appears more fully from a copy of the Journal of Neuroscience mini-symposium entitled "Pathological Choice: The Neuroscience of Gambling and Gambling Addiction" dated November 6, 2013, produced herein as **Exhibit P-27**;

52. By far, the most prevalent form of gambling is lotteries (instant win or scratchtickets). The following table charts the age distribution of Canadians who participated in gambling activities between June 2015 and June 2016, by type:



The whole as appears more fully from a copy of an extract from the Statista website at www.statista.com, produced herein as **Exhibit P-28**;

(b) Compulsive Eating/ Binge Eating

53. Binge-eating disorder is an eating disorder that is characterized by recurring episodes of binge eating. It is important to note that overeating and binge-eating are not the same. Overeating can be described as consuming more food than your body needs at a given time. Most people overeat on occasion. Binge-eating is less common and is marked by psychological distress, the whole as appears more fully from a copy of an extract from the National Eating Disorder Information Centre (NEDIC) website at https://nedic.ca, produced herein as **Exhibit P-29**;

54. A binge-eating episode is characterized by the consumption of an unusually large amount of food during a relatively short period of time and feeling out of control over what and how much is eaten and when to stop. A binge-eating episode also includes three or more of the following (Exhibit P-29):

(i) Eating very quickly
(ii) Eating regardless of hunger cues, even if one is already full
(iii) Eating until uncomfortably or painfully full

(iv) Eating alone due to embarrassment about the type and quantity of food ingested
(v) Feelings of self-disgust, guilt, and depression;

55. While overeating is defined as eating more calories than are necessary to maintain health and can become hard to control the urge to do so (compulsive), binge eating disorder (BED) is a mental health condition that involves recurring episodes of compulsively (uncontrollably) eating far more than normal, often after feeling full or otherwise when not hungry. It leads to physical and emotional discomfort of some kind, like guilt, shame, embarrassment, remorse, and self-disgust. While both binge eating disorder and otherwise compulsive overeating may involve eating in reaction to certain feelings (emotional eating), not everyone who overeats suffers from binge eating or any other eating disorder. However, overeating is a symptom for everyone who has binge eating disorder. BED is understood to be an impulse control disorder and involves compulsive behaviours, the whole as appears more fully from a copy of an extract from the MedicineNet website at www.medicinenet.com, produced herein as **Exhibit P-30**;

56. The DSM-5 classifies Binge-Eating Disorder under "Feeding and Eating Disorders" with the diagnostic criteria *inter alia* as follows (Exhibit P-15):

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:

1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most people would eat in a similar period of time under similar circumstances.
2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).

B. The binge-eating episodes are associated with three (or more) of the following:

1. Eating much more rapidly than normal.
2. Eating until feeling uncomfortably full.
3. Eating large amounts of food when not feeling physically hungry.
4. Eating alone because of feeling embarrassed by how much one is eating.
5. Feeling disgusted with oneself, depressed, or very guilty afterward.

57. Binge eating is classified as a mental health disorder on the ICD-11 and is described as follows:

> An episode in which an individual eats notably more than usual and feels that she or he is unable to stop or limit the amount or type of food eaten.

Overeating is classified as a mental health disorder on the ICD-11 and is described as follows:

> The consumption of excess food in relation to energy and nutritional requirements.

Binge eating disorder is classified as a mental health disorder on the ICD-11 and is described as follows:

> Binge eating disorder is characterized by frequent, recurrent episodes of binge eating (e.g., once a week or more over a period of several months). A binge eating episode is a distinct period of time during which the individual experiences a subjective loss of control over eating, eating notably more or differently than usual, and feels unable to stop eating or limit the type or amount of food eaten. Binge eating is experienced as very distressing, and is often accompanied by negative emotions such as guilt or disgust. However, unlike in Bulimia Nervosa, binge eating episodes are not regularly followed by inappropriate compensatory behaviours aimed at preventing weight gain (e.g., self-induced vomiting, misuse of laxatives or enemas, strenuous exercise).

The whole as appears more fully from copies of the ICD-11 entries for Binge eating, Overeating, and Binge eating disorder, produced herein *en liasse* as **Exhibit P-31**;

58. Health impacts of overeating and bingeing can include diabetes, high blood pressure, joint pain and distress (from carrying extra weight), depression, obesity, and heart disease, the whole as appears more fully from a copy of an extract from the Canadian Mental Health Association website at https://ontario.cmha.ca, produced herein as **Exhibit P-32**;

(c) Uncontrollable or Compulsive Shopping or Spending (Oniomania)

59. Compulsive buying disorder, or oniomania, is characterized by an obsession with shopping and buying behaviour that causes adverse consequences. Compulsive buying "is experienced as an irresistible–uncontrollable urge, resulting in excessive, expensive and time-consuming retail activity [that is] typically prompted by negative affectivity" and results in "gross social, personal and/or financial difficulties". Compulsive shopping is classified by the International Statistical Classification of Diseases and Related Health Problems (ICD) as an "impulse control disorder, not otherwise classified." Several authors consider compulsive shopping rather as a variety of dependence disorder, the whole as appears more fully from a copy of the

Clinical Psychology and Psychotherapy report entitled “Compulsive buying: A cognitive-behavioural model” dated March-April 2009, produced herein as **Exhibit P-33**;

60. The incidence of compulsive buying tends to affect women rather than men, accounting for over 90% of the affected demographic. People with compulsive buying tendencies tend to have a constant need to consume, personal dependence, and an affinity to lack of sense of control over self-behaviour. Individuals ailing from this disorder are often in the second decade to fourth decade of their lives and exhibit mannerisms akin to neurotic personality and impulse control disorders, the whole as appears more fully from a copy of the Psychiatria Polska report entitled “Compulsive buying in outline” dated 2016, produced herein as **Exhibit P-34**;

61. Proposed diagnostic criteria for compulsive buying are the following (Exhibit P-34):

    1. Faulty preoccupation with buying or shopping, or abnormal urge and behaviours towards buying, fulfilling at least one of the criteria below:

        - Frequent preoccupation with buying or urge to shopping which was experienced as an irresistible, intrusive and senseless activity;

        - Frequent shopping for a price exceeding an acceptable budget or frequent shopping for longer periods than planned;

    2. Preoccupation with buying as well as urges and behaviours related to a buying action caused crucial dissatisfactions, absorbed much time, had significant influence on social and occupational functioning (indebtedness, bankruptcy, etc.);

    3. Episodes of compulsive buying did not occur during hypomanic periods and mania episodes;

62. While initially triggered by a need to feel special, the failure of compulsive shopping to actually meet such needs may lead to a vicious cycle of escalation, with sufferers experiencing the highs and lows associated with other addictions. The ‘high’ of the purchasing may be followed by a sense of disappointment, and of guilt, precipitating a further cycle of impulse buying. With the now addicted person increasingly feeling negative emotions like anger and stress, they may attempt to self-medicate through further purchases, followed again by regret or depression once they return home, leading to an urge for buying more, the whole as appears more fully from a copy of extracts from the Handbook of Addictive Disorders dated 2004, produced herein as **Exhibit P-35**;

63. Compulsive buying-shopping disorder is in the ICD-11 as “Other specified impulse control disorders”;

64. The consequences of compulsive buying, which may persist long after a spree, can be devastating, with marriages, long-term relationships, and jobs all becoming strained. Further problems can include ruined credit history, theft or misappropriation of money, defaulted loans, general financial troubles and in some cases bankruptcy or extreme debt, as well as anxiety and a sense of life spiraling out of control. The resulting stress can lead to physical health problems and ruined relationships, or even suicide;

(d) Hypersexual Behaviours/ Sexual Addiction/ Hypersexuality/ Compulsive Sexual Behaviour

65. Compulsive sexual behaviour disorder is classified as a mental health disorder on the World Health Organization's International Classification of Diseases list (called ICD-11) and is described as follows:

> Compulsive sexual behaviour disorder is characterized by a persistent pattern of failure to control intense, repetitive sexual impulses or urges resulting in repetitive sexual behaviour. Symptoms may include repetitive sexual activities becoming a central focus of the person's life to the point of neglecting health and personal care or other interests, activities and responsibilities; numerous unsuccessful efforts to significantly reduce repetitive sexual behaviour; and continued repetitive sexual behaviour despite adverse consequences or deriving little or no satisfaction from it. The pattern of failure to control intense, sexual impulses or urges and resulting repetitive sexual behaviour is manifested over an extended period of time (e.g., 6 months or more), and causes marked distress or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. Distress that is entirely related to moral judgments and disapproval about sexual impulses, urges, or behaviours is not sufficient to meet this requirement.

The whole as appears more fully from a copy of the CNN article entitled "WHO classifies compulsive sexual behavior as mental health condition" dated July 10, 2018 and from a copy of the ICD-11 entry for Compulsive sexual behaviour disorder, produced herein *en liasse* as **Exhibit P-36**;

66. Paradoxically, although hypersexual disorder was rejected by the American Psychiatric Association for DSM-5, the previous version, DSM-4, did include an entry called "Sexual Disorders Not Otherwise Specified (Sexual Disorder NOS)" to apply to, among other conditions, "distress about a pattern of repeated sexual relationships involving a succession of lovers who are experienced by the individual only as things to be used", the whole as appears more fully from a copy of the Addiction article entitled "Diagnosis of Hypersexual or Compulsive Sexual Behavior Can Be Made Using ICD-10 and DSM-5 Despite Rejection of This Diagnosis by the American Psychiatric

Association" dated April 17, 2016 and from a copy of an extract from the Psychology Today website at www.psychologytoday.com, produced herein *en liasse* as **Exhibit P-37**;

F. The Scientific Studies on ABILIFY and Aripiprazole

67. ABILIFY emulates dopamine, a chemical that is critical for controlling the pleasure and reward centers in the brain. It is also a chemical that has often been implicated in relation to addiction. Researchers argue that dopamine has two key effects on patients: (i) it can impair decision-making and (ii) create urges that must be rewarded. The drug can minimize cognitive control while, at the same time, stimulate the brain's reward system. The studies and case reports that follow demonstrate that ingesting ABILIFY causes an increased risk of Impulse-Control Disorders;

68. Since as early as 2004, there have been numerous studies, case series, and case reports published in scientific medical journals that demonstrate that the ingestion of ABILIFY causes an increased risk of Impulse-Control Disorders. In addition, the studies indicate that for patients experiencing the Impulse-Control Disorders, the cessation of ABILIFY oftentimes alleviates these symptoms and that reintroducing the medication causes patients to rapidly relapse;

    (a) In 2004, the complex nature of reward processing in the brain and the role of the brain's reward circuitry in several psychiatric disorders including substance use disorders, schizophrenia, pathologic gambling, major depressive disorder, and attention-deficit/hyperactivity disorder was investigated. The report concluded that more research would be beneficial on the relationship between dopamine and various disorders including pathological gambling, the whole as appears more fully from a copy of the Current Psychiatry Reports report entitled "The neural circuitry of reward and its relevance to psychiatric disorders" dated November 2004, produced herein as **Exhibit P-38**;

    (b) In April 2007, a case report was published detailing the exacerbation of obsessive-compulsive disorder (OCD) during treatment with atypical antipsychotics (such as ABILIFY), the whole as appears more fully from a copy of the Journal of Clinical Psychopharmacology Letters to the Editors entitled "Worsening of Obsessive-Compulsive Symptoms After Treatment With Aripiprazole" dated April 2007, produced herein as **Exhibit P-39**;

    (c) In October 2008, a case report was published detailing an uncontrollable increase in sexual desire following the ingestion of aripiprazole. It was proposed that aripiprazole could be responsible for the induced increase in sexual desire and arousal in the patient because of its agonistic dopaminergic activity at the mesolimbic circuit, especially at the nucleus

accumbens, was associated with compulsive behaviour. The authors concluded the following:

> …further careful evaluation is required to elucidate mechanisms through which aripiprazole may affect sexual function.

The whole as appears more fully from a copy of the Journal of Clinical Psychopharmacology Letters to the Editors entitled “Aripiprazole Induced Hypersexuality in a 24-Year-Old Female Patient With Schizoaffective Disorder?” dated October 2008, produced herein as **Exhibit P-40**;

(d) In May 2009, 2 case studies were reported in which the administration of aripiprazole had induced behavioural changes related to impulse control and addictions such as hypersexuality and excessive shopping. The authors concluded the following:

> These two cases imply that aripiprazole can stimulate dopamine receptors in the specific brain regions associated with impulse control and addiction in the same way that full dopamine agonists do in a pathological state. Furthermore, it is known that the more the receptor reserve exists, the more activation a partial agonist can produce. The limbic dopaminergic projection from the ventral tegmental area has been implicated in addiction and reward experiences such as food, sex, and addictive drugs…
>
> … Because aripiprazole has a high affinity to D_2 receptors, about 90% of D_2 receptors are occupied by it, and both tonic and phasic dopamine transmissions are blocked. However, its intrinsic activity and long half-life adds to the constant dopaminergic tone (tonic component) (Hamamura & Harada, 2007). This unique effect of aripiprazole on dopaminergic transmission may account for the changes in impulsive behaviour…
>
> Another possible explanation for the behavioural effects of aripiprazole is participation of the dopamine D3 receptor, which is highly enriched in the nucleus accumbens and plays an important role in reward. It has been postulated that dopamine agonists with high D3 receptor affinity tend to produce impulsive-addictive behavioural abnormality in dopamine dysregulation syndrome (Dodd et al. 2005)…
>
> … Although aripiprazole is a new antipsychotic with a low risk of adverse effects, its distinctive feature as a dopamine partial agonist could cause unexpected side-effects. It is necessary to pay additional attention in clinical use.

The whole as appears more fully from a copy of the International Journal of Neuropsychopharmacology case study entitled “Aripiprazole-induced behavioural disturbance related to impulse control in a clinical setting” dated October 10, 2009, produced herein as **Exhibit P-41**;

(e) In March 2010, an article was published detailing the experience of a 64-year old woman who after being prescribed aripiprazole, she experienced an irresistible urge to gamble and compulsion to eat – these urges stopped one month after switching medications, the whole as appears more fully from a copy of the Australian & New Zealand Journal of Psychiatry correspondence entitled “Pathological Gambling and Compulsive Eating Associated with Aripiprazole” dated March 2010, produced herein as **Exhibit P-42**;

(f) In November 2010, a case report was published in which two patients with schizophrenia, previously treated with anti-psychotic drugs and no history of pathological gambling, who within a short time after starting aripiprazole, developed pathological gambling symptoms and criminal behaviour, which totally resolved after stopping the drug, the whole as appears more fully from a copy of the Journal of Forensic Sciences article Case Report entitled “Partial Agonist Therapy in Schizophrenia: Relevance to Diminished Criminal Responsibility” dated November 2010, produced herein as **Exhibit P-43**;

(g) In 2010, two case reports were published in which two patients experienced adverse behavioural changes related to impulse control and addictions such as hypersexuality and excessive shopping after administration of aripiprazole, the whole as appears more fully from a copy of the International Journal of Neuropsychopharmacology Letter to the Editor entitled “Aripiprazole-induced behavioural disturbance related to impulse control in a clinical setting” dated 2010, produced herein as **Exhibit P-44**;

(h) In 2011, three case reports were published that suggested that pathological gambling may have been caused following treatment with aripiprazole. All three subjects reported an escalation of gambling and uncontrollable urges upon being administered ABILIFY and all three reported these urges normalizing upon cessation of the drug, the whole as appears more fully from a copy of report from the British Journal of Psychiatry entitled “Pathological gambling and the treatment of psychosis with aripiprazole: case reports” dated 2011, produced herein as **Exhibit P-45**;

(i) In 2011, three cases of pathological gambling induced by Aripiprazole were reported whereby there was no prior history of pathological gambling and they started gambling after initiating treatment with Aripiprazole. The pathological behaviour disappeared when the medication ended, the

whole as appears more fully from a copy of the Current Drug Safety article entitled “Aripiprazole-Induced Pathological Gambling: A Report of 3 Cases” dated 2011, produced herein as **Exhibit P-46**;

(j) In 2013, two cases of hypersexuality were reported in patients receiving treatment with aripiprazole, the whole as appears more fully from a copy of the Case Report entitled “Two Cases of Hypersexuality Probably Associated with Aripiprazole” dated 2013, produced herein as **Exhibit P-47**;

(k) In November 2013, an article was published discussing *inter alia* dopamine abnormalities with pathological gambling due to its established roles in both drug addiction and rewarded behaviour and the observations of sudden-onset gambling, compulsive shopping, and hypersexuality in patients with Parkinson’s disease treated with dopamine agonist medication, the whole as appears more fully from a copy of the Journal of Neuroscience article entitled “Pathological Choice: The Neuroscience of Gambling and Gambling Addiction” dated November 6, 2013, produced herein as **Exhibit P-48**;

(l) In December 2014, a study was published that analyzed the records of 1,580 patients who had reported adverse drug effects involving compulsive gambling and other impulse behaviour issues. The researchers conducting the study reported that they found a “significant” link between use of ABILIFY and gambling, the whole as appears more fully from a copy of the JAMA Internal Medicine article entitled “Reports of Pathological Gambling, Hypersexuality, and Compulsive Shopping Associated With Dopamine Receptor Agonist Drugs” dated 2014, produced herein as **Exhibit P-49**;

(m) In March 2014, a study was published that involved eight people who were being treated for compulsive gambling. A direct link between the use of aripiprazole and the disorder was present in 7 of the patients. The researchers reported those patients could once again control their impulse to gamble after they were taken off of the medication, the whole as appears more fully from a copy of the Addictive Behaviors “Aripiprazole: a new risk factor for pathological gambling? A report of 8 case reports” dated March 2014, produced herein as **Exhibit P-50**;

(n) In February 2016, a study was published which compared the characteristics of possibly medication-induced (iatrogenic) problem gambling in patients taking ABILIFY with the characteristics of such gambling in patients taking a full dopamine replacement therapy. The authors of the study concluded that it was possible that the gambling behaviour in 16 of the 17 cases was “actually due to” ABILIFY, but cautioned that more research would be necessary to definitively establish that ABILIFY causes compulsive gambling, the whole as appears more

fully from a copy of the Journal of Clinical Psychopharmacology review article entitled “Pathological Gambling Associated with Aripiprazole or Dopamine Replacement Therapy: Do Patients Share the Same Features? A Review” dated February 2016, produced herein as **Exhibit P-51**;

(o) A July 2016 case report described a 28-year old man that experienced gambling disorder, hypersexuality and a new sexual orientation while taking aripiprazole, the whole as appears more fully from a copy of the Reactions case report entitled “Aripiprazole – Gambling addiction and compulsive sexual behaviour: case report” dated July 2, 2016, produced herein as **Exhibit P-52**;

(p) In January 2017, a case report was discussed whereby a 35-year old man had reported an increased urge to gamble and hypersexuality 4 weeks after starting ABILIFY and a further increase upon a dose increase. Upon another dose increase he began to compulsively shop as well. Two weeks after stopping ABILIFY, his urges ceased. This case report added to the existing literature and is one of the few specifically linking aripiprazole with induction of multiple Impulse-Control Disorders in a single patient with no history, with complete resolution of these symptoms following its cessation The whole as appears more fully from a copy of the Primary Care Companion for CNS Disorders case report entitled “Aripiprazole and Impulse-Control Disorders: A Recent FDA Warning and a Case Report” dated January 12, 2019, produced herein as **Exhibit P-53**;

(q) In February 2017, an epidemiological study was published in which a statistically significant association was found to exist between ABILIFY and Impulse-Control Disorder and between ABILIFY and gambling disorder (the “Etminan Study”), the whole as appears more fully from a copy of the Journal of Clinical Psychopharmacology brief report entitled “Risk of Gambling Disorder and Impulse Control Disorder With Aripiprazole, Pramipexole, and Ropinirole” dated February 2017, produced herein as **Exhibit P-54**;

(r) In May 2017, a case report was presented of a 33-year old mean who suffered aripiprazole induced excessive libido while on aripiprazole, which normalized upon stopping the medication, the whole as appears more fully from a copy of the Asian Journal of Psychiatry article entitled “Aripiprazole induced hypersexuality, when we should be cautious?” dated May 28, 2017, produced herein as **Exhibit P-55**;

(s) In June 2017, a case study was published demonstrating a clear temporal relationship between aripiprazole and impulse-control disorders and called for caution and monitoring when prescribing aripiprazole to high-risk patients, the whole as appears more fully from a copy of the Asian Journal of Psychiatry study entitled “Aripiprazole and impulse-control disorders in high-risk patients” dated June 2017, produced herein as **Exhibit P-56**;

(t) In December 2017, a case report was published demonstrating that aripiprazole causes or exacerbates problem gambling, including low-dose use of aripiprazole in the gambling naïve. The case was a 51-year old woman who, within a few days of starting aripiprazole 5 mg, developed a strong urge to gamble. She reduced her dosage, which did not alleviate the symptoms and then after ceasing completely, she lost the urge to gamble. The authors concluded:

> This case provides further support for the importance of screening for the emergence of pathological gambling and other impulse-control dysregulation when commencing a patient on aripiprazole…
>
> Aripiprazole-induced problem gambling and impulse-control dysregulation are side effects to assess for when commencing a patient on aripiprazole. This case reinforces that this risk is real even in those started on a low dose with no history of problem gambling or other impulse-control disorder. Awareness of this risk facilitates appropriate history-taking and surveillance upon commencing aripiprazole.

The whole as appears more fully from a copy of the Australasian Psychiatry case report entitled "Partial dopamine agonist-induced pathological gambling and impulse-control deficit on low-dose aripiprazole" dated December 2017, produced herein as **Exhibit P-57**;

(u) In 2017, a case report was published about a 24-year old man who suffered from spontaneous erections while taking aripiprazole. Upon reducing the dosage, they stopped. Because aripiprazole acts on serotoninergic receptors and has partial 5-HT_{1A} agonist and $5HT_{2A}$ antagonistic properties it promotes sexuality, the whole as appears more fully from a copy of the Archives of Neuropsychiatry article entitled "Spontaneous Ejaculations Associated with Aripiprazole" dated 2017, produced herein as **Exhibit P-58**;

(v) In 2018, two case studies were discussed relating to aripiprazole-induced hypersexuality whereby it was noted that because of its receptor profile and distinct mechanism of action non dopamine and serotonin, aripiprazole often contributes to a unique set of problems like hypersexuality and pathological gambling. The authors, in attempting to explain why ABILIFY causes the Impulse-Control Disorders wrote the following:

> The possible mechanisms related to the occurrence of this unique side effect are partial agonistic properties at D2, D3, and a partial agonist at 5 HT1A and antagonist at 5 HT2A (Cheon et al., 2013; Mété et al., 2016). Another hypothesis is that the

> treatment with drugs having strong dopaminergic antagonist properties prior to the Aripiprazole causes the up-regulation of the dopamine receptors, on which the subsequent addition of the Aripiprazole, can lead to the hypersexuality behaviors (Mohan et al., 2017).
> …
> As per literature search, the hypersexual behaviors start within 1st or 2nd weeks of the initiation of Aripiprazole, which might last up to 3 weeks even after the discontinuation…
>
> We can conclude this discussion by mentioning that the clinician need to be cautious about some of the factors which can increase the risk of Aripiprazole induced hypersexuality…

The whole as appears more fully from a copy of the Asian Journal of Psychiatry discussion paper entitled "Hypersexuality induced by Aripiprazole: Two case reports and review of the literature" dated 2018, produced herein as **Exhibit P-59**;

(w) In May 2018, a case report was published whereby a 45- year old woman with major depressive disorder had developed kleptomania while taking ABILIFY, with the onset of the symptoms commenced just after starting on ABILIFY 2 mg – when ABILFY was discontinued, she reported no further urges to steal or episodes of kleptomania, the whole as appears more fully from a copy of the Journal of Affective Disorders case report entitled "Aripiprazole-induced kleptomania: Case report" dated May 2018, produced herein as **Exhibit P-60**;

(x) In March 2019, a case report and literature review was published whereby a patient with bipolar disorder and previous gambling disorder experienced an escalation of gambling behaviour with the introduction of aripiprazole and its upward titration. The patient's gambling problems were alleviated with a decrease in aripiprazole dosage. The authors concluded that:

> Health care professionals should be vigilant concerning the possible association of aripiprazole with pathologic gambling. Patients, especially those with a history of impulse-control disorders and gambling behavior, should be assessed for the increased risk of pathological gambling before aripiprazole treatment. At each visit, patients being treated with aripiprazole should be closely monitored for impulse-control problems and gambling behavior so that early identification and appropriate management, such as a decrease in aripiprazole dosage or a change to a different medication, could possibly prevent severe consequences.

The whole as appears more fully from a copy of the Journal of Psychiatric Practice case report and literature review entitled “Escalation of Gambling Associated With Aripiprazole: A Case Report and Literature Review” dated March 2019, produced herein as **Exhibit P-61**;

(y) In May/June 2019, a case report was published whereby in discussing two cases where the patients experienced pathological gambling while on ABILIFY, which was resolved following replacement with another antipsychotic, the authors discussed the following:

> Our findings not only echo previous reports regarding the association of pathological gambling with aripiprazole treatment but also emphasize the importance of keeping this possible drawback of aripiprazole treatment in mind, especially when treating young patients who do not have known propensity of addictive behaviors but are sensitive to pharmacological effects and adverse effects.
> …
> The compulsion to gamble is postulated to be largely due to aripiprazole's partial agonist activity at dopamine D2 and D3 receptors. The overstimulation of dopaminergic receptors in the mesolimbic system might lead to pathological gambling.
> …
> Our cases revealed that pathological gambling associated with aripiprazole could emerge de novo simply due to exposure to this agent. Thus, those who respond well to a low-dose aripiprazole treatment yet accompanied by adverse somatic symptoms warrant careful inquiry to this potentially problematic behavioral side effect.

The whole as appears more fully from a copy of the Clinical Neuropharmacology case report entitled “Two Cases of De Novo Pathological Gambling Associated With Aripiprazole” dated May/June 2019, produced herein as **Exhibit P-62**;

69. The authors of the Etminan Study (Exhibit P-54) analyzed medical and pharmaceutical billing information for over 6 million individuals, drawn from a large insurance claims database known as LifeLink[12]. The database included, *inter alia*, patients’ diagnoses and all prescriptions they filled between 2006 and 2014. Within this data, the authors first identified all individuals whose insurance records reflected a diagnostic code for either pathological gambling

[12] The purpose of an epidemiological case-control study is to determine whether exposure to a drug is associated with a particular outcome (i.e., a disease or adverse effect). Researchers identify a group of individuals who have a disease (“cases”) and a group of similar individuals who do not have the disease (“controls”). See id. Then, they compare the two groups in terms of past exposure to the drug. See id. If individuals in the case group are found to have a higher proportion of past exposure than the controls, then an association is said to exist between exposure and the disease.

or impulse control disorder. These individuals served as the Etminan Study's "case" group. Next, from the same data, the authors drew a random sample of similar individuals whose records contained neither diagnostic code. These individuals served as "controls." The authors then compared the cases (individuals diagnosed with pathological gambling or impulse control disorders) to the controls (individuals with no such diagnoses) based on the prevalence of exposure to ABILIFY in each group. Exposure to Abilify was defined for the cases as one prescription for ABILIFY having been filled during the year before the pathological gambling or impulse control disorder diagnosis, and in corresponding calendar time for the controls. The study found that individuals exposed to Abilify had a statistically significant higher incidence of pathological gambling and impulse control disorder diagnoses than did unexposed individuals;

70. Many of these studies demonstrate what is known as a challenge, de-challenge, and re-challenge:

    (a) Challenge is the administration of a suspect product by any route,

    (b) De-challenge is the withdrawal of the suspected product from the patient's therapeutic regime. A positive de-challenge is the partial or complete disappearance of an adverse experience after withdrawal of the suspect product. For example, a positive de-challenge occurs when a patient ceases use of ABILIFY and pathological gambling behaviours cease,

    (c) Re-challenge is defined as a reintroduction of a product suspected of having caused an adverse experience following a positive de-challenge. A positive re-challenge occurs when similar signs and symptoms reoccur upon reintroduction of the suspect product. For example, a positive re-challenge occurs when a patient reintroduces ABILIFY into her treatment regime and pathological gambling behaviour reoccurs in a similar manner as such behaviours had existed when the patient previously used ABILIFY,

    The whole as appears more fully from a copy of the U.S. FDA draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biologic Products Including Vaccines dated 2001, produced herein as **Exhibit P-63**;

71. A positive de-challenge is considered evidence that a drug caused a particular effect, as is a positive re-challenge, the whole as appears more fully from a copy of the U.S. FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment dated March 2005 and from a copy of the Federal Judicial Center's Reference Manual on Scientific Evidence – Third Edition, dated 2011, produced herein *en liasse* as **Exhibit P-64**;

72. These studies indicate the importance of informing both patients and healthcare professionals of these adverse side-effects so that they may make

informed decisions regarding this medication. In addition, should the patient make an informed decision to take ABILIFY in spite of the serious risks, knowledge of these risks would have led to the cessation of its ingestion upon experiencing the Impulse-Control Disorders as they would have been able to identify the reason for their existence;

73. Even before there were studies indicating that ABILIFY could cause or materially contribute to a risk of developing the Impulse-Control Disorders (as well as during), the Defendants had to have been aware of the numerous studies on dopamine receptor agonist drugs, used to treat Parkinson disease, restless leg syndrome, and hyperprolactinemia[13]. Some of these studies prior to 2010 follow:

    (a) In 1989, a case report was published reporting observations of hypersexuality in a selected group of 13 patients as a consequence of taking dopamine agonists, the whole as appears more fully from a copy of the Clinical Neuropharmacology "Hypersexuality with Antiparkinsonian Therapy" dated 1989, produced herein as **Exhibit P-65**;

    (b) An August 1999 report described dopamine replacement therapy as a cause of behavioural disorders (hedonistic dysregulation), including punding [14], hypersexuality, pathological gambling and shopping, and alterations in appetite, the whole as appears more fully from a copy of the Journal of Neurology, Neurosurgery, and Psychiatry article entitled "Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies" dated August 24, 1999, produced herein as **Exhibit P-66**;

    (c) A February 2000, case report described a 59-year old lady who developed pathological gambling after dopamine treatment for Parkinson's disease and mentioned previous reports describing the emergence of impulsive behaviours, mood disorders, hyperkinesias [15], and dyskinesias [16] associated with dopamine therapy, the whole as appears more fully from a copy of the Depression and Anxiety article entitled "Pathological Gambling Behaviour: Emergence Secondary to Treatment of Parkinson's Disease with Dopaminergic Agents" dated February 24, 2000, produced herein as **Exhibit P-67**;

    (d) A March 2000, report on Parkinson's patients and pathological gambling concluded that pathologic gambling may be a behavioral manifestation of

[13] Hyperprolactinemia is a condition in which a person has higher-than-normal levels of the hormone prolactin in the blood.
[14] Punding activity is characterized by compulsive fascination with and performance of repetitive, mechanical tasks, such as assembling and dissembling, collecting, or sorting household objects.
[15] Hyperkinesia refers to an increase in muscular activity that can result in excessive abnormal movements, excessive normal movements or a combination of both.
[16] Dyskinesia refers to abnormality or impairment of voluntary movement

the pharmacologic treatment (i.e. dopamine agonists), the whole as appears more fully from a copy of the Movement Disorder article entitled "Pathologic Gambling in Parkinson's Disease: A Behavioral Manifestation of Pharmacologic Treatment?" dated March 15, 2000, produced herein as **Exhibit P-68**;

(e) In 2000, a case report was published whereby a 59-year old lady, with no previous history of pathological gambling, developed the disorder while on dopamine agonist treatment for Parkinson's disease. After adjusting dosage and adding medication, her gambling ceased. The authors expressed that "Additional neurobiological research that investigates the association between pathological gambling and correlates of dopamine, is necessary", the whole as appears more fully from a copy of the Depression and Anxiety article entitled "Pathological Gambling Behaviour: Emergence Secondary to Treatment of Parkinson's Disease with Dopaminergic Agents" dated February 24, 2000, produced herein as **Exhibit P-69**;

(f) A 2001 report, in exploring the connection between pathological gambling and overconsumption of dopamine agonists, described two patients with Parkinson's disease that developed pathological gambling in parallel with a dose increase of dopaminergic drug treatment. The authors concluded:

> The most likely explanation for this newly recognized behavioral disorder in patients with Parkinson's disease is enhanced novelty seeking as a consequence of overstimulation of mesolimbic dopamine receptors resulting from addiction to dopaminergic drugs.

The whole as appears more fully from a copy of the Clinical Neuropharmacology article entitled "Pathologic Gambling in Patients with Parkinson's Disease" dated 2001, produced herein as **Exhibit P-70**;

(g) In August 2003, a retrospective database review of all patients with Parkinson's disease seen at a research centre from May 1, 1999, to April 30, 2000, was performed for pathologic gambling. Nine patients were reported to have suffered pathological gambling, which was associated with chronic high dose dopamine agonist therapy, the whole as appears more fully from a copy of the Neurology article entitled "Pathological gambling associated with dopamine agonist therapy in Parkinson's disease" dated August 2003, produced herein as **Exhibit P-71**;

(h) In February 2004, a case report described two cases where increases in dopaminergic therapy was associated with pathological gambling. At this point, 29 cases of pathological gambling had been reported in patients with Parkinson's disease, the whole as appears more fully from a copy of the Neurological Sciences case report entitled "Pathological gambling in two

patients on dopamine replacement therapy for Parkinson's disease" dated February 22, 2004, produced herein as **Exhibit P-72**;

(i) In 2005, a study was conducted to analyze the complication of pathological gambling when medically treating Parkinson's disease – all 11 patients with Parkinson's disease and pathological gambling were taking therapeutic doses of a dopamine agonist. The following was concluded:

> Dopamine agonist therapy was associated with potentially reversible pathological gambling…This may relate to disproportionate stimulation of dopamine D3 receptors, which are primarily localized to the limbic system.

The whole as appears more fully from a copy of the Archives of Neurology "Pathological Gambling Caused by Drugs Used to Treat Parkinson Disease" dated 2005, produced herein as **Exhibit P-73**;

(j) In 2005, a study was published whereby pathological hypersexuality had developed in 15 patients after initiating medication with dopamine agonists to treat Parkinson's disease or multiple system atrophy, the whole more fully from a copy of the Parkinsonism and Related Disorders study entitled "Pathological hypersexuality predominantly linked to adjuvant dopamine agonist therapy in Parkinson's disease and multiple system atrophy" dated 2005, produced herein as **Exhibit P-74**;

(k) In 2005, a case study was published about a 55-year man with Parkinson's disease who presented with compulsive hypersexual behaviour and the authors discuss that hypersexuality has been associated with dopaminergic drug therapy, the whole as appears more fully from a copy of the American Journal of Therapeutics article entitled "Effects of Donepezil on Compulsive Hypersexual Behavior in Parkinson Disease" dated 2005, produced herein as **Exhibit P-75**;

(l) A December 2006 case report described two cases of Parkinson's patients experiencing paraphilia[17] and hypersexuality while on dopamine agonists, the whole as appears more fully from a copy of the Parkinsonism and Related Disorders case report entitled "Hypersexuality and paraphilia induced by selegiline in Parkinson's disease: Report of 2 cases" dated 2006, produced herein as **Exhibit P-76**;

(m) In 2007, a case report described three patients who developed pathological gambling while receiving treatment with dopamine agonists for restless legs syndrome, the whole as appears more fully from a copy of the Neurology article entitled "Pathologic gambling in patients with

[17] Paraphilia is a condition characterized by abnormal sexual desires, typically involving extreme or dangerous activities.

restless legs syndrome treated with dopaminergic agonists" dated 2007, produced herein as **Exhibit P-77**;

(n) In March 2008, a review of cases of impulse control disorders associated with Parkinson's disease revealed that dopaminergic drugs, particularly dopamine agonists, play an important role in triggering impulse control disorders, the whole as appears more fully from a copy of The Neurologist review article entitled "Impulse Control Disorders and Pathological Gambling in Patients With Parkinson Disease" dated March 2008, produced herein as **Exhibit P-78**;

(o) In May 2008, an article was published describing the impulse control disorders that develop in Parkinsonian patients taking dopamine agonists and which improve or stop when the medication is readjusted, the whole as appears more fully from a copy of the Revue Médicale Suisse article entitled "Troubles du contrôle des impulsions et maladie de Parkinson" dated May 7, 2008, produced herein as **Exhibit P-79**;

(p) An August 2008 case report detailed the experience of a 70-year old woman with Parkinson's disease on dopaminergic therapy presented with compulsive shopping. The authors noted that the impulse control disorder was not unique to Parkinson's disease and that the temporal association between the medication initiation and the onset of the behaviour indicated causality. The authors concluded:

> This report suggests that perhaps many dopaminergic medications can be associated with compulsive behaviors. So, educating the patients and their family of these possible side effects is essential. We need to check with both patient and family at follow-up visits for the emergence of a variety of troublesome pathological behaviors that may result from dopaminergic therapy. Future research will need to examine an accurate prevalence of such behavior in conjunction with dopaminergic therapy, as well as the exact mechanism for such behavior.

The whole as appears more fully from a copy of the Journal of Movement Disorders report entitled "Compulsive Shopping in Parkinson's Disease - A Case Report" dated October 2008, produced herein as **Exhibit P-80**;

(q) In September 2010, a study was published whereby the prevalence of impulse control disorders in Parkinson's patients using dopamine replacement therapy varied between 3.5% and 13.6%; a reasonable evidence of causal link, the whole as appears more fully from a copy of the Addiction article entitled "Impulse control disorders in patients with Parkinson's disease receiving dopamine replacement therapy: evidence

and implications for the addictions field" dated September 19, 2010, produced herein as **Exhibit P-81**;

(r) In November 2010, a letter was published describing a study that had been conducted whereby 12.8% of the Parkinson's patients on dopamine treatment had a current or part impulse control disorder. This indicated that it was not rare or atypical, that it was difficult to detect, that screening must be ongoing as onsets can differ and particularly so with changes in dosages, patients often deny or minimize their impulse control disorder(s), that active deception makes self-reporting insufficient, and finally, that "Clinicians must educate patients and caregivers proactively about medication-induced psychiatric disturbances, which masquerade as independent psychiatric disorders or can be misinterpreted as willful behavioral change", the whole as appears more fully from a copy of the Neurologist article entitled "Detection of Impulse Control Disorders in Parkinson Disease Patients" dated November 2010, produced herein as **Exhibit P-82**;

(s) In December 2010, a study was performed on patients with Parkinson's disease who were on dopaminergic agent treatment and who had self-reported experiencing impulse control disorders, the whole as appears more fully from a copy of the Addiction article entitled "Impulse Control Disorders in Parkinson Disease: A Multicenter Case–Control Study" dated December 3, 2010, produced herein as **Exhibit P-83**;

(t) In 2010, a study was published whereby it was concluded that impulse control disorders are common with the use of dopaminergic agents for treatment of restless legs syndrome. Given the potentially devastating psychosocial consequences of these behaviours, it is critical to actively screen for impulse control disorders in this population, the whole as appears more fully from a copy of the Sleep study entitled "Impulse Control Disorders with the use of Dopaminergic Agents in Restless Legs Syndrome: a Case-Control Study" dated 2010, produced herein as **Exhibit P-84**;

74. The Defendants, in failing to advise doctors and patients of the increased risks associated with ABILIFY, effectively usurped their ability to make informed decisions regarding its use and removed their ability to properly diagnose the origin of the Impulse-Control Disorder(s) and limit and/or control the risks through engaging in precautionary monitoring measures, including reducing the dosage or discontinuing altogether;

G. <u>Adverse Reaction/ Event Reporting in Canada, in the U.S., and in Europe</u>

75. Health Canada's Canada Vigilance Adverse Reaction Online Database contains information about suspected adverse reactions (also known as side effects) to health products submitted by consumers and health professionals

voluntarily or by manufacturers and distributors who are required to submit reports under the *Food and Drugs Act*, R.S.C., 1985, c. F-27. With regards to ABILIFY, the following Adverse Event Reports have been submitted:

(a) There are 54 Adverse Reaction Reports related to "Gambling", the first adverse reaction report having been reported to Health Canada on August 25, 2014, the whole as appears more fully from a copy of Health Canada's list of adverse reaction reports and from a copy of the actual reports, produced herein *en liasse* as **Exhibit P-85**;

(b) There are 9 Adverse Reaction Reports related to "Compulsive shopping", the first adverse reaction report having been reported to Health Canada on September 12, 2017, the whole as appears more fully from a copy of Health Canada's list of adverse reaction reports and from a copy of the actual reports, produced herein *en liasse* as **Exhibit P-86**;

(c) There are 18 Adverse Reaction Reports related to "Compulsive sexual behaviour", "Disturbance in sexual arousal", "Excessive sexual fantasies", High risk sexual behaviour", "Hypersexuality", "Sexual activity increased", "Sexual relationship change", "Sexual transmission of infection", "Sexually active", "Sexually inappropriate behaviour", and/or "Sexually transmitted disease", the first adverse reaction report having been reported to Health Canada on October 17, 2014, the whole as appears more fully from a copy of Health Canada's list of adverse reaction reports and from a copy of the actual reports, produced herein *en liasse* as **Exhibit P-87**;

76. In the United States, from May 1, 2009 to May 1, 2011, the U.S. FDA received thousands of serious adverse event[18] reports concerning ABILIFY (n=4599), including over two-thousand serious adverse drug experiences of which 193 involved children (0-16 years old), the whole as appears more fully from a copy of the slides from the U.S. FDA "Pediatric Focused Safety Review: Abilify® (aripiprazole) to May 1, 2011" dated September 22, 2011, produced herein as **Exhibit P-88**;

77. The U.S. FDA Adverse Events Reporting System (FAERS) reveals 2,724 potential Impulse-Control Disorders as a reaction to ABILIFY:

(a) 1,566 reports of "Gambling Disorder",
(b) 888 reports of "Compulsive Shopping",
(c) 626 reports of "Eating Disorder",
(d) 515 reports of "Compulsive Sexual Behaviour"
(e) 409 reports of "Gambling"
(f) 284 reports of "Increased Appetite"
(g) 262 reports of "Impulsive Behaviour"
(h) 197 reports of "Hypersexuality"

[18] Serious adverse events are drug experiences including the outcomes of death, life-threatening events, hospitalization, disability, congenital abnormality, and other harmful medical events.

(i) 172 reports of “Impulse-Control Disorder”
(j) 170 reports of “Shoplifting”
(k) 128 reports of “Hunger”
(l) 61 reports of “Binge Eating”
(m) 23 reports of “Appetite Disorder”

The whole as appears more fully from a copy of the U.S. FDA Adverse Events Reporting System (FAERS) results for ABILIFY and the above Impulse-Control Disorders (or indicators for the Impulse-Control Disorders), produced herein *en liasse* as **Exhibit P-89**;

78. A disproportionality study of the U.S. FDA Adverse Event Reporting System showed a proportional reporting ratio for compulsivity of 8.6 for ABILIFY (Exhibit P-49). A ratio of more than three indicates a signal of an adverse event, the whole as appears more fully from a copy of the International Journal of Medical Sciences article entitled “Data Mining of the Public Version of the FDA Adverse Event Reporting System” dated April 25, 2013, produced herein as **Exhibit P-90**;

79. Similarly, the European pharmacovigilance database, EudraVigilance[19], also reported impulse-control problems in association with aripiprazole, with pathologic gambling the most common problem followed by hypersexuality and compulsive shopping. Up to February 23, 2017, 160 reports were identified of persons who had taken ABILIFY and reported the words “impulse control disorders”, the whole as appears more fully from a copy of the International Clinical Psychopharmacology report entitled “Aripiprazole and impulse control disorders: higher risk with the intramuscular depot formulation?” dated 2017, produced herein as **Exhibit P-91**;

80. It is important to note that because of the feelings of guilt, shame, and distress that is oftentimes associated with the Impulse-Control Disorders, it is highly likely that these side effects are underreported. In many cases, the patients themselves are unaware of and may actually deny these behavioural changes;

H. <u>The General Causation Expert Report of Dr. Alain Dagher, Neurologist</u>

81. On March 28, 2019, Dr. Alain Dagher, neurologist, wrote an expert report concerning the mechanism of action and clinical indications of ABILIFY, along with its link to behavioural addictions such as problem gambling. Dr. Dagher opined the following:

> In sum, it is my opinion that the use of aripiprazole can materially contribute to an elevated risk of developing a behavioural addiction.

[19] EudraVigilance is the system for managing and analyzing information on suspected adverse reactions to medicines which have been authorized or being studied in clinical trials in the European Economic Area (EEA). The European Medicines Agency (EMA) operates the system on behalf of the European Union (EU) medicines regulatory network.

> The medical literature implicates aripiprazole in several forms of impulse control disorder, including cases of problem gambling, hypersexuality, compulsive eating, and compulsive shopping. While certainly individuals are at greater underlying risk than others, it can be stated that it is the drug itself rather than the pre-existing psychopathology or personality that is the direct cause of impulse control disorders in the cases described.

The whole as appears more fully from a copy of the Expert Report of Dr. Alain Dagher dated March 28, 2019, produced herein as **Exhibit P-92**;

I. Governmental Regulation of ABILIFY

82. In October 2012, following a safety review of ABILIFY, the European Medicines Agency required that the Defendants warn patients and the medical community in Europe of the risk of pathological gambling associated with the use of ABILIFY, the whole as appears more fully from a copy of the European Medicines Agency document for ABILIFY and from a copy of the European Medicines Agency's Annex I – Summary of Product Characteristics, produced herein *en liasse* as **Exhibit P-93**;

83. Specifically, the European Medicines Agency required the following labelling change in Europe in the "Special warnings and precautions" for use section of the label:

> Pathological gambling
> Post-marketing reports of pathological gambling have been reported among patients prescribed aripiprazole, regardless of whether these patients had a prior history of gambling. Patients with a prior history of pathological gambling may be at increased risk and should be monitored carefully (see section 4.8 of Exhibit P-93),

84. In addition, the risk of pathological gambling was included in the section entitled "Undesirable effects" along with agitation, nervousness, suicide attempt, suicidal ideation, and completed suicide;

85. On November 2, 2015, Health Canada concluded that there is "a link between the use of aripiprazole and a possible risk of pathological gambling or hypersexuality" and found an increased risk of pathological (uncontrollable) gambling and hypersexuality with the use of ABILIFY, the whole as appears more fully from a copy of the Health Canada Information Update entitled "Safety information for antipsychotic drug Abilify and risk of certain impulse-control behaviours" dated November 2, 2015, from a copy of the Health Canada Summary Safety Review - ABILIFY and ABILIFY MAINTENA (aripiprazole) - Evaluating the Risk of Certain Impulse Control Behaviours" dated November 2, 2015, and from a copy of the CTV News article entitled

"Health Canada updates list of possible side effects for 2 antipsychotic drugs" dated November 2, 2015, produced herein *en liasse* as **Exhibit P-94**;

86. On March 10, 2016, the U.S. FDA conducted a Pharmacovigilance Review on the subject of ABILIFY and Impulse-Control Disorders through an evaluation of the cases identified in the U.S. FDA Adverse Event Reporting System database and the published medical literature for an association between aripiprazole and impulse-control disorders and related disorders. The U.S. FDA identified an association between ABILIFY and the following Impulse-Control Disorders: pathological gambling, compulsive sexual behaviours, compulsive buying, compulsive eating, and a multiple of these disorders, the whole as appears more fully from a copy of the Pharmacovigilance Review dated March 10, 2016, produced herein as **Exhibit P-95**;

87. Based on the data analyzed (being 184 case reports), the U.S. FDA recommended that the following warnings/statements be added in 2 places to the ABILIFY product labelling (Exhibit P-95):

> Pathological Gambling and Impulse-Control Disorders Case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported less frequently than gambling, include: sexual urges, uncontrolled spending, binge or compulsive eating, and other urges with impulsive and compulsive features. These urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with aripiprazole. If left unrecognized, these urges may result in harm to the patient and to others. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole,

88. In addition, the U.S. FDA recommended that a Drug Safety Communication be issued containing the above warning information;

89. Since its introduction in the U.S. in November 2002 until mid-January 2016,184 case reports were identified indicating an association between ABILIFY and impulse-control problems. The specific impulse-control problems reported include: pathological gambling (164 cases reported and 89%); compulsive sexual behaviour (9 cases reported); compulsive buying (4 cases reported); compulsive eating (n=3); and multiple impulse-control problems (4 cases reported) and 4 cases had reported multiple Impulse-Control Disorders. These urges began only after starting to take ABILIFY and were resolved after reducing the dosage or discontinuing the treatment altogether, the whole as

appears more fully from a copy of the U.S. FDA Drug Safety Communications Safety Announcement entitled "FDA Drug Safety Communication: FDA warns about new impulse-control problems associated with mental health drug aripiprazole (Abilify, Abilify Maintena, Aristada)" dated May 3, 2016, produced herein as **Exhibit P-96**;

90. The U.S. FDA Drug Safety Communication (Exhibit P-96) stated the following:

> "compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex have been reported with the use of the antipsychotic drug aripiprazole (Abilify, Abilify Maintena, Aristada, and generics)";

91. It was not until February 23, 2017 that the Defendants finally decided to include a proper warning of Impulse-Control Disorders as a potential side effect of ingesting ABILIFY on the Product Monograph (as will be outlined in more detail below);

J. The Defendants' Marketing Practices

92. Despite the risks of serious adverse events and the clear lack of adequate testing, that Defendants aggressively promoted ABILIFY, including illegal promotion for off-label use. In the United States, in 2007, Bristol-Myers reportedly paid $515 million to settle federal and state investigations into off-label marketing of Abilify for pediatric use and to treat dementia-related psychosis. Otsuka American Pharmaceutical, Inc., later paid more than $4 million to resolve the allegations, the whole as appears more fully from a copy of the United States Department of Justice Press Release entitled "Bristol-Myers Squibb to Pay More Than $515 Million to Resolve Allegations of Illegal Drug Marketing and Pricing" dated September 28, 2007 and from a copy of the United States Department of Justice Press Release entitled "Otsuka to Pay More than $4 Million to Resolve off-label Marketing Allegations Involving Abilify" dated March 27, 2008, produced herein *en liasse* as **Exhibit P-97**;

93. The U.S. FDA issued a letter dated April 17, 2015 finding ABILIFY promotional material "false or misleading because it makes misleading claims and presentations about the drug." The U.S. FDA found the material "misleading because it implies that Abilify offers advantages over other currently approved treatments for bipolar disorder or MDD when this has not been demonstrated." The U.S. FDA also found the cited references "not sufficient to support claims and presentations suggesting that Abilify has been demonstrated to modulate dopaminergic and serotonergic activity, or modulate neuronal activity in both hypoactive and hyperactive environments in humans", the whole as appears more fully from a copy of the letter from the U.S. FDA Department of Health & Human Services to Otsuka Pharmaceutical Development & Commercialization, Inc. dated April 17, 2015 and from a copy of the PLoS Medicine article entitled "Questionable Advertising of Psychotropic

Medications and Disease Mongering" dated July 2006, produced herein *en liasse* as **Exhibit P-98**;

94. The Defendants have invested millions of dollars in teams of pharmaceutical sales representatives who visit and contact members of the medical community, including prescribing doctors, purporting to "educate" them about ABILIFY. These pharmaceutical sales representatives have not notified patients, the medical community, or prescribers that ABILIFY use causes, is linked to, or might be associated with compulsive gambling, pathological gambling, or gambling addiction;

95. The Defendants have made payments to doctors to promote ABILIFY. For example, from August 2013 to December 2014, $10.6 million in payments relating to ABILIFY were made to 21,155 physicians in the United States, the whole as appears more fully from a copy of the Pro Publica webpage entitled "Has Your Doctor Received Drug or Device Company Money?" for ABILIFY, produced herein as **Exhibit P-99**;

96. ABILIFY generated $5.501 billion in sales worldwide in 2013, being the tenth best-selling drug worldwide, the whole as appears more fully from a copy of an extract from the FiercePharma article for ABILIFY, produced herein as **Exhibit P-100**;

97. Bristol-Myers touted ABILFY as its "largest-selling product" in 2012, 2013 and 2014, the whole as appears more fully from copies of extracts from Bristol-Myers website at www.bms.com, produced herein *en liasse* as **Exhibit P-101**;

98. Bristol-Myers reported worldwide revenues from sales of ABILIFY of $2.020 billion in 2014, $2.289 billion in 2013, $2.827 in 2012, and $2.758 in 2011, the whole as appears more fully from copies of Bristol-Myers' Annual Reports dated 2014 and 2013, produced herein *en liasse* as **Exhibit P-102**;

99. According to Otsuka's Annual Report for the year 2014, sales of their "top-selling pharmaceutical product ABILIFY constitute approximately 40% of [their] total consolidated net sales". In 2013, Otsuka reported that it constituted over 30% of sales, the whole as appears more fully from copies of Otsuka's Annual Reports dated 2013 and dated 2014, produced herein *en liasse* as **Exhibit P-103**;

100. As stated above, Defendants Bristol-Myers and Otsuka entered into an agreement to co-market and promote ABILIFY in Canada (Exhibit P-3). Under the terms of this agreement, ABILIFY was to be marketed by Bristol-Myers under license by non-party Otsuka Pharmaceutical Co., Ltd. This agreement was originally formed for the marketing of ABILIFY in the U.S. in 1999 whereby it was agreed that Bristol-Myers and Otsuka would collaborate to complete clinical studies for schizophrenia, and that Bristol-Myers would conduct additional studies for new dosage forms and new indications, the whole as

appears more fully from a copy of the Press Release entitled “Bristol-Myers Squibb And Otsuka Announce Commercialization Agreement For Aripiprazole” dated September 21, 1999, produced herein as **Exhibit P-104**;

K. The Canadian Product Monographs for ABILIFY

101. In spite of the strong indication that ABILIFY was causing the Impulse-Control Disorders, the Defendants failed to timely inform consumers, health care professionals, Health Canada and the scientific community and they failed to perform further investigation into its safety;

102. From its introduction in Canada on July 9, 2009, there was absolutely no mention of any Impulse-Control Disorders until June 22, 2015, where, while there was a mention of pathological gambling, it was wholly insufficient;

103. This important information was hardly present in the eighty-four-page Product Monograph of ABILIFY at the time of the filing of the present class action as it was only mentioned three times; one in the “Warnings and Precautions” section as follows:

> Post-marketing reports of pathological gambling have been reported in patients treated with ABILIFY. In relation to pathological gambling, patients with a prior history of gambling disorder may be at increased risk and should be monitored carefully.

Under the section entitled “Post-Market Adverse Drug Reactions” the word “gambling” again appears as follows: “*Unknown*: Pathological gambling, Hypersexuality” and lastly in the Consumer Information section for ABILIFY, “an urge to gamble” appears under “side effects and what to do about them”,

The whole as appears more fully from a copy of the Product Monograph for ABILIFY last revised on June 22, 2015, produced herein as **Exhibit P-105**;

104. The product monograph for ABILIFY was revised again on February 23, 2017 to include information about Impulse-Control Disorders in its ABILIFY product monograph – this was the first mention of Impulse-Control Disorders (the portion in italics appeared in the June 22, 2015 revision (Exhibit P-105)):

> *Post-marketing reports of pathological gambling have been reported in patients treated with aripiprazole.* These reports suggest that patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. With regards to pathological gambling, *patients with a prior history of gambling disorder may be at increased risk and should be monitored carefully*. Other urges, reported very rarely, include: increased sexual urges, compulsive spending, binge or

> compulsive eating, and other impulsive and compulsive behaviors. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive spending, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, although not all, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Although impulse-control disorders have been reported very rarely, impulse-control disorders may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole.

The whole as appears more fully from a copy of the Product Monograph for ABILIFY last revised on February 23, 2017, produced herein as **Exhibit P-106**;

105. Previous versions of the Product Monographs for ABILIFY, from July 9, 2009 to May 27, 2013, which make no mention whatsoever about gambling or Impulse-Control Disorders, pathological or otherwise, are produced herein *en liasse* as **Exhibit P-107**;

106. There are many feasible alternatives to ABILIFY in the form of antipsychotics and/or atypical antipsychotics (such as, for example, Amisulpride, Ziprasidone, Quetiapine, Trifluoperazine, Chlorpromazine, etc.), which do not cause uncontrollable impulses such as compulsive or pathological gambling. The serious side effects of ABILIFY rendered their design defective, which was a substantial factor in causing the Plaintiff's and Class Members' injuries;

107. Despite various warning changes, the Defendants' marketing of ABILIFY failed to adequately warn consumers, healthcare professionals and the public of the serious risk of experiencing uncontrollable urges including compulsive or pathological gambling;

L. <u>The Defendants' Knowledge that ABILIFY Increases the Risk of Impulse-Control Disorders</u>

108. The Defendants knew or could not have been unaware that the ingestion of ABILIFY could cause, exacerbate or contribute to an increased risk of dangerous side effects including having uncontrollable and irrepressible impulses to engage in harmful impulse control behaviours prior to its introduction in Canada;

109. When the first studies were published, ABILIFY had not yet been launched in Canada and a reasonably prudent drug manufacturer ought to have conducted such further research and testing to ensure that its drug was safe for human ingestion;

110. Bristol-Myers Squibb Company's September 2011 6-Month Periodic Safety Update Report submitted to the European Medicines Agency acknowledges a plausible mechanism for pathological gambling. The Report states that an article, Chau et al., The Neural Circuitry of Reward and Its Relevance to Psychiatric Disorders (Exhibit P-38), "does suggest a possible mechanism by which drugs that act on dopamine neurons, like aripiprazole, might possibly have some effect on behavior related to reward", the whole as appears more fully from a copy of Bristol-Myers Squibb Company's September 1, 2011 6-Month Periodic Safety Update Report dated September 1, 2011, produced herein as **Exhibit P-108**;

111. The Safety Update Report (Exhibit P-108) acknowledged seven serious reports of pathological gambling, three in the medical literature and four spontaneous reports. The report also noted sixteen cases of pathological gambling in the Bristol-Myers Squibb company safety database;

112. The Medical Assessment of the pathological gambling cases in the Safety Update Report (Exhibit P-108) did not exclude ABILIFY as the cause of the compulsive gambling adverse events. The Defendants concluded that "a causal role of aripiprazole could not be excluded" or that "aripriprazole was suggested by the temporal relationship";

113. The European Final Assessment Report of the Safety Update Report concluded that with regard to compulsive gambling "in all of the reported cases we have a (+) temporal; (+) dechallenge and in one case a (+) rechallenge", the whole as appears more fully from a copy of the Final Assessment Report on the 15th Periodic Safety Update Report dated December 5, 2011, produced herein as **Exhibit P-109**;

114. Quite tellingly, even after the European Medicines Agency required the Defendants to make labelling changes in Europe to warn of the risk of pathological gambling associated with ABILIFY in October 2012 (Exhibit P-46), the Defendants still failed to make any changes to the product monograph in Canada until June 22, 2015 and it is alleged that these changes were insufficient until February 23, 2017 (see para. 104 hereinabove);

115. In spite of the strong indication that ABILIFY was causing the Impulse-Control Disorders, the Defendants failed to warn and failed to timely inform consumers, health care professionals, Health Canada and the scientific community and they failed to perform further investigation into its safety;

M. The Defendants' Solidary Liability

116. The Defendants have either not adequately studied ABILIFY or have failed to make public the results of any studies or investigations that they might have conducted. A review of all the randomized clinical trials comparing ABILIFY to other schizophrenia drugs concluded that the information on comparisons was of limited quality, incomplete, and problematic to apply clinically, the whole as appears more fully from a copy of the Cochrane Library Database of Systematic Reviews article entitled "Aripiprazole versus other atypical antipsychotics for schizophrenia (Review)" dated 2016, produced herein as **Exhibit P-110**;

117. Despite the vast amount of evidence that dopamine agonists generally, and ABILIFY specifically, cause or materially increase the risk of developing Impulse-Control Disorders and, despite calls from the medical community to conduct further research and warn patients about the possible side effects of ABILIFY, the Defendants have either failed to investigate or conduct any adequate studies on the compulsive behaviour side effects of ABILIFY and/or failed to make public the results of any studies or investigations that they may have conducted;

118. Despite a clear signal, the Defendants failed to either alert or warn the public and the scientific and medical community or to perform further investigation into the safety of ABILIFY;

119. A reasonably prudent drug developer, designer, manufacturer, tester, marketer, labeller, packager, promotor, advertiser, distributer, and/or seller in the Defendants' positions would have adequately warned both doctors and patients of the risks associated with the use of ABILIFY;

120. The Defendants knew, or by the reasonable and careful employment of known scientific methods and reasonable diligence should have known, and, in the exercise of reasonable care toward patients who would be expected to ingest ABILIFY, should have known that ABILIFY causes or materially contributes to the development of Impulse-Control Disorders;

121. The Defendants were negligent (at both civil and common law) in the development, design, manufacture, testing, marketing, labelling, packaging, promotion, advertising, distribution, and/or sale of ABILIFY in one or more of the following respects:

(a) They knew or should have known that ABILIFY increased the risks developing one or more Impulse-Control Disorders;

(b) They failed to ensure that ABILIFY was safe and not dangerous to consumers;

(c) They failed to conduct proper, adequate, appropriate, and through pre-market and post-market testing to determine whether and to what extent the ingestion and/or use of ABILIFY poses serious risks, including the Impulse-Control Disorders;

(d) They failed to adequately test ABILIFY to ensure that it was acceptably safe and free from defects prior to placing it on the market;

(e) They failed to properly, adequately, appropriately, correctly, and timely warn, advise, and inform the medical and healthcare community, Health Canada, the Plaintiff, Class Members, and the public in general of the significant and dangerous risks associated with ABILIFY and the severity thereof, both prior to releasing it into the Canadian marketplace and afterward;

(f) They failed to use care in researching, designing, developing, and manufacturing ABILIFY so as to avoid posing unnecessary health risks to users of the product;

(g) They failed to conduct adequate pre-clinical and clinical testing, post-marketing surveillance and follow-up studies to determine the safety of the drug;

(h) They failed to advise the medical and scientific communities that the ingestion and/or use of ABILIFY could result in severe side effects, including but not limited to the Impulse-Control Disorders;

(i) They misrepresented that ABILIFY was safe and that it was equivalent in safety as other forms of treatments;

(j) They failed to provide adequate and timely warnings or sufficient indications about the inherent risks associated with the use of ABILIFY;

(k) They consistently under-reported, underestimated, withheld, and downplayed serious dangers of ABILIFY and misrepresented its safety to the medical and health community, Health Canada, the Plaintiff, Class Members, and the public in general;

(l) They failed to provide adequate warnings regarding the need to assess impulse control behaviours prior to starting a patient on ABILIFY and to continue with periodic testing and monitoring while the patient is taking ABILIFY;

(m) They failed to provide adequate updated and current information to Class Members and their physicians regarding the risks of ABILIFY as such information became available;

(n) They failed to provide prompt warnings of potential hazards of ABILIFY in the product monographs and in the product labelling;

(o) They failed to warn Class Members and their physicians that the risks associated ABILIFY would exceed the potential risks of other available antipsychotic and atypical antipsychotic medications;

(p) After receiving actual or constructive notice of the Impulse-Control Disorders associated with ABILIFY, they failed to issue adequate warnings, to publicize the problem and otherwise act properly and in a timely manner to alert the public, Health Canada, Class Members and their physicians, and the healthcare community;

(q) They failed to establish any adequate procedures to educate their sales representatives and prescribing physicians respecting the risks associated with the drug;

(r) They falsely represented that ABILIFY was safe when they knew or ought to have known that this representation was false;

(s) They failed to ensure that ABILIFY was safe for use by Class Members, fit for its intended purposes and of merchantable quality;

(t) They disregarded reports of uncontrollable impulses, including the Impulse-Control Disorders, among patients;

(u) They failed to accurately and promptly disclose to Health Canada information relating to the Impulse-Control Disorders associated with ABILIFY and to modify the product monograph and product labelling accordingly in a timely manner;

(v) They failed to monitor and to initiate a timely review, evaluation and investigation of reports of uncontrollable impulses including the Impulse-Control Disorders associated with ABILIFY in Canada (and around the world);

(w) They failed to properly investigate cases of uncontrollable impulses, including Impulse-Control Disorders, caused by ABILIFY;

(x) They deprived patients of a chance for safe, effective and/or successful alternative treatments; and

(y) In all circumstances of this case, they applied callous and reckless disregard for the health and safety of their consumers;

122. Despite the vast availability of knowledge clearly indicating that ABILIFY use is causally-related to uncontrollable impulses including Impulse-Control Disorders, the Defendants not only failed to provide adequate labelling and

information to warn Class Members of the risks associated with the use of ABILIFY, but instead incongruously promoted and marketed ABILIFY as a safe and effective drug, effectively appropriating the ability of doctors and patients to make informed decisions regarding their health;

123. The Defendants concealed and failed to completely disclose their knowledge that ABILIFY were associated with or could cause uncontrollable impulses including Impulse-Control Disorders as well as their knowledge that they had failed to fully test or study said risk;

124. The Defendants ignored the association between the use of ABILIFY and the risk of uncontrollable impulses including Impulse-Control Disorders;

125. The Defendants' failure to disclose information that they possessed regarding the failure to adequately test and study ABILIFY for uncontrollable impulses including Impulse-Control Disorders risk further rendered warnings for this medication inadequate;

126. The Defendants' negligence involved both lawful and unlawful means with the predominant purpose of causing Class Members to acquire and use ABILIFY when they knew or should have known that such use would cause harm to the Class Members and their family members;

127. The Defendants further acted in concert to conceal the risk of Impulse-Control Disorders associated with the use of ABILIFY;

128. At all relevant times, Otsuka and Bristol-Myers, by their directors, officers, servants and agents wrongfully, unlawfully, maliciously and lacking bona fides, conspired and agreed together, to, among other things, conceal the risk of the Impulse-Control Disorders associated with the use of ABILIFY, and to mislead Class Members about the health and safety risks associated with the use of the drug;

129. The Defendants' conduct as described herein was unlawful and constituted material and misleading information in breach of sections 36 and 52 of the *Competition Act*;

130. In conspiring to conceal the risk of Impulse-Control Disorders from the Class Members, each of the Defendants was motivated, among other things:

(a) to increase or maintain sales volumes of ABILIFY;

(b) to increase or maintain revenue;

(c) to increase or maintain profit;

(d) to increase or maintain market share; and

(e) to avoid negative publicity and preserve public goodwill;

131. The conspiracy was unlawful because the Defendants knowingly or recklessly, directly and indirectly, and in pursuit of their mutual business interests, made representations to Class Members and the public which were false or misleading in a material respect and which deceived them as to the health and safety risks associated with the use of ABILIFY. In making the misrepresentations as described herein, the Defendants breached sections 36 and 52 of the *Competition Act*;

132. In the circumstances, the Defendants knew that the conspiracy would, and did, cause the Class Members to suffer damages as described herein;

133. The *Régie de l'assurance maladie du Québec* has suffered and will continue to suffer damages for which they are entitled to be compensated by virtue of their right of subrogation in respect of all past and future insured services. A claim is hereby advanced for the cost of such services under the *Health Insurance Act*, RSQ c A-29;

N. The U.S. Litigation

134. On October 3, 2016, the U.S. Judicial Panel on Multidistrict Litigation ("JPML") consolidated pretrial proceedings for *In Re: Abilify (Aripiprazole) Products Liability Litigation*, MDL No. 2734 in the United States District Court for the Northern District of Florida (the "U.S. MDL Court"), the whole as appears more fully from a copy of the Transfer Order in *In Re: Abilify (Aripiprazole) Products Liability Litigation*, MDL No. 2734 dated October 3, 2016, produced herein as **Exhibit P-111**;

135. On December 2, 2016, a Master Long Form Complaint and Jury Demand was filed in the U.S. MDL Court, the whole as appears more fully from a copy of the Master Long Form Complaint and Jury Demand in *In Re: Abilify (Aripiprazole) Products Liability Litigation*, MDL No. 2734 dated December 2, 2016, produced herein as **Exhibit P-112**;

136. On March 15, 2018, in ruling on the defendants' motion for summary judgment on the issue of general causation, the U.S. court adjudged that "that Plaintiffs have satisfied their burden to demonstrate that a genuine dispute of material fact exists as to whether Abilify can cause uncontrollable impulsive behaviors in individuals taking the drug", the whole as appears more fully from a copy of the Amended Order in *In Re: Abilify (Aripiprazole) Products Liability Litigation*, MDL No. 2734 dated March 15, 2018, produced herein as **Exhibit P-113**;

137. On April 28, 2018, after a successfully mediation, 4 individual cases from the MDL were settled with full releases, the whole as appears more fully from a copy of the Order in *In Re: Abilify (Aripiprazole) Products Liability Litigation*, MDL No. 2734 dated April 28, 2018, produced herein as **Exhibit P-114**;

138. As of the date of the filing of the Third Amended Application, over 2,100 cases had been consolidated in the MDL;

139. On May 2, 2018, the U.S. court ordered the U.S. parties to create a global settlement framework addressing the remaining ABILIFY lawsuits in the MDL – a confidential global settlement was reached on February 15, 2019, the whole as appears more fully from a copy of the Global Settlement Order No. 1, dated May 2, 2018 and from a copy of the Joint Notice of Proposed Settlement Program in *In Re: Abilify (Aripiprazole) Products Liability Litigation*, MDL No. 2734 dated February 15, 2019, produced herein *en liasse* as **Exhibit P-115**;

IV. THE EXAMPLE OF THE PLAINTIFF/ CLASS REPRESENTATIVE

140. In spring of 2013, the Plaintiff studied for and passed his General Education Diploma (GED)[20] in order to apply to West Island Career Centre (WICC), at 13700 Pierrefonds Blvd., in Pierrefonds, Quebec, in the Automobile Mechanics program. The Plaintiff was interested in the CPA certification course to eventually take the CPA certification exam and begin his career in auto mechanics. The Plaintiff was placed onto the wait list for admission;

141. In the end of October-beginning of November 2013, the Plaintiff's physician gave him several sample boxes of ABILIFY in the 2-mg dosage and directed him to take half of a pill every morning, which was intended to treat his severe anxiety associated with his obsessive-compulsive disorder (OCD), and to prevent depressive episodes;

142. By December 3, 2013, the Plaintiff noticed that his infrequent and casual gambling was turning into uncontrollable urges/ compulsions and that he was gambling more and more money, so he sought help from *Centre de réadaptation en dépendence Foster*[21] ("CRD Foster") on December 5, 2013 and he began CRD Foster's out-patient program on December 6, 2013 on their recommendation, the whole as appears more fully from a copy of the Plaintiff's file from *Centre de réadaptation en dépendence Foster*, produced herein under seal as **Exhibit P-116**;

143. By December 20, 2013, the Plaintiff was spending 5 to 7 hours per day, everyday, gambling at bars, exclusively playing video lottery machines (referred to as VLT in the Plaintiff's medical files);

144. Over the Christmas holidays of 2013, the Plaintiff's gambling became more and more uncontrollable and irrepressible;

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[20] The GED is the High School Equivalency Certificate.

[21] *Centre de réadaptation en dépendence Foster*, has since been renamed as *Centre Intégré de santé et de services sociaux de la Montérégie Ouest-département de santé mentale et dépendance*.

145. On January 3, 2014, the Plaintiff was prescribed ABILIFY by his physician in the 10-mg dosage[22];

146. The Plaintiff filled his prescription at the Thi Yen Nguyen Phaman affiliated pharmacy – Uniprix located at 5443 Rue Bannantyne, in Verdun, Quebec and he continued to take the medication as directed, namely, once daily in the mornings. Thereafter, he switched pharmacies several times depending on where he was living, the whole as appears more fully from a copy of the Plaintiff's file from the Uniprix pharmacy in Verdun and from a copy of the Plaintiff's file from the Brunet in Chateauguay, produced herein under seal and *en liasse* as **Exhibit P-117**;

147. The *fiche conseil* that was given to the Plaintiff when he was first dispensed ABILIFY (Exhibit P-117) did not mention the possibility of developing any Impulse-Control Disorders and contained only the following disclosure of "possible side effects":

> "In addition to its desired action, this medication may cause some side effects, notably:
>
> - it may cause headaches;
> - it may cause drowsiness or dizziness -- use caution if driving;
> - it may cause unusual tiredness;
> - it may cause nausea and vomiting";

148. Within a few months' time, the Plaintiff began experiencing increasingly uncontrollable and irrepressible urges to gamble. In approximately July 2013, he had gambled a few times with small sums of money in video lottery machines with colleagues at various bars. At first, he would gamble once a week with $20.00, then with $50.00, but beginning in December 2013 and continuing into January 2014, the urges escalated, rapidly becoming uncontrollable and he began regularly gambling at the video lottery machines, losing thousands of dollars within a short period of time;

149. The Plaintiff's gambling became so uncontrollable and compulsive that he would to do anything he could to find cash to gamble at the slot machines including, but not limited to the following:

(a) Withdrawing his RRSPs at the Laurentian Bank in the amount of $2,500.00,

(b) Selling his 2006 Pontiac G6 GT Coupe for $850.00 (approximately 10 to 15 percent of its worth at the time),

[22] The Plaintiff was weaned onto the medication, starting first with a lower dose of 2-mgs for a few months.

(c) Selling his Canada Goose jacket in the middle of winter for $60.00 (approximately 10 percent of its worth at the time),

(d) Accruing liabilities on various credit cards (owned by himself and by close friends and family) by purchasing new merchandise from stores on credit and then pawning them at pawn shops for a fraction of their value, and

(e) Pawning all the gold he could find, including sentimental family pieces;

150. In the end of January 2014, the Plaintiff received a phone call from WICC informing him that he had been admitted to the Automobile Mechanics program; however, at this point in time, his compulsive gambling had taken over his life and he had no interest in anything other than playing the video lottery machines and in figuring out how to get money in order to do so. He never accepted the admission or attended the program;

151. The Plaintiff's anxiety about his irrepressible and uncontrollable urges and about where he was going to find money to gamble with became unbearable. He lost interest in everything except gambling and he could not stop the cravings and urges. His therapist at CRD Foster had been recommending in-patient care (IPC) and informed him that a bed would be available on January 29, 2014. On January 29, 2014, the Plaintiff checked himself into the in-patient rehab centre of CRD Foster, at 6 Rue Foucreault, in Saint-Philippe, Quebec;

152. He stayed at the rehab centre on two occasions; the first being from January 29, 2014 to February 26, 2014 (a 28-day period), where he received individual and group therapy. During this first stay at the rehab centre the Plaintiff remained abstinent until his final weekend out when he lost $400 gambling. The Plaintiff was referred to "Recovery Management" groups on Friday mornings at CRD Foster's outpatient centre. Immediately after being released, the Plaintiff had a gambling relapse and he readmitted himself to the rehab centre a second time. He remained in rehab from March 31, 2014 to April 16, 2014 (a 17-day period). was administered ABILIFY everyday while at the rehab centre, but when he was released, he would continue compulsively gambling;

153. His urges and compulsions, and the accompanying anxiety, became so bad that on July 13, 2014, at approximately 11:15 pm, he attempted suicide by taking all the medication that he found in his mother's medicine cabinet (including 12-18 sertralines/ Zolofts). He was taken by ambulance to the Hôpital de Verdun at 4000 Boulevard LaSalle, in Verdun, Quebec, where, at approximately 12:30 am, he was administered charcoal to make him throw up the medications that he had taken, the whole as appears more fully from a copy of the Plaintiff's file from Hôpital de Verdun, produced herein under seal as **Exhibit P-118**;

154. Following the suicide attempt, on July 22, 2014, Mr. Scheer registered with another rehab centre, Portage Quebec Adult Day Centre Montreal, at 1640, rue Saint-Antoine West, in Montreal, Quebec, where he was accepted as an out-patient on Tuesdays, Wednesdays, and Thursdays from 10:00 A.M. to 4:00 P.M. The idea was to wait for an opening at their in-patient facility at 1790 chemin du Lac Écho, in Prévost, Quebec, the whole as appears more fully from a copy of the Plaintiff's file from Portage, produced herein under seal as **Exhibit P-119**;

155. Throughout this time period, the Plaintiff would continue to compulsively gamble, including on the way to and from the rehab centre;

156. On September 2, 2014, the Plaintiff was admitted to the Portage Quebec in-patient centre in Prévost, Quebec where he was administered ABILIFY daily and where his uncontrollable and unbearable gambling urges continued;

157. The Plaintiff's urges to gamble became so intense that by November 18, 2014, he had to check himself out of the rehab centre to gamble – after temporarily satiating his urges, the Plaintiff checked himself back into the rehab centre the following week on November 25, 2014;

158. The Plaintiff's gambling compulsions continued unabated for another approximate three months while at the rehab centre until his cravings again and his intense anxiety and aggression related thereto forced him to check himself out again on March 4, 2015, at which point he travelled directly to the Casino de Montreal to gamble all the money in his bank account at the time;

159. The Plaintiff continued gambling five to six days a week and losing approximately $1,000.00 to $1,500.00 each time;

160. This dismal situation continued until in or about August 2016 when his girlfriend's sister saw a commercial about ABILIFY and how it may cause gambling problems. The Plaintiff stopped taking ABILIFY immediately upon learning that his compulsive gambling may be related to the medication that he was taking;

161. About one month after stopping to take ABILIFY, the Plaintiff's compulsive gambling problems were completely gone, what remained was an intense fear of relapse, the whole as appears more fully from a copy of the Plaintiff's file from Jacqueline Aubie M.A., O.P.Q., produced herein under seal as **Exhibit P-120**;

162. The Plaintiff lost between $50,000.00 and $60,000.00 while taking ABILIFY over the course of approximately five years;

163. The Plaintiff had no gambling problems prior to taking ABILIFY and his gambling problems ended upon stopping to take ABILIFY;

164. At no time was the Plaintiff made aware of the risks of suffering from uncontrollable impulses including compulsive and/or pathological gambling associated with taking ABILIFY;

165. Had the Defendants properly disclosed the risks associated with ABILIFY, the Plaintiff would have avoided the risk of suffering from uncontrollable impulses, including compulsive and/or pathological gambling by not ingesting ABILIFY at all. Further, had the Plaintiff been made aware of the risks of suffering from uncontrollable impulses, including compulsive and/or pathological gambling, he would not have had to suffer injury for five long years without any explanation of the cause, and instead would have simply discontinued his use of ABILIFY at the first sign of the uncontrollable urges;

166. On April 1, 2019, Dr. Evan Brahm, psychiatrist, wrote an expert report that concluded the following:

> While Mr. Scheer is a young male with a previous alcohol use problem and a family history of addiction (his father's alcohol use issues), he never manifested any problem with gambling prior to starting Abilify and in my opinion, the fact that he has had no craving to gamble and no problem prudently managing his finances for 2.5 years since discontinuing Abilify, without the need for further addiction treatment, strongly suggests that Abilify either solely caused his compulsive gambling or markedly exacerbated any potential for addictive or compulsive behaviour that he already had. His compulsive gambling from the end of 2013 to August 2016 coincides exactly with his taking Abilify and ceased quickly when he discontinued taking Abilify.
>
> Even acknowledging the known risk factors and, despite Mr. Scheer having those that I cite, the clinical evidence is that both prior to being on Abilify and since he stopped, until the present, he has not manifested any symptoms of pathological gambling and his capacity to stop gambling so quickly after discontinuing is demonstrative of Abilify being the cause of him having developed the Gambling Disorder (as defined in the DSM-5). In my opinion, there is no evidence of any likelihood that this would have occurred had he not taken Abilify.

The whole as appears more fully from a copy of the Expert Report of Dr. Brahm dated April 1, 2018, produced herein as **Exhibit P-123**;

167. In his Expert Report (Exhibit P-92), Dr. Dagher opined the following:

> The strongest evidence linking the medication to the gambling disorder in this case is the very strong time-locked relationship between the medication and the gambling urges. The description by

> Mr. Scheer of a spontaneous resolution of gambling urges following discontinuation of the medication is consistent with the medical literature and strongly supportive of a causal relationship between aripiprazole and gambling in this case;

168. As a result of the Defendants' conduct, the Plaintiff suffered damages including, but not limited to physical and mental/emotional injuries, including pain, suffering, anxiety (the very problem he was trying to resolve), fear (including fear of relapse), loss of quality and enjoyment of life, damage to or loss of reputation, extensive financial losses (including the loss of sentimental family jewelry pieces), loss of income, expenses relating to his treatment in the rehab centres, and the apportioned cost of ABILIFY;

169. Plaintiff's damages are a direct and proximate result of his use of the drug ABILIFY, Defendants' negligence and/or lack of adequate warnings, wrongful conduct, and the unreasonably dangerous and defective characteristics of ABILIFY;

170. In consequence of the foregoing, the Plaintiff is justified in claiming damages;

171. In pursuing this litigation, the Plaintiff has given instructions to his attorneys to put information about this class action on its website and to collect the coordinates of those Class Members that wish to be kept informed and participate in any resolution of the present matter, the whole as will be shown at the hearing, the whole as appears more fully from a copy of a redacted chart of Class Members who have inputted their information through the CLG webpage, produced herein as **Exhibit P-124**;

V. THE DAMAGES

172. Every member of the Class has been prescribed and has ingested and/or used ABILIFY or is the successor, family member, assign, and/or dependant of a person who ingested and/or used ABILIFY;

173. The Class Members' damages would not have occurred, but for the acts, omissions and/or negligence of the Defendants in failing to ensure that ABILIFY was safe to use, for failing to provide adequate warning of the unreasonable risks associated with using the drug, for false or misleading representations and for omitting to disclose important information to Class Members, to their physicians, and to Health Canada;

174. In consequence of the foregoing, each member of the Class is justified in claiming at least one or more of the following as damages:

(a) Physical and mental/emotional injuries, including pain, suffering, anxiety, fear, loss of quality and enjoyment of life, increased risk of mental problems, damage to and/or loss of reputation;

(b) Out-of-pocket expenses incurred or to be incurred, including those connected with hospital stays, medical treatment, life care, medications, medical monitoring services, and the diagnosis and treatment of the compulsive behaviours;

(c) Extensive financial losses (such as from gambling or spending) and out-of-pocket expenses, including loss of income and loss of future income;

(d) Refund of the purchase price of ABILIFY or alternatively, the incremental costs of ABILIFY as paid for by the Class Members and/or by the *Régie de l'assurance maladie du Québec*, the Ontario Health Insurance Plan, and other provincial health insurers; and

(e) Punitive damages;

175. As a direct result of the Defendants' conduct, the users' family members and dependants have, had, and/or will suffer damages and loss including:

(a) Out-of-pocket expenses, including debts accrued and/or paying or providing nursing, housekeeping and other services;

(b) Loss of income and loss of future income; and

(c) Loss of support, marital/ familial harmony, guidance, care, consortium, and companionship that they might reasonably have expected to receive if the injuries had not occurred;

176. All of these damages to the Class Members are a direct and proximate result of the use of ABILIFY and the Defendants' conduct, negligence (at common law or civil law) and reckless failure to adequately disclose necessary information and the risks associated with the drug;

VI. APPLICABLE LEGISLATION

177. The Class Members plead and rely upon, *inter alia*, the following provincial statutes (all as amended):

(a) *Family Compensation Act*, R.S.B.C. 1996 c. 126 (British Columbia)

(b) *Tort-Feasors Act*, R.S.A. 2000, c. T-5 (Alberta)

(c) *Fatal Accidents Act*, R.S.A. 2000 c. F-8 (Alberta)

(d) *Fatal Accidents Act*, R.S.S. 1978, c.F-11 (Saskatchewan)

(e) *Fatal Accidents Act*, C.C.S.M. c. F50 (Manitoba)

(f) *Family Law Act*, R.S.O. 1990, c. F.3 (Ontario)

(g) *Fatal Injuries Act*, R.S.N.S. 1989. c.163 (Nova Scotia)

(h) *Fatal Accidents Act*, R.S.N.B. 2012, c. 104 (New Brunswick)

(i) *Fatal Accidents Act*, R.S.N.L. 1990, c.F-6 (Newfoundland)

(j) *Fatal Accidents Act*, R.S.P.E.I. 1988, c.F-5 (Prince Edward Island)

178. The Class Members plead and rely upon the following health insurance acts:

(a) *Health Care Costs Recovery Act*, S.B.C. 2008, C. 27 (British Columbia)

(b) *Crown's Right of Recovery Act*, S.A. 2009, c.C-35 (Alberta)

(c) *The Health Administration Act*, R.S.S. 1978, c. H-0.0001 (Saskatchewan)

(d) *The Health Services Insurance Act*, C.C.S.M., c. H35 (Manitoba)

(e) *Health Insurance Act*, R.S.O. 1990, c. H.6 (Ontario)

(f) *Health Insurance Act*, R.S.Q., c. A-29 (Quebec)

(g) *Health Services and Insurance Act*, S.N.S 1989 c.197 (Nova Scotia)

(h) *Hospital Services Act*, R.S.N.B. 1973, c.H-9 (New Brunswick)

(i) *Medical Care and Hospital Insurance Act*, S.N.L. 2016, c. M-5.01 (Newfoundland)

(j) *Health Services Payment Act*, R.S.P.E.I. 1988, c. H-2 (Prince Edward Island)

(k) *Hospital Insurance and Health and Social Services Administration Act*, R.S.N.W.T. 1988, c. T-3 (Northwest Territories)

(l) *Health Care Insurance Plan Act*, R.S.Y. 2002, c. 107 (Yukon)

(m) *Hospital Insurance and Health and Social Services Administration Act*, R.S.N.W.T. (Nu) 1988, c. T-3 (Nunavut)

FOR THESE REASONS, MAY IT PLEASE THIS HONOURABLE COURT TO:

GRANT the class action of the Plaintiff and each of the members of the Class;

DECLARE that the Defendants failed to provide adequate warnings with regard to the dangerous side effects of ABILIFY;

RESERVE the right of each of the members of the Class to claim future damages related to the use of ABILIFY;

DECLARE the Defendants solidarily liable for the damages suffered by the Plaintiff and each of the members of the Class;

CONDEMN the Defendants to pay to each member of the Class a sum to be determined in compensation of the damages suffered, and ORDER collective recovery of these sums;

CONDEMN the Defendants to pay to each of the members of the Class, punitive damages, and ORDER collective recovery of these sums;

CONDEMN the Defendants to pay interest and additional indemnity on the above sums according to law from December 12, 2016, the date of service of the application to authorize a class action;

ORDER the Defendants to deposit in the office of this Court the totality of the sums which forms part of the collective recovery, with interest and costs;

ORDER that the claims of individual Class Members be the object of collective liquidation if the proof permits and alternately, by individual liquidation;

CONDEMN the Defendants to bear the costs of the present action including expert and notice fees;

RENDER any other order that this Honourable Court shall determine and that is in the interest of the members of the Class;

Montreal, March 12, 2020

_____

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CANADA

PROVINCE OF QUEBEC
DISTRICT OF MONTREAL

NO: 500-06-000831-160

(Class Action)
SUPERIOR COURT

STEVEN SCHEER

Plaintiff / Class Representative

-vs.-

BRISTOL-MYERS SQUIBB CANADA CO.
and
OTSUKA CANADA PHARMACEUTICAL INC.

Defendant

NOTICE OF DISCLOSURE OF EXHIBITS

TAKE NOTICE that the Plaintiff / Class Representative intends producing the following exhibits at the hearing:

P-1: Copy of an extract from the *Registraire des enterprises* updated to February 29, 2020

Copy of an extract from the *Registraire des enterprises* updated to September 26, 2016

Copies of extracts from Defendant Bristol-Myers' websites at www.bms.com/ca and www.bmscanada.ca, *en liasse*;

P-2: Copy of an extract from the *Registraire des enterprises* updated to March 2, 2020

Copy of an extract from the *Registraire des enterprises* updated to September 26, 2016

Copy of an extract from Otsuka's website at https://otsukacanada.com, *en liasse*;

P-3: Copy of an extract from Defendant Otsuka's website at www.otsukacanada.com

Copy of Defendant Bristol-Myers' News Release entitled "Newest Treatment for Schizophrenia & Related Psychotic Disorders now Available to all Quebecers" dated October 26, 2010, *en liasse*;

P-4: Copy of the Psychopharmacology article entitled "Unique pharmacological profile of aripiprazole as the phasic component buster" dated January 5, 2007;

P-5: Copy of the Scientific American article entitled "Dopamine Determines Impulsive Behavior" dated July 29, 2010

Copy of the Current neurology and neuroscience reports article entitled "The Functional Anatomy of Impulse Control Disorders" dated August 21, 2013

Copy of the Frontiers in Behavioral Science article entitled "How central is dopamine to pathological gambling or gambling disorder?" dated December 23, 2013

Copy of the Frontiers in Behavioral Science article entitled "What motivates gambling behavior? Insight into dopamine's role" dated December 2, 2013

Copy of the Scientific American article entitled "How the Brain Gets Addicted to Gambling"

Copy of the Gambling Research Exchange Ontario article entitled "Dopamine release in ventral striatum of pathological gamblers losing money" dated 2010

Copy of the Journal of Neuroscience article entitled "Dopamine, Time, and Impulsivity in Humans" dated June 30, 2010, *en liasse*;

P-6: Copy of the Amended Order dated March 15, 2018 in *In Re: Abilify (Aripiprazole) Products Liability Litigation* – Case No. 3:16-md-2734;

P-7: Copies of the five (5) Notices of Compliance obtained from Defendant Bristol-Myers from Health Canada dated July 9, 2009, May 12, 2011, November 21, 2011, March 13, 2012, and May 29, 2013 and from a copy of the Health Canada Summary Basis of Decision (SBD) for ABILIFY dated July 9, 2009, produced herein *en liasse*;

P-8: Copy of the Approval Letter – Application 21-436;

P-9: Copy of the Approval Package Application Number NDA 21-436/S-001 dated August 28, 2003;

P-10: Copy of the Approval Letter and Package for Application Number NDA 21-436/S-002 dated September 29, 2004;

P-11: Copy of the Approval Letter from the Department of Health & Human Services dated November 16, 2007;

P-12: Copy of the European Medicines Agency Press Release entitled "Otsuka Pharmaceutical Europe Ltd withdraws its application for an extension of indication for Abilify (aripiprazole)" dated November 19, 2009

Copy of the European Medicines Agency Withdrawal Assessment Report for ABILIFY dated January 20, 2010

Copy of the European Public Assessment Report (EPAR) for ABILIFY;

Copy of the European Medicines Agency's "Procedural steps taken and scientific information after the authorization" for ABILIFY;

P-13: Copy of the World Health Organization Fact Sheet

Copy of an extract from the Schizophrenia Society of Canada at www.schizophrenia.ca, *en liasse*;

P-14: Copy of an extract from the Public Health Agency of Canada – A Report on Mental Illness in Canada: Chapter 3 Schizophrenia

Copy of the Statistics Canada publication at Section G – Schizophrenia, *en liasse*;

P-15: Copy of extracts from the DSM-5;

P-16: Copy of the Psych Central article entitled "The Two Types of Bipolar Disorder"

Copy of an extract from the Canadian Mental Health Association website at www.cmha.ca entitled "Bipolar Disorder"

Copy of the Canadian Mental Health Association brochure for Depression and Bipolar Disorder, dated 2014

Copy of the Public Health Agency of Canada article entitled "What Should I Know about Bipolar Disorder (Manic-Depression)?" dated April 23, 2009, *en liasse*;

P-17: Copy of an extract from the National Institute of Mental Health website at www.nimh.gov

Copy of an extract from the Centre for Addiction and Mental Health website at www.camh.ca, *en liasse*;

P-18: Copy of an extract from the Ontario Ministry of Health website at www.health.gov.on.ca;

P-19: Copy of an extract from the Government of Canada website at www.canada.ca;

P-20: Copy of the Frontiers in Psychiatry review article entitled "Impulse control disorders: updated review of clinical characteristics and pharmacological management" dated February 21, 2011

Copy of the Science Magazine article entitled "'Behavioral' Addictions: Do They Exist?" dated November 2, 2001, produced herein *en liasse*;

P-21: Copy of the Neuron Review article entitled "Impulsivity, compulsivity, and top-down cognitive control" dated February 24, 2011;

P-22: Copy of the Journal of Gambling Studies article entitled "Pathologic Gambling and Impulse Control Disorders" dated March 2005;

P-23: Copy of an extract from the Centre for Addiction and Mental Health website at www.problemgambling.ca;

P-24: Copy of an extract from American Psychiatric Association website at www.psychiatry.org;

P-25: Copy of the ICD-11 entry for Gambling disorder;

P-26: Copy of an extract from the Gambling Research Exchange Ontario website at www.greo.ca;

P-27: Copy of the Journal of Neuroscience mini-symposium entitled "Pathological Choice: The Neuroscience of Gambling and Gambling Addiction" dated November 6, 2013;

P-28: Copy of an extract from the Statista website at www.statista.com;

P-29: Copy of an extract from the National Eating Disorder Information Centre (NEDIC) website at https://nedic.ca;

P-30: Copy of an extract from the MedicineNet website at www.medicinenet.com;

P-31: Copies of the ICD-11 entries for Binge eating, Overeating, and Binge eating disorder, *en liasse*;

P-32: Copy of an extract from the Canadian Mental Health Association website at https://ontario.cmha.ca;

P-33: Copy of the Clinical Psychology and Psychotherapy report entitled "Compulsive buying: A cognitive-behavioural model" dated March-April 2009;

P-34: Copy of the Psychiatria Polska report entitled "Compulsive buying in outline" dated 2016;

P-35: Copy of extracts from the Handbook of Addictive Disorders dated 2004;

P-36: Copy of the CNN article entitled "WHO classifies compulsive sexual behavior as mental health condition" dated July 10, 2018

Copy of the ICD-11 entry for Compulsive sexual behaviour disorder, *en liasse*;

P-37: Copy of the Addiction article entitled "Diagnosis of Hypersexual or Compulsive Sexual Behavior Can Be Made Using ICD-10 and DSM-5 Despite Rejection of This Diagnosis by the American Psychiatric Association" dated April 17, 2016;

P-38: Copy of the Current Psychiatry Reports report entitled "The neural circuitry of reward and its relevance to psychiatric disorders" dated November 2004;

P-39: Copy of the Journal of Clinical Psychopharmacology Letters to the Editors entitled "Worsening of Obsessive-Compulsive Symptoms After Treatment With Aripiprazole" dated April 2007;

P-40: Copy of the Journal of Clinical Psychopharmacology Letters to the Editors entitled "Aripiprazole Induced Hypersexuality in a 24-Year-Old Female Patient With Schizoaffective Disorder?" dated October 2008;

P-41: Copy of the International Journal of Neuropsychopharmacology case study entitled “Aripiprazole-induced behavioural disturbance related to impulse control in a clinical setting” dated October 10, 2009;

P-42: Copy of the Australian & New Zealand Journal of Psychiatry correspondence entitled “Pathological Gambling and Compulsive Eating Associated with Aripiprazole” dated March 2010;

P-43: Copy of the Journal of Forensic Sciences article Case Report entitled “Partial Agonist Therapy in Schizophrenia: Relevance to Diminished Criminal Responsibility” dated November 2010;

P-44: Copy of the International Journal of Neuropsychopharmacology Letter to the Editor entitled “Aripiprazole-induced behavioural disturbance related to impulse control in a clinical setting” dated 2010;

P-45: Copy of report from the British Journal of Psychiatry entitled “Pathological gambling and the treatment of psychosis with aripiprazole: case reports” dated 2011;

P-46: Copy of the Current Drug Safety article entitled “Aripiprazole-Induced Pathological Gambling: A Report of 3 Cases” dated 2011;

P-47: Copy of the Case Report entitled “Two Cases of Hypersexuality Probably Associated with Aripiprazole” dated 2013;

P-48: Copy of the Journal of Neuroscience article entitled “Pathological Choice: The Neuroscience of Gambling and Gambling Addiction” dated November 6, 2013;

P-49: Copy of the JAMA Internal Medicine article entitled “Reports of Pathological Gambling, Hypersexuality, and Compulsive Shopping Associated With Dopamine Receptor Agonist Drugs” dated 2014;

P-50: Copy of the Addictive Behaviors “Aripiprazole: a new risk factor for pathological gambling? A report of 8 case reports” dated March 2014;

P-51: Copy of the Journal of Clinical Psychopharmacology review article entitled “Pathological Gambling Associated with Aripiprazole or Dopamine Replacement Therapy: Do Patients Share the Same Features? A Review” dated February 2016;

P-52: Copy of the Reactions case report entitled “Aripiprazole – Gambling addiction and compulsive sexual behaviour: case report” dated July 2, 2016;

P-53: Copy of the Primary Care Companion for CNS Disorders case report entitled “Aripiprazole and Impulse-Control Disorders: A Recent FDA Warning and a Case Report” dated January 12, 2019;

P-54: Copy of the Journal of Clinical Psychopharmacology brief report entitled “Risk of Gambling Disorder and Impulse Control Disorder With Aripiprazole, Pramipexole, and Ropinirole” dated February 2017;

P-55: Copy of the Asian Journal of Psychiatry article entitled “Aripiprazole induced hypersexuality, when we should be cautious?” dated May 28, 2017;

P-56: Copy of the Asian Journal of Psychiatry study entitled “Aripiprazole and impulse-control disorders in high-risk patients” dated June 2017;

P-57: Copy of the Australasian Psychiatry case report entitled “Partial dopamine agonist-induced pathological gambling and impulse-control deficit on low-dose aripiprazole” dated December 2017;

P-58: Copy of the Archives of Neuropsychiatry article entitled “Spontaneous Ejaculations Associated with Aripiprazole” dated 2017;

P-59: Copy of the Asian Journal of Psychiatry discussion paper entitled “Hypersexuality induced by Aripiprazole: Two case reports and review of the literature” dated 2018;

P-60: Copy of the Journal of Affective Disorders case report entitled “Aripiprazole-induced kleptomania: Case report” dated May 2018;

P-61: Copy of the Journal of Psychiatric Practice case report and literature review entitled “Escalation of Gambling Associated With Aripiprazole: A Case Report and Literature Review” dated March 2019;

P-62: Copy of the Clinical Neuropharmacology case report entitled “Two Cases of De Novo Pathological Gambling Associated With Aripiprazole” dated May/June 2019;

P-63: Copy of the U.S. FDA draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biologic Products Including Vaccines dated 2001;

P-64: Copy of the Federal Judicial Center’s Reference Manual on Scientific Evidence – Third Edition, dated 2011;

P-65: Copy of the Clinical Neuropharmacology “Hypersexuality with Antiparkinsonian Therapy” dated 1989;

P-66: Copy of the Journal of Neurology, Neurosurgery, and Psychiatry article entitled “Hedonistic homeostatic dysregulation in patients with Parkinson’s disease on dopamine replacement therapies” dated August 24, 1999;

P-67: Copy of the Depression and Anxiety article entitled “Pathological Gambling Behaviour: Emergence Secondary to Treatment of Parkinson’s Disease with Dopaminergic Agents” dated February 24, 2000;

P-68: Copy of the Movement Disorder article entitled “Pathologic Gambling in Parkinson’s Disease: A Behavioral Manifestation of Pharmacologic Treatment?” dated March 15, 2000;

P-69: Copy of the Depression and Anxiety article entitled “Pathological Gambling Behaviour: Emergence Secondary to Treatment of Parkinson’s Disease with Dopaminergic Agents” dated February 24, 2000;

P-70: Copy of the Clinical Neuropharmacology article entitled “Pathologic Gambling in Patients with Parkinson’s Disease” dated 2001;

P-71: Copy of the Neurology article entitled “Pathological gambling associated with dopamine agonist therapy in Parkinson’s disease” dated August 2003;

P-72: Copy of the Neurological Sciences case report entitled “Pathological gambling in two patients on dopamine replacement therapy for Parkinson’s disease” dated February 22, 2004;

P-73: Copy of the Archives of Neurology “Pathological Gambling Caused by Drugs Used to Treat Parkinson Disease” dated 2005;

P-74: Copy of the Parkinsonism and Related Disorders study entitled “Pathological hypersexuality predominantly linked to adjuvant dopamine agonist therapy in Parkinson’s disease and multiple system atrophy” dated 2005;

P-75: Copy of the American Journal of Therapeutics article entitled “Effects of Donepezil on Compulsive Hypersexual Behavior in Parkinson Disease” dated 2005;

P-76: Copy of the Parkinsonism and Related Disorders case report entitled "Hypersexuality and paraphilia induced by selegiline in Parkinson's disease: Report of 2 cases" dated 2006;

P-77: Copy of the Neurology article entitled "Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists" dated 2007;

P-78: Copy of The Neurologist review article entitled "Impulse Control Disorders and Pathological Gambling in Patients With Parkinson Disease" dated March 2008;

P-79: Copy of the Revue Médicale Suisse article entitled "Troubles du contrôle des impulsions et maladie de Parkinson" dated May 7, 2008;

P-80: Copy of the Journal of Movement Disorders report entitled "Compulsive Shopping in Parkinson's Disease - A Case Report" dated October 2008;

P-81: Copy of the Addiction article entitled "Impulse control disorders in patients with Parkinson's disease receiving dopamine replacement therapy: evidence and implications for the addictions field" dated September 19, 2010;

P-82: Copy of the Neurologist article entitled "Detection of Impulse Control Disorders in Parkinson Disease Patients" dated November 2010;

P-83: Copy of the Addiction article entitled "Impulse Control Disorders in Parkinson Disease: A Multicenter Case–Control Study" dated December 3, 2010;

P-84: Copy of the Sleep study entitled "Impulse Control Disorders with the use of Dopaminergic Agents in Restless Legs Syndrome: a Case-Control Study" dated 2010;

P-85: Copy of Health Canada's list of adverse reaction reports and from a copy of the actual reports, *en liasse*;

P-86: Copy of Health Canada's list of adverse reaction reports and from a copy of the actual reports, *en liasse*;

P-87: Copy of Health Canada's list of adverse reaction reports and from a copy of the actual reports, *en liasse*;

P-88: Copy of the slides from the U.S. FDA “Pediatric Focused Safety Review: Abilify® (aripiprazole) to May 1, 2011” dated September 22, 2011;

P-89: Copy of the U.S. FDA Adverse Events Reporting System (FAERS) results for ABILIFY and the above Impulse-Control Disorders (or indicators for the Impulse-Control Disorders), produced herein *en liasse*;

P-90: Copy of the International Journal of Medical Sciences article entitled “Data Mining of the Public Version of the FDA Adverse Event Reporting System” dated April 25, 2013;

P-91: Copy of the International Clinical Psychopharmacology report entitled “Aripiprazole and impulse control disorders: higher risk with the intramuscular depot formulation?” dated 2017;

P-92: Copy of the Expert Report of Dr. Alain Dagher dated March 28, 2019;

P-93: Copy of the European Medicines Agency document for ABILIFY

Copy of the European Medicines Agency’s Annex I – Summary of Product Characteristics, *en liasse*;

P-74: Copy of the Health Canada Information Update entitled “Safety information for antipsychotic drug Abilify and risk of certain impulse-control behaviours” dated November 2, 2015

Copy of the Health Canada Summary Safety Review - ABILIFY and ABILIFY MAINTENA (aripiprazole) – Evaluating the Risk of Certain Impulse Control Behaviours” dated November 2, 2015

Copy of the CTV News article entitled “Health Canada updates list of possible side effects for 2 antipsychotic drugs” dated November 2, 2015, *en liasse*;

P-95: Copy of the Pharmacovigilance Review dated March 10, 2016;

P-96: Copy of the U.S. FDA Drug Safety Communications Safety Announcement entitled “FDA Drug Safety Communication: FDA warns about new impulse-control problems associated with mental health drug aripiprazole (Abilify, Abilify Maintena, Aristada)” dated May 3, 2016;

P-97: Copy of the United States Department of Justice Press Release entitled “Bristol-Myers Squibb to Pay More Than $515 Million to

Resolve Allegations of Illegal Drug Marketing and Pricing" dated September 28, 2007

Copy of the United States Department of Justice Press Release entitled "Otsuka to Pay More than $4 Million to Resolve off-label Marketing Allegations Involving Abilify" dated March 27, 2008, *en liasse*;

P-98: Copy of the letter from the U.S. FDA Department of Health & Human Services to Otsuka Pharmaceutical Development & Commercialization, Inc. dated April 17, 2015

Copy of the PLoS Medicine article entitled "Questionable Advertising of Psychotropic Medications and Disease Mongering" dated July 2006, *en liasse*;

P-99: Copy of the Pro Publica webpage entitled "Has Your Doctor Received Drug or Device Company Money?" for ABILIFY;

P-100: Copy of an extract from the FiercePharma article for ABILIFY;

P-101: Copies of extracts from Bristol-Myers website at www.bms.com, *en liasse*;

P-102: Copies of Bristol-Myers' Annual Reports dated 2014 and 2013, produced herein *en liasse*;

P-103: Copies of Otsuka's Annual Reports dated 2013 and dated 2014, produced herein *en liasse*;

P-104: Copy of the Press Release entitled "Bristol-Myers Squibb And Otsuka Announce Commercialization Agreement For Aripiprazole" dated September 21, 1999;

P-105: Copy of the Product Monograph for ABILIFY last revised on June 22, 2015;

P-106: Copy of the Product Monograph for ABILIFY last revised on February 23, 2017;

P-107: Copies of previous versions of the Product Monographs for ABILIFY, from July 9, 2009 to May 27, 2013, *en liasse*;

P-108: Copy of Bristol-Myers Squibb Company's September 1, 2011 6-Month Periodic Safety Update Report dated September 1, 2011;

P-109: Copy of the Final Assessment Report on the 15th Periodic Safety Update Report dated December 5, 2011;

P-110: Copy of the Cochrane Library Database of Systematic Reviews article entitled “Aripiprazole versus other atypical antipsychotics for schizophrenia (Review)” dated 2016;

P-111: Copy of the Transfer Order in *In Re: Abilify (Aripiprazole) Products Liability Litigation*, MDL No. 2734 dated October 3, 2016;

P-112: Copy of the Master Long Form Complaint and Jury Demand in *In Re: Abilify (Aripiprazole) Products Liability Litigation*, MDL No. 2734 dated December 2, 2016;

P-113: Copy of the Amended Order in *In Re: Abilify (Aripiprazole) Products Liability Litigation*, MDL No. 2734 dated March 15, 2018;

P-114: Copy of the Order in *In Re: Abilify (Aripiprazole) Products Liability Litigation*, MDL No. 2734 dated April 28, 2018;

P-115: Copy of the Global Settlement Order No. 1, dated May 2, 2018

Copy of the Joint Notice of Proposed Settlement Program in *In Re: Abilify (Aripiprazole) Products Liability Litigation*, MDL No. 2734 dated February 15, 2019, *en liasse*;

P-116: Copy of the Plaintiff’s file from *Centre de réadaptation en dépendence Foster* (under seal);

P-117: Copy of the Plaintiff’s file from the Uniprix pharmacy in Verdun (under seal);

Copy of the Plaintiff’s file from the Brunet in Chateauguay, (under seal) *en liasse*;

P-118: Copy of the Plaintiff’s file from Hôpital de Verdun (under seal);

P-119: Copy of the Plaintiff’s file from Portage (under seal);

P-120: Copy of the Plaintiff’s file from Jacqueline Aubie M.A., O.P.Q. (under seal);

P-121: Copy of the Plaintiff’s file from Dr. Gary Barrs, (under seal);

P-122: Copy of the Plaintiff’s file from the Douglas Hospital (under seal);

P-123: Copy of the Expert Report of Dr. Brahm dated April 1, 2018;

P-124: Copy of a redacted chart of Class Members who have inputted their information through the CLG webpage.

Montreal, March 12, 2020

_____
CONSUMER LAW GROUP INC.
Per: Me Andrea Grass
Attorneys for the Plaintiff / Class Representative

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Nº: 500-06-000831-160

(Class Action)
SUPERIOR COURT
DISTRICT OF MONTREAL

STEVEN SCHEER
Plaintiff/ Class Representative

-vs.-

BRISTOL-MYERS SQUIBB CANADA CO. *et al.*
Defendants

APPLICATION TO INSTITUTE PROCEEDINGS
(Art. 141 and following *C.C.P.*)

COPY

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Me Andrea Grass, Ext. 3
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