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TITLE:

An Observational Post-Authorization Safety Surveillance (PASS) Study of SYCREST® (asenapine) among Patients aged 18 and older Diagnosed with Bipolar Disorder

ETHICS REVIEW COMMITTEE:

Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA)

Multi-Centre Research Ethics Committee (MREC)

TABLE OF CONTENTS

List of Abbreviations **4**

List of Definitions **5**

I. Protocol **7**

A. BACKGROUND AND RATIONALE *7*
1. Background 7
2. Study Rationale 9

B. OBJECTIVES *10*
1. Primary Objectives: 10
2. Secondary Objectives: 10

C. STUDY DESIGN AND DURATION *12*
1. Summary of Study Design and Duration 12
2. Study Population 12
3. Inclusion Criteria 14

D. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS *14*
1. Definition of Primary Exposure 14
2. Definition of Comparison Exposure 18
3. Exposure Period Assumptions 19
4. Definition of Identified and Potential Risks 19
5. Definition of Covariates 20

E. STUDY PROCEDURES *20*
1. Informed Consent 20

F. SAFETY *20*
1. Definition of Serious Adverse Experience 20
2. Reporting of Adverse Experience 20
3. Safety Review Committee 21

G. STATISTICAL ANALYSIS PLAN *21*
1. Description of Baseline Characteristics 21
2. Calculation of Incidence Rates for Identified and Potential Risks 22
3. Calculation of Rate Ratios for Identified and Potential Risks 23
4. Bias 26
5. Sample Size and Power Considerations 28

LIST OF REFERENCES **29**

Appendix A: Data Quality Markers **30**

Appendix B: Methodology for Identifying the same Practice in CPRD and THIN **32**

Appendix C: Coding Lists and Algorithms **34**

Appendix D: Covariates **56**

Attachment A: Product Circular.....70

Table Shells 108

LIST OF ABBREVIATIONS

Abbreviations	
AMR	Acceptable Mortality Reporting
DDD	Defined Daily Dose
DFDR	Double False Discovery Rate
DSRU	Drug Safety Research Unit
EMA	European Medicines Agency
EPIC	Epidemiology and Pharmacology Information Core
EPS	Extrapyramidal Symptoms
FDR	False Discovery Rate
GP	General Practitioner
CPRD	Clinical Practice Research Datalink
ISAC	Independent Scientific Advisory Committee
MHRA	Medicines and Healthcare products Regulatory Agency
M-PEM	Modified Prescription-Event Monitoring Study
MREC	Multi-Centre Research Ethics Committee
NMS	Neuroleptic Malignant Syndrome
PASS	Post-Authorization Safety Surveillance
SCEM	Specialist Cohort Event Monitoring Study
THIN	The Health Improvement Network
UK	United Kingdom
UTS	Up-to-Standard

LIST OF DEFINITIONS

Definitions	
Acceptable Patient (CPRD Only)	A CPRD quality indicator determining whether the patient has met certain quality standards listed in Appendix A
Acceptable Mortality Reporting year	A THIN quality indicator that identifies the year in which longitudinal mortality reporting for a given practice is deemed complete. The Acceptable Mortality Reporting year provides a natural filter for research and avoids biases associated with "immortal periods", record updating and under-reporting.
Up-to-Standard Practice (CPRD Only)	A CPRD quality indicator identifying the date at which the practice data is deemed to be of research quality according to quality standards listed in Appendix A
Registration Date (CPRD Only)	Date the patient first registered with the practice
Transfer Out Date (CPRD Only)	Date the patient transferred out of the practice
Last Data Collection Date (CPRD Only)	Date of the last data collection for the practice by CPRD
Computerization Date (THIN Only)	Date the practice first started issuing prescriptions from the computer every day for consecutive months.
Vision Date (THIN Only)	Date the practice started using the Vision practice management software to record consultations.
Study Time Window	Predefined time period to identify inclusion/exclusion criteria, exposure and outcome
Index Bipolar Disorder Prescription Date	First date a prescription for asenapine or comparator is observed in the study time window after the registration and quality indicator dates and entry into the bipolar disorder cohort.
Baseline Time or Baseline Evaluation Period	The duration of observation period prior to the beginning of the follow-up period to describe the patient's characteristics at the beginning of the follow-up period.
Follow-up Time	(CPRD) Time accumulated by patient starting the day after the index bipolar disorder event date until the earliest occurrence of the date of the health outcome of interest (for specific analyses), transfer out date, last data collection date, or last date in current CPRD dataset
Channeling	Channeling is a form of allocation bias, where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences

Confounding	A *confounding variable* or a *confounder* is a variable other than the risk factor and outcome under study that is independently related both to the risk factor and to the outcome. A confounder can create an apparent association between the risk factor and outcome or mask a real one

I. PROTOCOL

A. BACKGROUND AND RATIONALE

1. Background

The group of disorders commonly referred to as 'bipolar disorders' are chronic, typically cyclic mood disorders and is comprised of bipolar I disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified (NOS). Mania is the hallmark of bipolar disorders, with individuals experiencing periodic episodes, which may be manic (or hypomanic), depressive (meeting criteria for major depressive episode), or mixed (i.e., the criteria are met for both a manic episode and a major depressive episode, except for the duration requirement).

Bipolar I disorder is a severe and chronic mood disorder characterized by the occurrence of at least one manic or mixed episode according to the criteria of DSM-IV-TR. Often, individuals have experienced one or more episodes of major depression. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. The duration of a manic episode can extend from days to months. Typical symptoms during the mood disturbance include inflated self-esteem or grandiosity, decreased need for sleep, increases in goal-directed activity, logorrhea, flight of ideas and excessive involvement in high-risk hedonic activities. Manic patients are at increased risk to engage in unrestrained buying sprees, sexual indiscretions or foolish business investments. During a mixed episode individuals experience rapidly alternating moods, which may either coexist or alternate during different periods of the day and include symptoms of a manic episode and of a major depressive episode. These episodes cause marked impairment in social or occupational functioning and have a minimum duration requirement of at least one week.

Bebbington and Ramana conducted a review of studies examining the epidemiology of bipolar affective disorder, as the group of bipolar disorders are also referred to. The incidence of bipolar affective disorder ranges from 2.0 to 32.5 per 100,000 per year for females, from 3.0 to 15.2 per 100,000 per year for males, and 2.6 to 20.8 per 100,000 per year combined (Bebbington et al. 1995).

Based on studies in the US, Germany and Switzerland, current prevalence estimates for bipolar spectrum disorders are reported to be in the range of 2.8-6.5% (Bauer, M. and Pfennig, A., 2005). The prevalence estimates for bipolar spectrum disorders are higher than the estimates for bipolar I disorder since 'bipolar disorder' includes bipolar II disorder and hypomania which are more prevalent than bipolar I. In a systematic review, the lifetime prevalence rate of bipolar I disorder has been estimated to be 0.82 per 100 persons (95% CI: 0.56% to 1.1%) (Waraich et al. 2004). Similarly, in Europe the reported lifetime prevalence of bipolar I disorder ranges from 0.3% to 1.5% (Pini et al. 2005). This review found that the lifetime prevalence rate for bipolar disorder was very similar across the European countries. The rates were similar in men and women with the rate in women being slightly greater in the majority of studies.

Management of bipolar disorders is comprised of effective treatment of the acute phases of manic, mixed, hypomanic and depressive episodes, and maintenance treatment aimed to prevent relapses. The treatment of bipolar depression differs substantially from the treatment of unipolar depression due to the increased risk of a switch into mania, and mood stabilizers are recommended when antidepressants are used. An important long term goal is mood stabilization, ideally in the state of euthymia. For the treatment of manic symptoms, a variety of drug treatment options have been used in the past decades. Lithium and antiepileptic drugs such as valproate or carbamazepine have demonstrated antimanic effects. Typical antipsychotics have frequently been used to control manic symptoms; their use however, was often limited by the occurrence of extrapyramidal symptoms (EPS). More recently, atypical antipsychotics have increasingly been used successfully and approved to treat manic episodes associated with bipolar I disorder.

Asenapine is a novel atypical antipsychotic agent indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. Current medications for the treatment of Bipolar Disorder do not satisfy all important medical needs in a large proportion of patients with this indication due to incomplete relief of symptoms and treatment side effects. Asenapine has been generally well tolerated in investigated clinical trial populations and has a unique pharmacological profile that differs from other atypical antipsychotics, making it an important addition to the bipolar treatment armamentarium.

Evaluation of all safety data and possible risk factors related to the use of asenapine, revealed the following important risks:

Important identified risks, including class effects, are

- Extrapyramidal symptoms (EPS)
- Somnolence and sedation
- Weight gain
- Increased exposure in patients with severe hepatic impairment
- Oral hypoaesthesia
- Swelling of tongue and throat
- Increased liver transaminases and Gamma-Glutamyl Transferase (GGT)
- Orthostatic hypotension in the elderly
- Allergic reactions

Important potential risks, including class effects, are

- Neuroleptic Malignant Syndrome (NMS)

- Rhabdomyolysis
- Seizures
- Hyperprolactinaemia
- Cardiovascular effects (QT prolongation and orthostatic hypotension)
- Neutropenia
- Metabolic effects other than weight gain
- Overdose
- Non compliance with the 10-minute requirement for no food or fluids after sublingual administration

(Atypical) antipsychotic agents are associated with a number of class effects. Effects that have at this point in time not been associated with the use of asenapine, but which may be expected based on class labelling, are the following:

- Increased mortality in elderly with dementia-related psychosis
- Suicidality
- Liver related signs and symptoms
- Dysphagia
- Body temperature dysregulation

Important missing information includes:

- Use during pregnancy and lactation
- Misuse for illegal purposes
- Off-label use
- Off-label paediatric use

2. Study Rationale

In addition to the routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), Merck Sharp & Dohme Corp. proposed to conduct this active post-licensure observational safety surveillance study to monitor clinically important identified and potential risks within a cohort of patients diagnosed with Bipolar Disorder and treated with asenapine. EMA requested that the

PASS specifically monitor the occurrence of allergic reactions, diabetes mellitus, dyslipidaemia, EPS, hyperprolactinaemia, NMS, neutropenia, orthostatic hypotension, rhabdomyolysis, seizures, somnolence and sedation. This study is part of a broader post-marketing commitment to augment routine evaluation of the safety profile of asenapine in clinical practice. In addition to the PASS, this broad commitment includes a drug utilization study of off-label use conducted by Merck Sharp & Dohme Corp.in the CPRD and two independent safety and use monitoring studies conducted in primary and specialty care in the United Kingdom by the Drug Safety Research Unit.

B. OBJECTIVES

The following primary objectives were developed in collaboration with the European Medicines Agency (EMA).

1. Primary Objectives:

1) Describe the "baseline" demographic and physical characteristics, including prior health status, comorbidities, and concomitant medications of patients aged 18+ diagnosed with Bipolar Disorder newly treated with asenapine in routine post-licensure use

2) Assess the incidence rate of identified and potential risks, including extrapyramidal symptoms, somnolence and sedation, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinaemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidaemia and diabetes mellitus, in patients aged 18+ diagnosed with Bipolar Disorder and newly treated with asenapine in routine post-licensure use

3) For comparison purposes, describe the "baseline" demographic and physical characteristics as described above and calculate incidence rate ratios of identified and potential risks, including extrapyramidal symptoms, somnolence and sedation, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinaemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidaemia and diabetes mellitus, between new users of asenapine and two control cohorts:

a) A post-licensure concurrent control cohort of patients aged 18+ diagnosed with Bipolar Disorder and newly treated with risperidone

b) A post-licensure concurrent control cohort of patients aged 18+ diagnosed with Bipolar Disorder and newly treated with olanzapine

2. Secondary Objectives:

A. *Use* in Schizophrenia Patients

Comparative analyses will be performed when adequate power (80%) is achieved (see table of power calculations in section G5). As an example, analyses will be performed when 763 patient-years of exposure to asenapine have been reached for specific health outcomes to which annual reports assessed incidence rates in at least one of the reference group of or above 2% per year:

1) Describe the "baseline" demographic and physical characteristics, including prior health status, comorbidities, and concomitant medications of patients aged 18+ diagnosed with Schizophrenia, with no prior and/or concomitant diagnosis of Bipolar Disorder, and newly treated with asenapine in routine post-licensure use

2) Assess the incidence rate of identified and potential risks, including extrapyramidal symptoms, somnolence and sedation, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinaemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidaemia and diabetes mellitus, in patients aged 18+ diagnosed with Schizophrenia, with no prior and/or concomitant diagnosis of Bipolar Disorder, and newly treated with asenapine in routine post-licensure use

3) For comparison purposes, describe the "baseline" demographic and physical characteristics as described above and calculate incidence rate ratios of identified and potential risks, including extrapyramidal symptoms, somnolence and sedation, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinaemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidaemia and diabetes mellitus, between new users of asenapine and two control cohorts:

a) A post-licensure concurrent control cohort of patients aged 18+ diagnosed with Schizophrenia, with no prior and/or concomitant diagnosis of Bipolar Disorder, and newly treated with risperidone

b) A post-licensure concurrent control cohort of patients aged 18+ diagnosed with Schizophrenia, with no prior and/or concomitant diagnosis of Bipolar Disorder, and newly treated with olanzapine

B. *Use* in Patients without Diagnoses for Bipolar Disorder or Schizophrenia

Comparative analyses will be performed when adequate power (80%) is achieved (see table of power calculations in section G5). As an example, analyses will be performed when 763 patient-years of exposure to asenapine have been reached for specific health outcomes to which annual reports assessed incidence rates in at least one of the reference group of or above 2% per year:

1) Describe the "baseline" demographic and physical characteristics, including prior health status, comorbidities, and concomitant medications of patients aged 18+ newly treated with asenapine with no prior and/or concomitant diagnoses of Bipolar Disorder or Schizophrenia ***but diagnosed with i) Alzheimer's disease, ii) "Other diagnoses: Mental disorders", and iii) "No diagnosis"***.

2) Assess the incidence rate of identified and potential risks, including extrapyramidal symptoms, somnolence and sedation, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinaemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidaemia and diabetes mellitus, in patients aged 18+ newly treated with asenapine with no prior and/or concomitant diagnoses of Bipolar Disorder or Schizophrenia ***but diagnosed with i) Alzheimer's disease, ii) "Other diagnoses: Mental disorders", and iii) "No diagnosis"***.

C. STUDY DESIGN AND DURATION

1. Summary of Study Design and Duration

This PASS study will be a retrospective new users cohort design for the purposes of conducting analyses of safety data related to asenapine when the product is used in the post-licensure period under conditions of usual care use. Of note, this active surveillance does not involve active administration of asenapine by Merck Sharp & Dohme Corp. All recipients of asenapine who will be followed in this study will have received marketed drug in the course of ordinary clinical practice after licensure of the drug (16 January 2012). Detailed information on recommended dosages can be found in the product circular (Attachment A).

The initial study period will be from 1 January 2012 to 31 ***January*** 2014. The study period will extend with each annual refresh of the database. The proposed end of this PASS study is the first occurrence of either ***5*** years post-launch (approximately 2012 - ***2017***) or until at least 3,000 patient and 3,000 patient-years of exposure to asenapine are accrued. Annual reports will assess incidence of health outcomes in the reference groups. Comparative analyses will be performed when adequate power (80%) is achieved (see table of power calculations in section G5). As an example, analyses will be performed when 763 patient-years of exposure to asenapine have been reached for specific health outcomes to which annual reports assessed incidence rates in at least one of the reference group of or above 2% per year. At the end of study for all of the events of interests (including those for which sample size was underpowered) 95% confidence intervals with the rate ratios to illustrate sufficient power to detect differences in effect estimates will be reported. The retrospective data collection of this study will begin immediately following launch of asenapine on 16 January 2012. Since the safety surveillance is observational and follows the outcome of routinely administered patient care, the duration of the surveillance will depend upon the size of the cohort to which asenapine is prescribed and the general uptake of asenapine in patients diagnosed with Bipolar Disorder.

2. Study Population

This PASS study will be conducted in a cohort of patients 18+ diagnosed with Bipolar Disorder[1] as identified through Read diagnosis codes in an electronic healthcare database.

The Bipolar Disorder cohort will be extracted from the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK). In the UK, "up to one half of people

[1] If pre-specified sample size and exposure criteria are met, secondary objectives will be conducted in two separate study populations: 1. Patients treated with asenapine and diagnosed with Schizophrenia and no prior and/or concomitant diagnosis of Bipolar Disorder; 2. Patients treated with asenapine and no prior and/or concomitant diagnoses of Bipolar Disorder or Schizophrenia

who have a serious mental illness are seen only in a primary care setting,"[2] making the use of the Clinical Practice Research Datalink (CPRD) an appropriate study population to evaluate safety of asenapine. Data for the CPRD database are collected from the UK general practitioner (GP) practices using the practice management software. The database includes 3.5 million currently active patients with research quality data and over 10 million persons with research usable data from over 460 practices, and 39 million person years of research quality data. The database (5.5% of the UK population) is generally representative of UK general population. The data elements include demographics, medical diagnoses and procedures, prescriptions, hospital and specialist referrals, hospital discharge and specialist reports, and miscellaneous patient care information, such as smoking status, height, weight, immunizations, and lab results. The CPRD database is managed by the Medicines and Healthcare products Regulatory Agency (MHRA).

Given the low lifetime prevalence of Bipolar Disorder in Europe (0.1-0.2 % to 1.8%), the ability to perform comparisons with a reasonable level of statistical precision may be hindered by slow uptake of asenapine in routine use as indicated for patients with diagnoses of Bipolar Disorder. (Pini et al. 2005) Therefore, Merck Sharp & Dohme Corp. proposes that new use of asenapine in patients with Bipolar Disorder be evaluated two years after the initiation of this PASS study. In the event that new use remains limited[3], Merck Sharp & Dohme Corp. proposes that the Bipolar Disorder cohort be extracted from the combination of the Clinical Practice Research Datalink (CPRD) in the UK and The Health Improvement Network (THIN) database in the UK. This combination of databases will allow for more rapid accumulation of patients.

The THIN database also includes computerized, anonymous, longitudinal patient medical records retrieved from GPs in the UK. THIN contains data from 6.9 million patients in 390 practices, and is also demographically representative of the UK population. The data available to researchers consist of demographic, medical and prescription information at individual patient level. In addition, there is information on referral to specialists, diagnostics and laboratory results, some lifestyle characteristics and other measurements taken in the GP practice. At the patients' postal code level, socioeconomic (Townsend) and area of living (rural/urban) information is also available. Cegedim Strategic Data Medical Research is the company that manages THIN.

Both databases contain quality control metrics that assist in identifying data of the highest research quality (Appendix A). These metrics will be utilized when creating the Bipolar Disorder cohort. In addition, some general medical practices in the UK are included in both the CPRD and THIN databases, thus there are some patient records that are

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[2] Quality and Outcomes Framework guidance for GMS contract 2009/10; The NHS Confederation (Employers) Company Ltd; p 82.

[3] Limited use is defined as less than 500 patients per year diagnosed with Bipolar Disorder and subsequently treated with asenapine. An average of 500 patients per year over 3 years will provide approximately 80% power to detect a 3-fold increase in the incidence of a health outcome that has an annual background rate of 1.0%.

duplicated when both databases are combined for analysis. Because the practices that are common to both databases are not publicly known, Merck has developed an algorithm for this study to identify the common practices (Appendix B). (Cai 2010) This algorithm has been applied in previous Post-Authorization Safety Surveillance studies in support of Merck marketed products. For those practices that are identified as contributing to both databases, the data from the CPRD database will be used.

3. Inclusion Criteria

Bipolar Disorder Cohort[4]

This PASS study will first identify a cohort of patients diagnosed with Bipolar Disorder in CPRD that meet the following criteria for inclusion:

1) A diagnostic code indicating Bipolar Disorder[5]

The date that each patient meets all of the above entry criteria will be his/her cohort entry date. Patients that enter the Bipolar Disorder cohort will be stratified into those with incident or prevalent disease. The time accumulated between cohort entry date and the latter of either (a) the registration date with their general practitioner or (b) the database specific quality indicator date, will be used to make this distinction. Incident patients will be defined as a set of patients who have accumulated ≥ 365 days before first recorded diagnosis of Bipolar Disorder; whereas, prevalent patients will be defined as a set of patients who have accumulated < 365 days before first recorded diagnosis of Bipolar Disorder.

D. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

1. Definition of Primary Exposure

Asenapine Inception (new user) Cohort

This study utilizes an inception cohort (new users) design. (Schneeweiss 2010) Patients treated with asenapine will be identified within the Bipolar Disorder cohort[6]. Each patient must meet the following criteria:

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[4] A Schizophrenia cohort will be constructed with similar inclusion criteria and the addition of an exclusion criterion where patients with a prior and/or concomitant diagnosis of Bipolar Disorder will be excluded.

[5] Given that CPRD is general practitioner-based electronic medical record databases, it is not specifically designed to capture psychiatric disorders for research purposes. As such, the diagnostic information recorded may lack the specificity required to differentiate between bipolar I disorder, the condition associated with the indication, from other Bipolar Disorders. As a result, the bipolar cohort will initially be constructed using a general coding algorithm that would categorize bipolar I disorder, bipolar II disorder, Bipolar Disorder not otherwise specified (NOS) under the label 'Bipolar Disorder'.

1) First written prescription for asenapine after entry into the Bipolar Disorder cohort or first written prescription for asenapine within 2 years before entry into the Bipolar Disorder cohort (***treatment before diagnosis***) [7] In CPRD, among patients receiving a prescription of olanzapine and / or risperidone prior to their diagnosis (i.e., ***patients receiving treatment before diagnosis***), the cumulative distribution shows approximately 70% have a duration of time between initiation of treatment and first diagnosis of Bipolar Disorder within 2 years.

2) No use of asenapine within 365 days prior to the first written prescription for asenapine defined above

3) ≥ 365 days of time accumulated between asenapine prescription date and the latter of either (a) the registration date with the general practitioner or (b) the database specific quality indicator date

For each patient, date of the first written prescription for asenapine will be identified as their index date. All patients in the asenapine inception cohort will have 365 days of baseline data looking back from their index date. All patients will be considered 'new users' since there will be no use of asenapine in this baseline period (Figure 1). A 365 days antipsychotic-free period will be considered equivalent to a first ever atypical antipsychotic treatment. Sensitivity analyses will nonetheless be conducted extending the 'new user' definition to no use of asenapine within 545 days prior to their first prescription after cohort entry. The asenapine inception cohort design will be stratified into two mutually exclusive groups consisting of patients with 1st ever use of an atypical antipsychotic or patients with prior recent use[8] of atypical antipsychotics (Figure 2).

Exposure to asenapine will follow an as-treated approach where exposure will start with the index prescription date and end at a date calculated by an algorithm used to derive continuous exposure. The algorithm will utilize quantity and dosing instructions to calculate days supply for each prescription and combine this with the refill sequence of successive prescriptions to calculate duration of continuous exposure. An allowable gap between successive prescriptions in calculating continuous exposure will be defined empirically based on the median gap between all prescriptions for asenapine for all patients included in the analytic dataset. However, this allowable gap will not be less than 30 days. A pre-determined risk window equal to 45 or 365 days, depending on type

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[6] The same definition for an asenapine inception cohort will be applied to the previously described Schizophrenia cohort.

[7] For the secondary objective specific to use in patients without diagnoses for Bipolar Disorder or Schizophrenia, first written prescription for asenapine where a patient does not a have a prior and/or concomitant diagnosis of Bipolar Disorder or Schizophrenia will satisfy the first inclusion criterion for an asenapine inception cohort. The second criterion will remain the same, however, the third criterion no longer applies for this specific study population.

[8] Prior recent use is defined as records for use of other atypical antipsychotics in the 365 days prior to the index prescription

of event (i.e. acute vs. chronic) will also be added to the exposure end date (as determined by the algorithm) in order to capture latent effects of exposure that may result in an outcome of interest. In the event that a patient receives a written prescription for a comparator exposure (risperidone or olanzapine), time at risk and follow-up will be censored on the date of that written prescription. Patients will not be eligible to enter the concurrent comparison cohort after exposure to asenapine has ended.

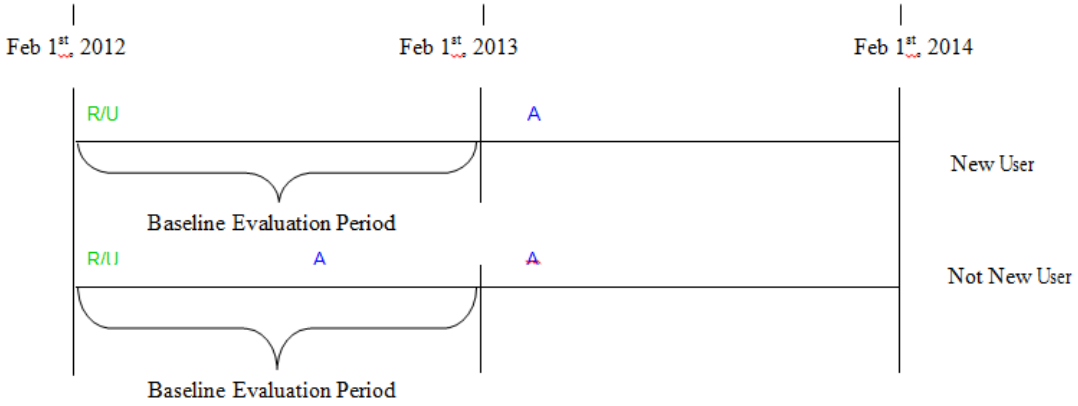

Figure 1. Definition of an inception cohort (new user) in CPRD

A = Asenapine Prescription
BD = Bipolar Disorder Diagnosis
18+ = Date Patient Turned 18
R/U = Max of Registration and UTS Dates

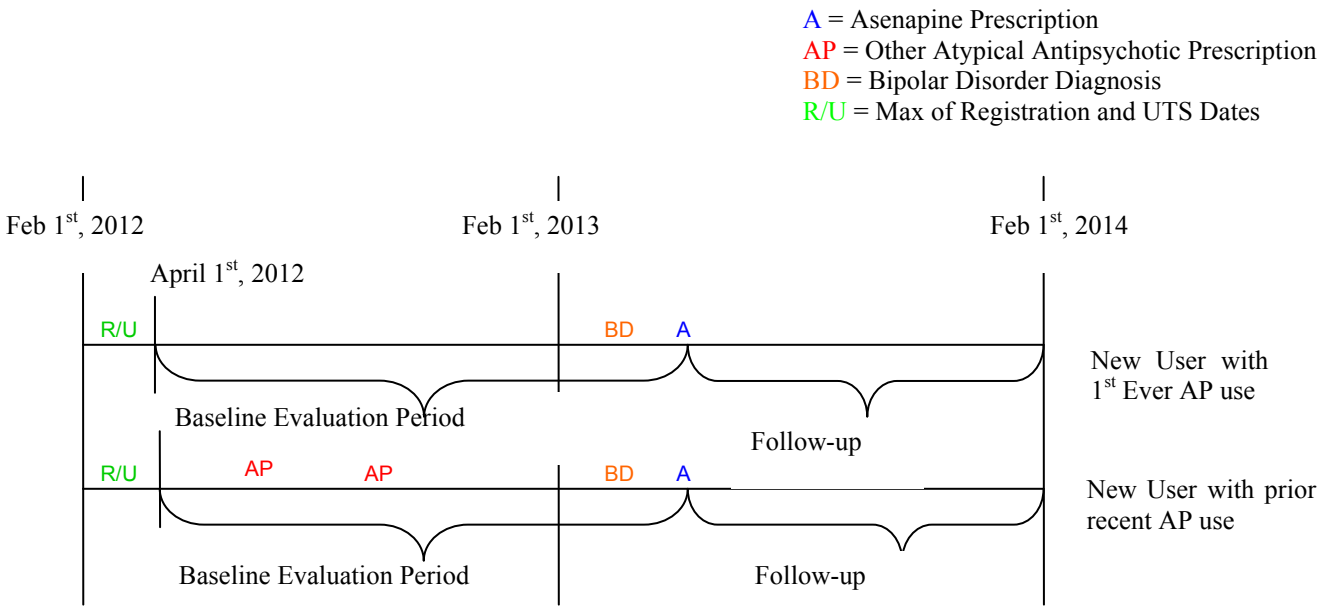

Figure 2. Definition of 1st ever use versus prior recent use of atypical antipsychotic among an inception cohort (new user) in CPRD

Follow-up

Each patient will be followed starting with the prescription index date and ending with the earliest of:

1) Exposure end date (as determined by the algorithm) plus pre-determined risk window

2) Date of a written prescription for risperidone or olanzapine (comparator exposures)

3) Date transferred out of the practice

4) Date of the last data collection from the practice

5) Date of clinical event (since multiple outcomes are being evaluated, this date will vary within each patient by outcome)

6) The end of the study period

7) Date of death

Handling of Missing or Erroneous Data

Multiple imputation using Markov chain Monte Carlo (MCMC) methods (Gilks, Richardson & Spiegelhalter, 1996) will be used to correct for missing or erroneous prescription and covariate data. Erroneous prescription data includes abnormal values for a defined daily dose (DDD) (e.g., >10) for a given drug. In this example, it is reasonable to consider 10 DDDs (i.e., 200 mg/day asenapine) to be abnormal or erroneous since the recommended dosing instructions for asenapine is take one 5mg or 10mg tablet twice a day equating to a maximum DDD of 20mg/day. For univariate analyses, data will be imputed according to the mean or median value of the same drug or covariate for the same patient. If this value is not available or the number of observations is less than 3, the data will be imputed according the mean or median value of the same drug or covariate for all patients in the Bipolar Disorder cohort. For incomplete multivariate data, Schafer (1997) has adapted and implemented MCMC methods for multiple imputation.

2. Definition of Comparison Exposure

Several comparison groups will be used to put the results from primary objectives 1 and 2 into clinical perspective. The bipolar disorder[9] cohort will be used to identify two concurrent control groups which include patients receiving a first written prescription for risperidone or olanzapine after cohort entry. Patients in the concurrent comparison

[9] The same definition for comparison exposure will be applied to the previously described Schizophrenia cohort.

cohort will be matched closest to the date of asenapine prescription +/- 1 year[10]. All branded and generic prescriptions for risperidone or olanzapine are considered bioequivalent and will be defined by the main ingredient for this study. Identification of the index prescription date, 'new user', inception cohort strata, calculation of duration of continuous exposure for each control group, follow-up, and handling of missing or erroneous data will follow the same logic described for asenapine. Patients are only eligible to serve as a comparator once (matched with no replacement) as a result they cannot enter the other concurrent comparison cohort.

3. Exposure Period Assumptions

In view that this study will measure GP prescribing and not actual drug use by patients, any inferences about drug utilization by patients will require that the following set of assumptions all hold true: 1) all prescriptions were dispensed to patients on the same day that they were issued by each practice's computer system; 2) patients consumed a prescription for asenapine, risperidone, and olanzapine as directed on consecutive days after the date that each prescription was issued; and 3) patients consumed the entire quantity of drug supplied in each prescription. The CPRD does not capture prescriptions issued by hospital-based specialists (e.g., psychiatrists). Hence, this study only will measure the quantity of prescriptions prescribed by GP's, and not all health care providers in the UK National Health Service (NHS).

4. Definition of Identified and Potential Risks

The identified and potential risks include extrapyramidal symptoms, somnolence, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinaemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidaemia and diabetes mellitus. Each risk will be classified as acute or longer onset based on the natural course of disease progression from biologic onset to development of clinical symptoms and subsequent diagnosis. Acute onset risks include allergic reactions, extrapyramidal symptoms, neuroleptic malignant syndrome, somnolence, seizure, and orthostatic hypotension. The risk window for acute onset risks will include time while exposed plus a 45 day risk window once exposure ends. Longer onset risks include diabetes mellitus, dyslipidaemia, hyperprolactinaemia, neutropenia, rhabdomyolysis. The risk window for longer onset risks will include time while exposed plus a 365 day risk window once exposure ends.

Identified and potential risks for study will be defined according to coding algorithms (initial list provided in Appendix C) developed through a systematic process utilizing previously published literature, medical coding expertise, and expert opinion from practicing clinicians. A coding algorithm is defined as a single diagnosis, procedure, drug or lab value code (e.g. Read) or combination of codes and/or conditions (e.g. hospitilization) that could be applied to identify a specific risk of interest. Despite the

[10] The +/1 year matching window was selected in order to control for temporal differences and at the same time allow for a match to be identified in a disease where lifetime prevalence is low.

efforts taken to define algorithms specific to each identified and potential risk, it should be noted that since CPRD is a general practitioner-based electronic medical record database, under-reporting or misclassification of identified and potential risks may occur. Events occurring in emergency care will be missed. Diagnostic codes or laboratory data may lack the specificity needed to determine if an event of interest occurred.

5. Definition of Covariates

Covariates included in the study are those determined to be confounders or risk factors for a given outcome of interest. Covariates will be used for descriptive analyses and as measured controls for propensity score development. A list of potential confounders and risk factors for each outcome of interest are listed in the Appendix D.

E. STUDY PROCEDURES

1. Informed Consent

The CPRD database licensed by Merck & Co., Inc. contain de-identified data; therefore, Merck & Co., Inc. will not have access to any individual patient's medical information. Prior to being finalized the study protocol will be reviewed by the CHMP of the EMA and will undergo review and approval by the Independent Scientific Advisory Committee (ISAC) of the CPRD and the Multi-Centre Research Ethics Committee (MREC) for the Epidemiology and Pharmacology Information Core (EPIC) company.

F. SAFETY

1. Definition of Serious Adverse Experience

"Serious Adverse Experience" (SAE) means an adverse experience which is fatal or life threatening, results in persistent or significant disability, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, or is a congenital anomaly, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a Serious Adverse Experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Safety data will be collected and analyzed on an ongoing basis, with updates on the study progress being reported in the 6-month periodic safety update report (PSUR) (e.g., accumulated person-years of exposure).

2. Reporting of Adverse Experience

No reporting of individual cases to regulatory agencies is planned as part of this retrospective observational study. This is consistent with Council for International Organizations of Medical Sciences (CIOMS) V, which states that for epidemiological studies, individual case reporting is generally not appropriate unless there is specific attribution of an individual case (i.e., within the medical record). Because there is no access to individual patient charts for this study, no specific attribution of cases is possible. The data being used for this study are anonymized at both the patient level and the general practitioner/practice level. The analysis results will be at the group (aggregate) level. The results of this PASS study will be presented to the regulatory agencies on an interim basis starting after the first year of data accrual following the implementation of the project and then on an annual basis until the final report provided at the end of the project. The final results will also be provided to regulatory agencies in Periodic Safety Update Reports when available.

3. Safety Review Committee

A single Safety Review Committee will be established to monitor safety data emerging from this PASS. The voting members of the committee are external to the Sponsor. The members of the SRC must not be involved with the studies in any other way (e.g., they cannot be Investigators) and must have no competing interests that could affect their roles with respect to the studies.

Specific details regarding responsibilities and governance, including the roles and responsibilities of the various members, the Sponsor; meeting facilitation; the study governance structure; and requirements for and proper documentation of SRC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the SRC. The SRC will monitor the studies at an appropriate frequency, as described in the detailed SRC charter. The SRC will also make recommendations to the Sponsor regarding steps to ensure both patient safety and the continued ethical integrity of the studies.

Although non-serious adverse events (NSAEs) are not actively solicited in this study, if any attributed NSAEs are reported by the investigator, they must be collected for tabulation in interim and/or study report and submitted to Global Safety using the same method as described above for SAEs.

G. STATISTICAL ANALYSIS PLAN

1. Description of Baseline Characteristics

For each patient, baseline characteristics (i.e. covariates) will be described using the clinical record accumulated prior to the prescription index date and the latter of the registration date with their general practitioner or the database specific quality indicator date. Baseline descriptive statistics will be calculated for new users of the study drugs of interest (asenapine, risperidone control, olanzapine control) after cohort entry and will be calculated from the medical history provided in the 365 days accumulated between the first written prescription (index) date and latter of the registration date with the general

practitioner or the database specific quality indicator date. All baseline characteristics measured during this time period will be considered fixed as of the index date. There will be no time-dependent covariates in this study. All descriptive analyses will be stratified[11] according to patients with incident or prevalent Bipolar Disorder and according the inception cohort strata (1st ever atypical antipsychotic or prior recent atypical antipsychotic use). Baseline characteristics to be described include:

- Demographic (e.g. age, gender)
- Physical and Behavioral (e.g. Body Mass Index, smoking status, alcohol use)
- Pre-existing conditions and comorbidities (e.g. Charlson comorbidity index, alcohol or substance abuse disorder, Axis I or II psychiatric disorder, cardiovascular disease)
- Prior and concomitant treatments (e.g. lithium, anti-epileptics, antidepressant, anxiolytics)
- Healthcare resources utilization (e.g. number of hospitalizations, number of prescriptions, referral to a psychiatrist, number of GP visits)

Characteristics presented as continuous data will be summarized in a table through means, standard deviations, medians, minimum and maximum values; whereas, categorical data will be summarized in a table as counts and proportions.

2. Calculation of Incidence Rates for Identified and Potential Risks

Each of the identified and potential risks will be analyzed separately. Incidence rates for each risk will be stratified[12] according to patients with incident or prevalent Bipolar Disorder[13] and according the inception cohort strata (1st ever atypical antipsychotic or prior recent atypical antipsychotic use). During follow-up, incident (or first occurrence) of each type of identified and potential risk within each patient will be identified. An event will be attributed to a given exposure if observed during the exposure or in the risk window described in the previous study design section Definition of Primary Exposure. Given the new user design, all patients will have 365 days of baseline data. Patients with a history of a given outcome 365 days prior to the prescription index date will be considered prevalent cases and will be excluded from the incident analysis of that type of event.

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[11] In the event that patients from THIN are included in the study population, the descriptive analyses will be stratified further according to database (CPRD or THIN) and a combined result will also be provided.

[12] In the event that patients from THIN are included in the study population, the incidence rates will be stratified further according to database (CPRD or THIN) and a combined result will also be provided.

[13] The same definition for calculation of incidence rates for identified and potential risks will be applied to the previously described Schizophrenia cohort and to patients with ***prescribed treatment*** and without diagnoses for Bipolar Disorder or Schizophrenia.

A given patient may contribute different amounts of person-time to each separate analysis of an identified or potential risk, depending on whether or not he/she experiences one of the identified or potential risks of interest.

For the analysis of each identified or potential risk, exact mid-probability confidence intervals will be calculated based on person-time and the Poisson distribution. Incidence rates will be calculated for each exposure group and reported per 1,000 person-years. Only the first event of a given type will be counted in the analysis. The incidence rate for an exposure group will be calculated as the number of first occurrences of each type of identified or potential risk divided by the total aggregate person-time accrued by all patients in that exposure groups in the current CPRD dataset.

Because the Bipolar Disorder cohort contains patients who receive treatment before and after their diagnosis, exploratory stratified analyses for identified and potential risks will be performed for each of these groups to assess the magnitude of differences, if any, between the two groups.

Sensitivity analysis will also be performed after excluding from the Bipolar Disorder Cohort patients with first prescription for asenapine occurring more than 2 years after the last diagnosis of Bipolar Disorder. In CPRD, among olanzapine and / or risperidone patients receiving a Bipolar Disorder diagnosis before initiation of treatment, the cumulative distribution shows approximately 75% have a duration of time between last bipolar disorder diagnosis and first prescription of olanzapine or risperidone of less than 2 years.

Accrued person-time for patients that experience an event is calculated as the total number of days accrued between the date of the first prescription of one of the study drugs of interest following cohort entry until the date of the event; whereas, accrued person-time for patients that do NOT experience an event is calculated as the total number of days accrued between the first prescription date until the earliest occurrence of the exposure end date (as determined by the algorithm) plus pre-determined risk window, transfer out date, last data collection date, or last date in current CPRD dataset.

3. Calculation of Rate Ratios for Identified and Potential Risks[14]

Comparisons of incidence rates for identified and potential risks will only be conducted in the new user strata where the index exposure was the 1st ever atypical antipsychotic received for that given patient. These patients will have no record of an atypical antipsychotic in the 365 day baseline period (Figure 3). Prior use of atypical antipsychotics can introduce confounding given that many of the identified and potential risks evaluated in this study are class effects.

[14] The same definition for calculation of rate ratios for identified and potential risks will be applied to the previously described Schizophrenia cohort.

Univariate incidence rate ratios will first be used to compare the incidence rates among the asenapine-treated, risperidone control, and olanzapine control groups. Rate ratios (RR) for each identified and potential risk will then be calculated adjusting for potential confounders (using propensity score matching if possible) for comparisons between the control groups and the asenapine group.[15] In order to perform comparisons with a reasonable level of statistical precision (power = 80%, Rate Ratio > 2.0, two-sided alpha = 0.05), no formal comparisons will be conducted for a given identified or potential risk until the number of events of that identified or potential risk observed in the combined (asenapine and comparator) new users strata of 1st ever atypical antipsychotic reach a set threshold as defined by the McMahon and MacDonald formulae[16] with 80% power, a two-sided alpha=0.05, and the ratio of person-time between the exposed (asenapine) and unexposed (comparator) ranging from 1:1 to 1:16. Given that subjects are not followed up for equal amounts of exposure and that the analysis assumes a Poisson distribution, the McMahon and MacDonald formulae for the null hypothesis of equal risk uses the Poisson weights of person-years rather than the number of patients in the asenapine and comparator groups.

[15] In the event that patients from THIN are included in the study population, the rate ratios will be stratified further according to database (CPRD or THIN) and a combined result will also be provided.

[16] Formulae that include the Yates' correction.

Ratio of person-time (exposed:unexposed)	Rate Ratio > 2.0 Power 80%	Rate Ratio > 3.0 Power 80%
1:1	74	33
1:2	71	29
1:4	86	32
1:8	126	44
1:16	211	70

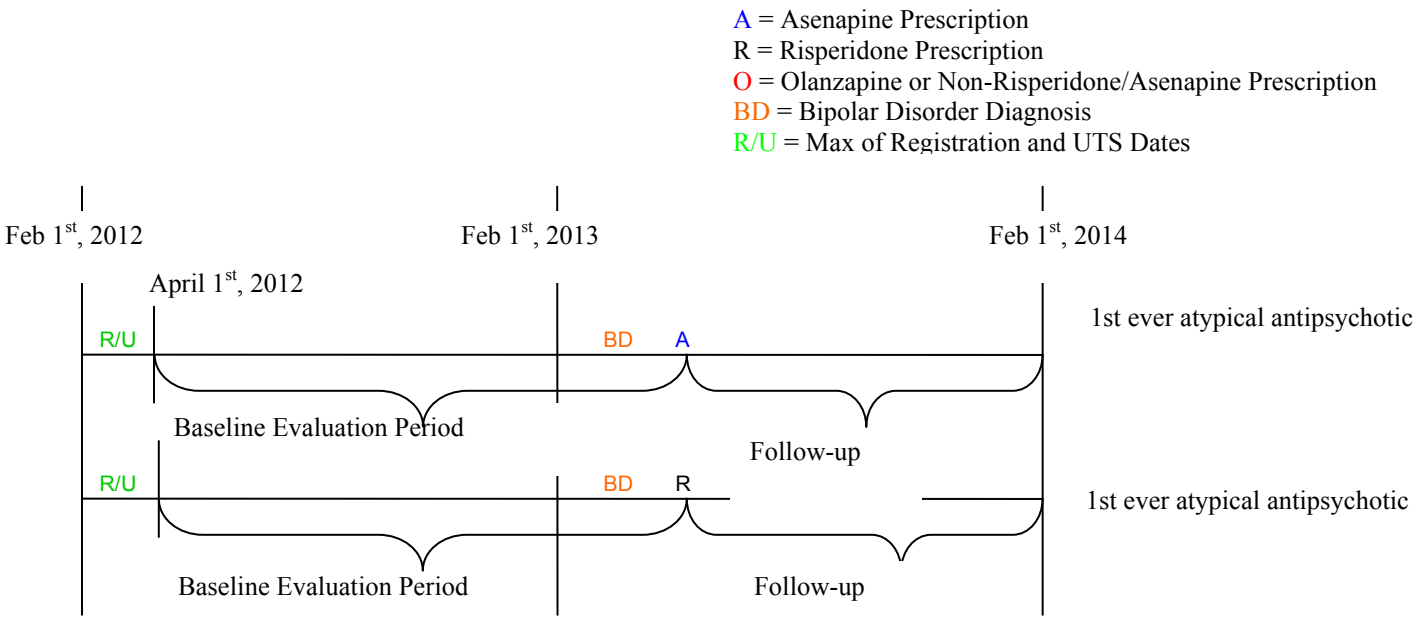

Figure 3. Definition of acceptable comparison among patients with 1st ever atypical antipsychotic use among an inception cohort (new user) in CPRD

4. Bias

Description of Methods to Minimize Biases

Rate ratios for identified and potential risks will be based on propensity scores to balance covariates that predict the specific outcomes. Propensity score models will be developed for each outcome of interest and for each comparison separately. The propensity score, defined as the conditional expectation or probability of being exposed given a vector of observed covariates, has been shown to effectively balance covariates across treatment groups (Rosenbaum and Rubin 1983). The primary propensity score approach to balancing covariates will be a 5 to 1 digit matching algorithm (Parsons 2001). Before employing the matching algorithm, the concordance statistic (or c-statistics) will be used to measure the discriminatory power of the predictive model for treatment. If the c-statistic exceeds 0.8, then it will be determined that the ability of the model to predict treatment status using the observed covariates is too powerful. This will result in the exclusion of too many patients when matching on propensity score is performed. If this does occur in both comparisons for a specific risk, the matched analysis will continue and a third comparator (aripiprazole) could be used if the c-statistic for this comparison demonstrates less discriminatory power (< 0.8). After assessing balance of covariates across treatment groups, asymmetric restriction of the propensity score distribution ('trimming') may be applied after propensity score derivation in all matched comparisons. 'Trimming' in matching may include the exclusion patients in the non-overlapping tails of the propensity score distributions for asenapine compared to a concurrent control; or, it may include the exclusion of patients based on percentile (e.g. 1 and 99th) that were treated contrary to prediction. (Sturmer et al 2010) Covariate balance will be assessed using standardized differences. When applied appropriately, comparing treatment groups, conditional on the estimated propensity score, will provide unbiased estimates of average treatment effects (McCandless et al. 2008).

Adjustment for Multiple Comparisons

It is possible that, through multiple comparisons and evaluations, the incidence of a given identified or potential risk during exposure could appear statistically elevated by chance alone. To mitigate the likelihood of Type I error arising from the evaluation of multiple identified or potential risks, adjustment using the Double False Discovery Rate (FDR) method will be used for every comparative analysis. (Mehrotra 2004) The Double False Discovery Rate method is a two-step application of an adverse event flagging method to reduce false discoveries (FDR) by leveraging the natural grouping of adverse events by body system (DFDR). More specifically, for rate ratios which are nominally statistically significantly elevated (i.e., lower bound of the 95% confidence interval of the relative risk >1), the FDR-adjusted p-value will be provided in the results tables. Both the unadjusted and FDR-adjusted p-values will be listed for all statistically significant comparisons. The FDR adjustment will consist of a simple calculation method, which adjusts the p-value based on the number of comparisons performed in a given set of analyses.

Limitations

This study has a number of limitations that potentially affect the validity of findings or the interpretation of the results. Some of the limitations most pertinent to the analysis described in this protocol are as follows:

1) Identification of Bipolar Disorder (specifically Bipolar I Disorder): Given that CPRD is general practitioner based electronic medical record databases, it is not specifically designed to capture psychiatric disorders for research purposes. As such, the diagnostic information recorded often lacks the specificity required to differentiate between Bipolar I Disorder, the condition associated with the indication, from other Bipolar Disorders. In addition, during the "baseline" period, some patients with remote histories of Bipolar Disorder may have been misclassified as not having the diagnosis. Similarly, some patients with Bipolar Disorder may have never been given the diagnosis yet could still be treated as such.

2) Ascertainment of identified and potential risks: Since CPRD is a general practitioner-based electronic medical record database, under-reporting or misclassification of identified and potential risks may occur. Events occurring in emergency care will be missed. Diagnostic codes or laboratory data may lack the specificity needed to determine if an event of interest occurred.

3) Channeling or confounding by indication: A form of selection bias where the disease that forms the indication being treated (irrespective of severity) is not only associated with treatment but also an independent risk factor for selected outcomes (events of interest) in patients not exposed to atypical antipsychotics. Channeling may be introduced through prescribing of treatment based on certain characteristics of a patient such as those whose prior alternative treatment was poorly tolerated or ineffective. These patients may be selectively prescribed the new treatment and may result in apparent association of increased risk of events of interest in this population. For this study, the use of concurrent control groups may be subject to certain biases (e.g., channeling bias) that will have to be considered when interpreting the results. Propensity score matching methodology will be applied to address measured confounding at first prescription of asenapine and the control (risperidone or olanzapine) groups after Bipolar Diagnosis. Covariates in the propensity score model will include demographic factors, profile of previous or current therapies, previous medical diagnoses, and measures of healthcare resource utilization.

4) Accrual of patients and exposure: Given the low lifetime prevalence of Bipolar Disorder and multiple atypical antipsychotic treatment options, there could be a delay in accrual of patients treated with asenapine if adoption by primary care physicians is low. In addition, treatment initiation and diagnostic information originating in secondary care may be missed if the general practitioner is not aware of or does not record the information provided in the discharge summaries.

5) The lack of data on exposure in the hospital setting may result in immeasurable time bias. (Suissa 2008)

5. Sample Size and Power Considerations

A sample size of 1,525 patients and 1,525 patient-years of exposure to asenapine allows reasonably good power to monitor health outcomes. For example, the proposed study will have approximately 80% power to detect a 2-fold increase and greater than 80% power to detect a 3-fold increase in the incidence of a health outcome that has an annual background rate of 1.0%[17] (1/100 person-years) (assuming two-sided alpha=0.05 using exact binomial statistics). If the background rate of the health outcome is 0.5% (i.e., 1/200 person-years), the study will have greater than 80% power to detect a 3-fold increase in incidence.

Background Rate (%)	Rate Ratio > 1.5 Power 80%	Rate Ratio > 2.0 Power 80%	Rate Ratio > 3.0 Power 80%
2.0	2,330	763	277
1.0	4,660	1,525	553
0.5	9,319	3,049	1,106
0.2	23,297	7,623	2,763

Notes: alpha = 0.05 (two-sided); PASS statistical program; Reference: Signorini, David. 1991. 'Sample size for Poisson regression', Biometrika, Volume 78, 2, pages 446-450

[17] The majority of the background incidence rates provided for identified and potential risks (e.g. seizure, hyperprolactinaemia) in the asenapine Risk Management plan exceeded 2% which is the highest rate listed in the sample size table.

LIST OF REFERENCES

Bauer M and Pfennig A. Epidemiology of bipolar disorders. *Epilepsia.* 2005; 46: 8-13.

Bebbington P and Ramana R. The epidemiology of bipolar affective-disorder. *Social Psychiatry and Psychiatric Epidemiology.* 1995; 30: 279-292.

Cai B, Xu W, Bortnichak E, Watson D. An algorithm to identify practices common to both GPRD and THIN database. *Pharmacoepidemiology and Drug Safety*. 2010; 19 (supplement 1): S86.

Cole SR. and Hernan MA. Constructing inverse probability weights for marginal structural models. *American Journal of Epidemiology*. 2008; 168 (6): 656-664.

McMahon AD and MacDonald TM. Sample size for cohort studies in pharmacoepidemiology. *Pharmacoepidemiology and Drug Safety.* 1997; 6: 331-335.

Mehrotra DV and Heyse JF. Use of false discovery rate for evaluating clinical safety data. *Statistical Methods in Medical Research*. 2004; 13: 227-238.

Pini S, de Queiroz V, Pagnin D, Pezawas J, Angst J, Cassano GB, Wittchen HU. Prevalence and burden of bipolar disorders in European countires. *European Neuropsychopharmacology*. 2005; 15: 425-434.

Quality and Outcomes Framework guidance for GMS contract 2009/10; The NHS Confederation (Employers) Company Ltd; p 82.

Sturmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: Dealing with observations in the tails of the propensity score distribution – A simulation study. *American Journal of Epidemiology*. 2010; 172 (7): 843-854.

Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. *Pharmacoepidemiology and Drug Safety*. 2010; 19: 858-868.

Suissa S. Immeasurable time bias in observational studies of drug effects on mortality. *Pharmacoepidemiology and Drug Safety*. 2008; 168: 329-335.

Waraich P, Goldner EM, Somers JM, Hsu L. Prevalence and incidence studies of mood disorders: A systematic review of the literature. *Canadian Journal of Psychiatry-Revue Canadienne de Psychiatrie.* 2004; 49: 124-138.

APPENDIX A: DATA QUALITY MARKERS

CPRD:

A patient is deemed "Acceptable" unless any one of the following is true:

1. First registration date or current registration date is missing

2. The birth year is missing

3. The first registration date or current registration date is prior to their birth date

4. The current registration date is prior to the first registration date

5. A transferred out reason but no transferred out date

6. A transferred out date but no transferred out reason

7. A transferred out date prior to their first or current registration date

8. A gender other than Female/Male/Indeterminate

9. Patient is > 115 years (last collection year - birth year), when patient has not transferred out

10. Patient is > 115 years (transfer out year - birth year), when patient has transferred out

11. Patient's records contain events prior to patient's year of birth in the patient's clinical, consultation, immunisation, referral, test or therapy records

12. No permanent registration records

13. All events for the patient have invalid or missing event dates

The Up-To-Standard (UTS) date of a practice is calculated using a combination of gap analysis and assessment of mortality rates, every time a collection from the practice is processed.

Death recording: this takes the practice size into account, and adjusts the number of days between two deaths that is allowable before the practice is deemed not up-to-standard.

Gap Analysis: A gap date is calculated which is the earliest date after which there are no significant gaps in the data. A sliding window approach is used, meaning there must be 5 consecutive 7 day windows where the number of events in each window falls below 30%

of the median. The gap date is calculated for each of the event types (Clinical, Consultation, and Therapy), and is set to be the latest of these. Gaps in Immunisation, Test and Referral data do not affect the UTS date.

THIN:

EPIC validate patient records in the THIN data to check that for every patient with a registration status of 'Applied', 'Permanent', 'Transferred Out' & 'Death' the following applies:

1. There is a year of birth and it is in the format YYYYMMDD.

2. There is a registration date and it is in the format YYYYMMDD.

3. For every patient with registration status 'Applied' or 'Permanent' there is no transfer out date

4. For every patient with registration status 'Transferred Out' or 'Death' there is a transfer out date that is in the format YYYYMMDD.

5. If the year of birth (YYYY) is equal to or less than 1892 and there is a Registration status of 'Transferred Out' or 'Death' and a transfer out date. The patient should not be over 115 years of age.

6. For every patient with registration status of 'Transferred Out' or 'Death' and a transfer out date. The transfer out date is after both the year of birth and registration date

7. For every patient with registration status of 'Transferred Out' or 'Death' that the Transfer out date is before or equal to practice last collection date.

8. That the date of birth is before or equal to original registration date

9. That the year of birth is before or equal to practice last collection date.

10. That the registration date is before or equal to the transfer-out date (if there).

11. That the registration date is before or equal to the practice last collection date.

12. That the deathdate is after registration and year of birth

13. That the transfer out date is at least registration date + 1 day

14. The patids are unique and in sequence

If the patient record passes the validation check then the patflag is set to 'Acceptable Record' or 'Acceptable: Transferred out dead without additional death information'.

APPENDIX B: METHODOLOGY FOR IDENTIFYING THE SAME PRACTICE IN CPRD AND THIN

Step 1 – Used algorithms to identify general practitioner practices that are present in both the CPRD and THIN databases (duplicate practices).

Algorithm 1:

1. Identified the 'old' CPRD practices from the THIN database using the spreadsheet previously provided by EPIC that shows which practices provide data to both EPIC and the 'old' CPRD.

2. Determined a time window when both the CPRD and the THIN databases had complete records for comparison purposes. We used the data for January 1, 1996 to December 31, 2010 from the most current databases.

3. Grouped the practices by the following variables.

- Practice locations (region)
- Total number of patients in the prescription dataset +/-10% (different data cleaning and quality control checks in the two databases result in slightly different numbers of prescription records for the same practice in the different databases).
- Total number of patients in the clinical dataset +/-10% (different data cleaning and quality control checks in the two databases result in slightly different numbers of patient records for the same practice in the different databases).
- Total number of bipolar disorder patients match +/-3 users (different data cleaning and quality control checks in the two databases result in slightly different numbers of bipolar disorder records for the same practice in the different databases).

4. Identify the match of the practices at the patient level.

- Age and gender of patients with bipolar disorder diagnosis
- Dates of first and last bipolar disorder diagnosis at patient level

5. Removed the newly discovered duplicate practices (based on results of step 4) from the THIN database.

6. Repeat steps 3 to 5 with data for January 1, 1996 to December 31, 2009, year by year.

7. For the practices that were not identified as duplicates, repeat steps 2-5 using only criteria a-c in step 3 above.

Algorithm 2:

1. For both CPRD and THIN practices, identified the number of patients in 8 categories: by gender and by the following 4 categories of birth years.

- Birth year less than 1900.
- Birth year less than the earliest birth year in the practice plus 10 years.
- Birth year between 1900-1905.
- Birth year between 1905-1910.

2. Considered practices from CPRD to match those in THIN if the difference in patient numbers was less than 5% for at least 4 out of 8 categories.

Step 2 – Further validated the results of Step 1 by checking patient level clinical visits.

After using algorithms 1 and 2 to identify duplicate practices, listed patient IDs and dates of clinic visit. Determined if the matched practices had patients with the same pattern of clinic visits. This step was applied to all matched pairs from either Algorithm 1 or Algorithm 2, and to randomly selected pairs from both Algorithm 1 and Algorithm 2.

Step 3 – Removed the duplicate practices from the THIN database and combined the remaining practices with all practices from the CPRD database.

Step 4 –Steps 1 through 3 will be repeated with each update to the analysis to identify new (added) practices to the databases that are duplicates.

APPENDIX C: CODING LISTS AND ALGORITHMS

Clinical Term of Interest from List	Code	Code Description
Bipolar Disorders	Eu31.00	[X]Bipolar affective disorder
Bipolar Disorders	Eu31.11	[X]Manic-depressive illness
Bipolar Disorders	E117.00	Unspecified bipolar affective disorder
Bipolar Disorders	E11..11	Bipolar psychoses
Bipolar Disorders	E110100	Single manic episode, mild
Bipolar Disorders	Eu30z11	[X]Mania NOS
Bipolar Disorders	Eu30.00	[X]Manic episode
Bipolar Disorders	146D.00	H/O: manic depressive disorder
Bipolar Disorders	E11y000	Unspecified manic-depressive psychoses
Bipolar Disorders	E110.00	Manic disorder, single episode
Bipolar Disorders	212T.00	Psychosis, schizophrenia + bipolar affective disord resolved
Bipolar Disorders	E110000	Single manic episode, unspecified
Bipolar Disorders	E116.00	Mixed bipolar affective disorder
Bipolar Disorders	E115.11	Manic-depressive - now depressed
Bipolar Disorders	Eu31.12	[X]Manic-depressive psychosis
Bipolar Disorders	Eu30100	[X]Mania without psychotic symptoms
Bipolar Disorders	Eu30.11	[X]Bipolar disorder, single manic episode
Bipolar Disorders	Eu31000	[X]Bipolar affective disorder, current episode hypomanic
Bipolar Disorders	Eu30200	[X]Mania with psychotic symptoms
Bipolar Disorders	E11..13	Manic psychoses
Bipolar Disorders	E114.11	Manic-depressive - now manic
Bipolar Disorders	E115.00	Bipolar affective disorder, currently depressed
Bipolar Disorders	E111000	Recurrent manic episodes, unspecified
Bipolar Disorders	E114.00	Bipolar affective disorder, currently manic
Bipolar Disorders	Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn
Bipolar Disorders	1S42.00	Manic mood
Bipolar Disorders	ZV11111	[V]Personal history of manic-depressive psychosis

Clinical Term of Interest from List	Code	Code Description
Bipolar Disorders	E11y.00	Other and unspecified manic-depressive psychoses
Bipolar Disorders	Eu31z00	[X]Bipolar affective disorder, unspecified
Bipolar Disorders	E116000	Mixed bipolar affective disorder, unspecified
Bipolar Disorders	E111.00	Recurrent manic episodes
Bipolar Disorders	E117z00	Unspecified bipolar affective disorder, NOS
Bipolar Disorders	E116z00	Mixed bipolar affective disorder, NOS
Bipolar Disorders	Eu31700	[X]Bipolar affective disorder, currently in remission
Bipolar Disorders	212V.00	Bipolar affective disorder resolved
Bipolar Disorders	E111z00	Recurrent manic episode NOS
Bipolar Disorders	Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Bipolar Disorders	ZV11112	[V]Personal history of manic-depressive psychosis
Bipolar Disorders	Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Bipolar Disorders	Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp
Bipolar Disorders	Eu31400	[X]Bipol aff disord, curr epis sev depress, no psychot symp
Bipolar Disorders	Eu31600	[X]Bipolar affective disorder, current episode mixed
Bipolar Disorders	Eu30z00	[X]Manic episode, unspecified
Bipolar Disorders	Eu31200	[X]Bipolar affect disorder cur epi manic with psychotic symp
Bipolar Disorders	Eu31y00	[X]Other bipolar affective disorders
Bipolar Disorders	E110z00	Manic disorder, single episode NOS
Bipolar Disorders	E115z00	Bipolar affective disorder, currently depressed, NOS
Bipolar Disorders	Eu31y12	[X]Recurrent manic episodes
Bipolar Disorders	E11yz00	Other and unspecified manic-depressive psychoses NOS
Bipolar Disorders	E115000	Bipolar affective disorder, currently depressed, unspecified
Bipolar Disorders	E115200	Bipolar affective disorder, currently depressed, moderate
Bipolar Disorders	E116400	Mixed bipolar affective disorder, severe, with psychosis

Clinical Term of Interest from List	Code	Code Description
Bipolar Disorders	E117000	Unspecified bipolar affective disorder, unspecified
Bipolar Disorders	E115100	Bipolar affective disorder, currently depressed, mild
Bipolar Disorders	E110400	Single manic episode, severe, with psychosis
Bipolar Disorders	E111400	Recurrent manic episodes, severe, with psychosis
Bipolar Disorders	E114100	Bipolar affective disorder, currently manic, mild
Bipolar Disorders	E116200	Mixed bipolar affective disorder, moderate
Bipolar Disorders	Eu30211	[X]Mania with mood-congruent psychotic symptoms
Bipolar Disorders	E114z00	Bipolar affective disorder, currently manic, NOS
Bipolar Disorders	E111200	Recurrent manic episodes, moderate
Bipolar Disorders	E114000	Bipolar affective disorder, currently manic, unspecified
Bipolar Disorders	Eu31y11	[X]Bipolar II disorder
Bipolar Disorders	E110200	Single manic episode, moderate
Bipolar Disorders	E114300	Bipolar affect disord, currently manic, severe, no psychosis
Bipolar Disorders	E116600	Mixed bipolar affective disorder, in full remission
Bipolar Disorders	Eu30y00	[X]Other manic episodes
Bipolar Disorders	E115300	Bipolar affect disord, now depressed, severe, no psychosis
Bipolar Disorders	E111100	Recurrent manic episodes, mild
Bipolar Disorders	E114200	Bipolar affective disorder, currently manic, moderate
Bipolar Disorders	E114400	Bipolar affect disord, currently manic,severe with psychosis
Bipolar Disorders	E117400	Unspecified bipolar affective disorder,severe with psychosis
Bipolar Disorders	Eu31.13	[X]Manic-depressive reaction

Clinical Term of Interest from List	Code	Code Description
Bipolar Disorders	E115400	Bipolar affect disord, now depressed, severe with psychosis
Bipolar Disorders	Eu31100	[X]Bipolar affect disorder cur epi manic wout psychotic symp
Bipolar Disorders	E114500	Bipolar affect disord,currently manic, part/unspec remission
Bipolar Disorders	E117600	Unspecified bipolar affective disorder, in full remission
Bipolar Disorders	E110300	Single manic episode, severe without mention of psychosis
Bipolar Disorders	E111600	Recurrent manic episodes, in full remission
Bipolar Disorders	E115600	Bipolar affective disorder, now depressed, in full remission
Bipolar Disorders	E116100	Mixed bipolar affective disorder, mild
Bipolar Disorders	E117100	Unspecified bipolar affective disorder, mild
Bipolar Disorders	Eu30212	[X]Mania with mood-incongruent psychotic symptoms
Bipolar Disorders	E111300	Recurrent manic episodes, severe without mention psychosis
Bipolar Disorders	E114600	Bipolar affective disorder, currently manic, full remission
Bipolar Disorders	E116300	Mixed bipolar affective disorder, severe, without psychosis
Bipolar Disorders	E116500	Mixed bipolar affective disorder, partial/unspec remission
Bipolar Disorders	E11y300	Other mixed manic-depressive psychoses
Bipolar Disorders	E111500	Recurrent manic episodes, partial or unspecified remission
Bipolar Disorders	E117200	Unspecified bipolar affective disorder, moderate
Bipolar Disorders	E117500	Unspecified bipolar affect disord, partial/unspec remission
Bipolar Disorders	E110500	Single manic episode in partial or unspecified remission

Clinical Term of Interest from List	Code	Code Description
Bipolar Disorders	E110600	Single manic episode in full remission
Bipolar Disorders	E115500	Bipolar affect disord, now depressed, part/unspec remission
Bipolar Disorders	***E117300***	***Unspecified bipolar affective disorder, severe, no psychosis***
Bipolar Disorders	***Eu31800***	***[X]Bipolar affective disorder type I***
Bipolar Disorders	***Eu31900***	***[X]Bipolar affective disorder type II***
Bipolar Disorders	***Eu31911***	***[X]Bipolar II disorder***
Bipolar Disorders	***E11y100***	***Atypical manic disorder***
Bipolar Disorders	***Eu30000***	***[X]Hypomania***
Bipolar Disorders	***E110.11***	***Hypomanic psychoses***
Bipolar Disorders	***ZRby100***	***Profile of mood states, bipolar***
Bipolar Disorders	***13Y3.00***	***Manic-depression association member***
Bipolar Disorders	***E11y100***	***Atypical manic disorder***
Allergic reaction	M28..00	Urticaria
Allergic reaction	M280.00	Allergic urticaria
Allergic reaction	2525.00	O/E - lip swelling
Allergic reaction	F4Kz200	Swelling of eye NOS
Allergic reaction	M151.00	Erythema multiforme
Allergic reaction	R042011	[D]Swelling face
Allergic reaction	F4Ey700	Swelling of eyelid
Allergic reaction	SN50.00	Anaphylactic shock

Clinical Term of Interest from List	Code	Code Description
Allergic reaction	M28z.00	Urticaria NOS
Allergic reaction	1835.11	Periorbital oedema
Allergic reaction	M28y.00	Other specified urticaria
Allergic reaction	M281.00	Idiopathic urticaria
Allergic reaction	SN52.00	Drug hypersensitivity NOS
Allergic reaction	SN51.11	Angioedema
Allergic reaction	M151700	Stevens-Johnson syndrome
Allergic reaction	22C9.00	O/E - periorbital oedema
Allergic reaction	SN53.11	Hypersensitivity NOS
Allergic reaction	F4Ey100	Oedema of eyelid
Allergic reaction	1835.00	Swelling round eyes
Allergic reaction	M151800	Toxic epidermal necrolysis
Allergic reaction	M151z00	Erythema multiforme NOS
Allergic reaction	R055.00	[D]Shock without mention of trauma
Allergic reaction	M28yz00	Other specified urticaria NOS
Allergic reaction	G752.00	Hypersensitivity angiitis
Allergic reaction	H1y6.00	Oedema of larynx
Allergic reaction	G752z00	Hypersensitivity angiitis NOS
Allergic reaction	M280.11	Drug induced urticaria
Allergic reaction	H1y8.00	Upper respiratory tract hypersensitivity reaction NOS
Allergic reaction	H35z100	Hypersensitivity pneumonitis NOS
Allergic reaction	SN50100	Anaphy shock due/adv efect/correct drug or med proprly admin

Clinical Term of Interest from List	Code	Code Description
Allergic reaction	H1y2400	Pharynx or nasopharynx oedema
Allergic reaction	M151.12	Toxic epidermal necrolysis
Allergic reaction	Myu4000	[X]Other urticaria
Allergic reaction	H040000	Acute oedematous laryngitis
Allergic reaction	H1y6z00	Oedema of larynx NOS
Allergic reaction	Myu4.00	[X]Urticaria and erythema
Allergic reaction	Myu4100	[X]Other erythema multiforme
Allergic reaction	R055z00	[D]Shock without mention of trauma NOS
Allergic reaction	G752.11	Hypersensitivity arteritis
Allergic reaction	M151y00	Other specified erythema multiforme
Allergic reaction	2227.00	O/E - rash present
Allergic reaction	2227.11	O/E - allergic rash
Allergic reaction	2227.12	O/E - itchy rash
Allergic reaction	SN53000	Allergic reaction
Extrapyramidal Symptoms/Syndrome	F13z200	Restless legs syndrome
Extrapyramidal Symptoms/Syndrome	F13X.00	Dystonia, unspecified
Extrapyramidal Symptoms/Syndrome	F13zz00	Extrapyramidal disease and abnormal movement disorder NOS
Extrapyramidal Symptoms/Syndrome	F131.00	Essential and other specified forms of tremor
Extrapyramidal Symptoms/Syndrome	R013.11	[D]Dyskinesia
Extrapyramidal Symptoms/Syndrome	F121.11	Drug induced parkinsonism
Extrapyramidal Symptoms/Syndrome	2977.00	O/E - intention tremor
Extrapyramidal Symptoms/Syndrome	2975.00	O/E - fine tremor

Clinical Term of Interest from List	Code	Code Description
Extrapyramidal Symptoms/Syndrome	F138111	Tardive dyskinesia
Extrapyramidal Symptoms/Syndrome	F4Jy911	Oculogyric crisis
Extrapyramidal Symptoms/Syndrome	29M..00	Extrapyramidal movements
Extrapyramidal Symptoms/Syndrome	2987.11	O/E - Parkinson posture
Extrapyramidal Symptoms/Syndrome	F135.00	Other choreas
Extrapyramidal Symptoms/Syndrome	2994.11	O/E - Parkinson gait
Extrapyramidal Symptoms/Syndrome	2976.11	O/E - coarse tremor
Extrapyramidal Symptoms/Syndrome	F138100	Orofacial dyskinesia
Extrapyramidal Symptoms/Syndrome	F121.00	Parkinsonism secondary to drugs
Extrapyramidal Symptoms/Syndrome	F12X.00	Secondary parkinsonism, unspecified
Extrapyramidal Symptoms/Syndrome	F131z00	Essential and other specified forms of tremor NOS
Extrapyramidal Symptoms/Syndrome	F13..11	Extrapyramidal disease excluding Parkinson's disease
Extrapyramidal Symptoms/Syndrome	F122.00	Malignant neuroleptic syndrome
Extrapyramidal Symptoms/Syndrome	F135000	Hemiballismus
Extrapyramidal Symptoms/Syndrome	1P04.00	C/O - akathisia
Extrapyramidal Symptoms/Syndrome	294..11	O/E - rigid muscle
Extrapyramidal Symptoms/Syndrome	F135z00	Other choreas NOS
Extrapyramidal Symptoms/Syndrome	F13..00	Other extrapyramidal disease and abnormal movement disorders
Extrapyramidal Symptoms/Syndrome	F13z.00	Other/unspecified extrapyramidal/abnormal movement disorders

Clinical Term of Interest from List	Code	Code Description
Extrapyramidal Symptoms/Syndrome	F139.00	Paroxysmal dyskinesia
Extrapyramidal Symptoms/Syndrome	F137200	Drug-induced dystonia
Extrapyramidal Symptoms/Syndrome	F13A.00	Paroxysmal dystonia
Extrapyramidal Symptoms/Syndrome	2994.00	O/E-festination-Parkinson gait
Extrapyramidal Symptoms/Syndrome	F13B.00	Myoclonic dystonia
Extrapyramidal Symptoms/Syndrome	2987.00	O/E -Parkinson flexion posture
Extrapyramidal Symptoms/Syndrome	F13z000	Unspecified extrapyramidal disease
Extrapyramidal Symptoms/Syndrome	F131200	Drug-induced tremor
Extrapyramidal Symptoms/Syndrome	PH02.11	Meige's disease
Extrapyramidal Symptoms/Syndrome	Fyu2400	[X]Other dystonia
Extrapyramidal Symptoms/Syndrome	F12W.00	Secondary parkinsonism due to other external agents
Extrapyramidal Symptoms/Syndrome	ZS42500	Extrapyramidal dysarthria
Extrapyramidal Symptoms/Syndrome	F135200	Drug-induced chorea
Extrapyramidal Symptoms/Syndrome	Fyu2A00	[X]Dystonia, unspecified
Extrapyramidal Symptoms/Syndrome	Fyu2200	[X]Parkinsonism in diseases classified elsewhere
Extrapyramidal Symptoms/Syndrome	Fyu2600	[X]Other chorea
Extrapyramidal Symptoms/Syndrome	SL6y.00	Antiparkinsonism drug poisoning
Extrapyramidal Symptoms/Syndrome	F139100	Paroxysmal kinesigenic dyskinesia
Extrapyramidal Symptoms/Syndrome	Fyu2500	[X]Other specified forms of tremor

Clinical Term of Interest from List	Code	Code Description
Extrapyramidal Symptoms/Syndrome	Fyu2900	[X]Secondary parkinsonism, unspecified
Extrapyramidal Symptoms/Syndrome	2943.00	O/E - muscle rigid-clasp knife
Extrapyramidal Symptoms/Syndrome	Fyu2.00	[X]Extrapyramidal and movement disorders
Extrapyramidal Symptoms/Syndrome	Fyu2100	[X]Other secondary parkinsonism
Metabolic syndrome	C1A0.00	Metabolic syndrome
Metabolic syndrome	C10F811	Metabolic syndrome X
Metabolic syndrome	C10F800	Reaven's syndrome
Metabolic syndrome	C109800	Reaven's syndrome
Overdose	SLHz.67	Drug and medicament poisoning NOS
Overdose	U1A..79	[X]Accidental drug overdose / other poisoning
Overdose	SL...83	Overdose of drug
Overdose	TK05.68	Suicide + selfinflicted poisoning by drug or medicine NOS
Overdose	TK...79	Cause of overdose - deliberate
Overdose	U20..79	[X]Deliberate drug overdose / other poisoning
Overdose	T8...1485	Cause of overdose - accidental
Overdose	T8...1496	Accidental poisoning by drugs, medicines and biologicals
Overdose	SL...68	Poisoning
Somnolence and Sedation	R000000	[D]Drowsiness
Somnolence and Sedation	1B67.11	Drowsiness - symptom
Somnolence and Sedation	2234.00	O/E - drowsy
Somnolence and Sedation	R000100	[D]Somnolence
Somnolence and Sedation	R00z400	[D]Sedation
Somnolence and	F271.00	Narcolepsy

Clinical Term of Interest from List	Code	Code Description
Sedation		
Somnolence and Sedation	1B1B.12	C/O - somnolence
Somnolence and Sedation	1B67.00	Gets drowsiness
Somnolence and Sedation	E274311	Hypersomnia NOS
Somnolence and Sedation	Fy01.00	Disorders of excessive somnolence
Somnolence and Sedation	R005300	[D]Hypersomnia with sleep apnoea
Somnolence and Sedation	R005400	[D]Hypersomnia NOS
Somnolence and Sedation	7M35100	Sedation NEC
Somnolence and Sedation	E274300	Transient hypersomnia
Somnolence and Sedation	E274400	Persistent hypersomnia
Somnolence and Sedation	1B69.00	Intermittent drowsiness
Somnolence and Sedation	F27..00	Cataplexy and narcolepsy
Somnolence and Sedation	E274.11	Hypersomnia of non-organic origin
Somnolence and Sedation	F27z.00	Cataplexy or narcolepsy NOS
Somnolence and Sedation	Eu51100	[X]Nonorganic hypersomnia
Weight Gain	R031.00	[D]Abnormal weight gain
Weight Gain	1622.00	Weight increasing
Weight Gain	1624.00	Abnormal weight gain
Weight Gain	ZC2CN00	Dietary advice for weight gain
Weight Gain	C380100	Drug-induced obesity
Swelling of tongue and throat	183..00	Oedema
Swelling of tongue and throat	183..11	Oedema - symptom

Clinical Term of Interest from List	Code	Code Description
Swelling of tongue and throat	1D11.00	C/O: a swelling
Swelling of tongue and throat	R023.00	[D]Oedema
Swelling of tongue and throat	16J..00	Swelling
Swelling of tongue and throat	R042000	[D]Swelling in head or neck
Swelling of tongue and throat	R023z00	[D]Oedema NOS
Swelling of tongue and throat	22C..00	O/E - oedema
Swelling of tongue and throat	183..12	Swelling - oedema - symptom
Swelling of tongue and throat	R022000	[D]Swelling, local and superficial
Swelling of tongue and throat	R023300	[D]Oedema, localized
Swelling of tongue and throat	2I12.00	O/E - a swelling
Swelling of tongue and throat	183Z.00	Oedema NOS
Swelling of tongue and throat	22C..11	O/E - swelling - oedema
Swelling of tongue and throat	R042400	[D]Localized swelling, mass and lump, head
Swelling of tongue and throat	R042.11	[D]Swelling, mass or lump in head
Swelling of tongue and throat	22CZ.00	O/E - oedema NOS
Swelling of tongue and throat	H1y6200	Supraglottic oedema
Swelling of tongue and throat	R042z00	[D]Swelling, mass or lump in head or neck NOS
Swelling of tongue and throat	H1y6.00	Oedema of larynx
Swelling of tongue and throat	H1y2400	Pharynx or nasopharynx oedema
Swelling of tongue and throat	H1y6z00	Oedema of larynx NOS

Clinical Term of Interest from List	Code	Code Description
Swelling of tongue and throat	H1y6000	Oedema of glottis
Malignant neuroleptic syndrome	F122.00	Malignant neuroleptic syndrome
Rhabdomyolysis	SK08.00	Acute renal failure due to rhabdomyolysis
Rhabdomyolysis	N233300	Rhabdomyolysis
Rhabdomyolysis	F394000	Drug-induced myopathy
Rhabdomyolysis	467C.00	Urine myoglobin level
Hyponatremia	C361.11	Hyponatraemia
Hyponatremia	C361.00	Hyposmolality and or hyponatraemia
Seizures	R003.00	[D]Convulsions
Seizures	R003z11	[D]Seizure NOS
Seizures	8BL3.00	Patient on maximal tolerated anticonvulsant therapy
Seizures	F251600	Grand mal seizure
Seizures	1B64.11	Convulsion - symptom
Seizures	282..13	O/E - a seizure
Seizures	2828.00	Absence seizure
Seizures	R003z00	[D]Convulsion NOS
Seizures	2822.00	O/E - grand mal fit
Seizures	1B64.00	Had a convulsion
Seizures	F254500	Complex partial epileptic seizure
Seizures	8B66.00	Anticonvulsant therapy
Seizures	R003300	[D]Reflex anoxic seizure
Seizures	F132z12	Myoclonic seizure
Seizures	282..11	O/E - a convulsion
Seizures	2823.00	O/E - petit mal fit
Seizures	Q480.00	Convulsions in newborn
Seizures	282..00	O/E - fit/convulsion
Seizures	F258.00	Post-ictal state
Seizures	F253.00	Grand mal status
Seizures	Q480.12	Seizures in newborn

Clinical Term of Interest from List	Code	Code Description
Seizures	1B27.00	Seizures in response to acute event
Seizures	F255000	Jacksonian, focal or motor epilepsy
Seizures	F252.00	Petit mal status
Seizures	667Q.00	1 to 12 seizures a year
Seizures	14P4.00	H/O: anticonvulsant therapy
Seizures	1B26.00	Trigger factor for seizure
Seizures	2824.12	O/E - focal fit
Seizures	F24y100	Todd's paralysis
Seizures	R003100	[D]Convulsions, infantile
Seizures	14I4.00	H/O: perinatal convulsion
Seizures	667T.00	Daily seizures
Seizures	R003y00	[D]Other specified convulsion
Seizures	282Z.00	O/E - fit/convulsion NOS
Seizures	667R.00	2 to 4 seizures a month
Seizures	667S.00	1 to 7 seizures a week
Seizures	44WF000	Anticonvulsant level therapeutic
Seizures	667V.00	Many seizures a day
Seizures	2824.00	O/E - focal (Jacksonian) fit
Seizures	Eu44500	[X]Dissociative convulsions
Seizures	Ryu7100	[X]Other and unspecified convulsions
Hyperprolactinemia	C131000	Hyperprolactinaemia
Hyperprolactinemia	B7H2.11	Pituitary adenoma
Hyperprolactinemia	BB5y400	[M]Prolactinoma
Hyperprolactinemia	4435100	Prolactin level raised
Hyperprolactinemia	C134z00	Other anterior pituitary disorder NOS
Hyperprolactinemia	B7H2.00	Benign neoplasm of pituitary gland and craniopharyngeal duct
Hyperprolactinemia	B7H2000	Benign neoplasm of pituitary gland

Clinical Term of Interest from List	Code	Code Description
Hyperprolactinemia	BB5V.00	[M]Pituitary adenomas and carcinomas
Hyperprolactinemia	C134.00	Other anterior pituitary disorder
Hyperprolactinemia	BB5Vz00	[M]Pituitary adenoma or carcinoma NOS
Hyperprolactinemia	B7H2z00	Benign neoplasm of pituitary and craniopharyngeal duct NOS
Hyperprolactinemia	C131.11	Forbes - Albright syndrome
Hyperprolactinemia	C131.00	Other anterior pituitary hyperfunction
Hyperprolactinemia	C131.11	Forbes - Albright syndrome
Hyperprolactinemia	C131000	Hyperprolactinaemia
Hyperprolactinemia	B7H2.00	Benign neoplasm of pituitary gland and craniopharyngeal duct
Hyperprolactinemia	B7H2.11	Pituitary adenoma
Hyperprolactinemia	B7H2000	Benign neoplasm of pituitary gland
Hyperprolactinemia	B7H2200	Benign neoplasm of sella turcica
Hyperprolactinemia	B7H2z00	Benign neoplasm of pituitary and craniopharyngeal duct NOS
Hyperprolactinemia	4435100	Prolactin level raised
Orthostatic Hypotension	G870.11	Postural hypotension
Orthostatic hypotension	G870.00	Orthostatic hypotension
Neutropenia	D400.12	Neutropenia
Neutropenia	42J2.00	Neutropenia
Neutropenia	D400011	Idiopathic neutropenia
Neutropenia	D400600	Drug-induced neutropenia
Neutropenia	D400800	Acquired neutropenia NEC
Neutropenia	D400211	Neutropenia - drug induced
Neutropenia	7Q09200	Neutropenia drugs band 1
Dyslipidemia	C320.00	Pure hypercholesterolaemia

Clinical Term of Interest from List	Code	Code Description
Dyslipidemia	C324.00	Hyperlipidaemia NOS
Dyslipidemia	44P3.00	Serum cholesterol raised
Dyslipidemia	C322.00	Mixed hyperlipidaemia
Dyslipidemia	44O6.00	Lipids abnormal
Dyslipidemia	C320z00	Pure hypercholesterolaemia NOS
Dyslipidemia	1442.00	H/O: raised blood lipids
Dyslipidemia	C321.00	Pure hyperglyceridaemia
Dyslipidemia	C321000	Hypertriglyceridaemia
Dyslipidemia	44Q3.00	Serum triglycerides raised
Dyslipidemia	C328.00	Dyslipidaemia
Dyslipidemia	44O4.00	Serum lipids high
Dyslipidemia	C320200	Hyperlipidaemia, group A
Dyslipidemia	44P4.00	Serum cholesterol very high
Dyslipidemia	C320y00	Other specified pure hypercholesterolaemia
Dyslipidemia	Cyu8D00	[X]Other hyperlipidaemia
Hyperglycaemia/diabetes mellitus	C10..00	Diabetes mellitus
Hyperglycaemia/diabetes mellitus	C10F.00	Type 2 diabetes mellitus
Hyperglycaemia/diabetes mellitus	C100112	Non-insulin dependent diabetes mellitus
Hyperglycaemia/diabetes mellitus	C109.00	Non-insulin dependent diabetes mellitus
Hyperglycaemia/diabetes mellitus	C109.12	Type 2 diabetes mellitus
Hyperglycaemia/diabetes mellitus	C100011	Insulin dependent diabetes mellitus
Hyperglycaemia/diabetes mellitus	C108.00	Insulin dependent diabetes mellitus
Hyperglycaemia/diabetes mellitus	R105712	[D]Hyperglycaemia
Hyperglycaemia/diabetes mellitus	C100111	Maturity onset diabetes

Clinical Term of Interest from List	Code	Code Description
Hyperglycaemia/diabetes mellitus	C100100	Diabetes mellitus, adult onset, no mention of complication
Hyperglycaemia/diabetes mellitus	66A1.00	Initial diabetic assessment
Hyperglycaemia/diabetes mellitus	C101.00	Diabetes mellitus with ketoacidosis
Hyperglycaemia/diabetes mellitus	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
Hyperglycaemia/diabetes mellitus	C10FJ00	Insulin treated Type 2 diabetes mellitus
Hyperglycaemia/diabetes mellitus	Ryu8A00	[X]Hyperglycaemia, unspecified
Hyperglycaemia/diabetes mellitus	C321.00	Pure hyperglyceridaemia
Hyperglycaemia/diabetes mellitus	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
Hyperglycaemia/diabetes mellitus	C109.13	Type II diabetes mellitus
Hyperglycaemia/diabetes mellitus	C109J00	Insulin treated Type 2 diabetes mellitus
Hyperglycaemia/diabetes mellitus	C10F.11	Type II diabetes mellitus
Hyperglycaemia/diabetes mellitus	8Hj0.00	Referral to diabetes structured education programme
Hyperglycaemia/diabetes mellitus	C100.00	Diabetes mellitus with no mention of complication
Hyperglycaemia/diabetes mellitus	44Uz.11	Blood hyperglycaemia NOS
Hyperglycaemia/diabetes mellitus	C100z00	Diabetes mellitus NOS with no mention of complication
Hyperglycaemia/diabetes mellitus	C100000	Diabetes mellitus, juvenile type, no mention of complication
Hyperglycaemia/diabetes mellitus	R10C.00	[D]Drug induced hyperglycaemia
Hyperglycaemia/diabetes mellitus	C10F900	Type 2 diabetes mellitus without complication
Hyperglycaemia/diabetes mellitus	C102.00	Diabetes mellitus with hyperosmolar coma

Clinical Term of Interest from List	Code	Code Description
Hyperglycaemia/diabetes mellitus	C10y.00	Diabetes mellitus with other specified manifestation
Hyperglycaemia/diabetes mellitus	C109900	Non-insulin-dependent diabetes mellitus without complication
Hyperglycaemia/diabetes mellitus	C10F911	Type II diabetes mellitus without complication
Hyperglycaemia/diabetes mellitus	C10N.00	Secondary diabetes mellitus
Hyperglycaemia/diabetes mellitus	Cyu2.00	[X]Diabetes mellitus
Hyperglycaemia/diabetes mellitus	C10N000	Secondary diabetes mellitus without complication
Hyperglycaemia/diabetes mellitus	C10FL11	Type II diabetes mellitus with persistent proteinuria
Hyperglycaemia/diabetes mellitus	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
Hyperglycaemia/diabetes mellitus	C103z00	Diabetes mellitus NOS with ketoacidotic coma
Hyperglycaemia/diabetes mellitus	C109912	Type 2 diabetes mellitus without complication
Hyperglycaemia/diabetes mellitus	Cyu2000	[X]Other specified diabetes mellitus
Hyperglycaemia/diabetes mellitus	R105711	[D]Drug induced hyperglycaemia
Schizophrenia	E10..00	Schizophrenic disorders
Schizophrenia	E103.00	Paranoid schizophrenia
Schizophrenia	E10z.00	Schizophrenia NOS
Schizophrenia	1464.00	H/O: schizophrenia
Schizophrenia	E100200	Chronic schizophrenic
Schizophrenia	Eu20.00	[X]Schizophrenia
Schizophrenia	E100000	Unspecified schizophrenia

Clinical Term of Interest from List	Code	Code Description
Schizophrenia	212T.00	Psychosis, schizophrenia + bipolar affective disord resolved
Schizophrenia	Eu2..00	[X]Schizophrenia, schizotypal and delusional disorders
Schizophrenia	Eu20000	[X]Paranoid schizophrenia
Schizophrenia	E104.00	Acute schizophrenic episode
Schizophrenia	E100.00	Simple schizophrenia
Schizophrenia	ZV11000	[V]Personal history of schizophrenia
Schizophrenia	Eu20511	[X]Chronic undifferentiated schizophrenia
Schizophrenia	E102.00	Catatonic schizophrenia
Schizophrenia	E101.00	Hebephrenic schizophrenia
Schizophrenia	E103z00	Paranoid schizophrenia NOS
Schizophrenia	E106.00	Residual schizophrenia
Schizophrenia	E103200	Chronic paranoid schizophrenia
Schizophrenia	Eu20600	[X]Simple schizophrenia
Schizophrenia	Eu20z00	[X]Schizophrenia, unspecified
Schizophrenia	Eu23200	[X]Acute schizophrenia-like psychotic disorder
Schizophrenia	Eu23100	[X]Acute polymorphic psychot disord with symp of schizophren
Schizophrenia	E10y000	Atypical schizophrenia
Schizophrenia	Eu05212	[X]Schizophrenia-like psychosis in epilepsy
Schizophrenia	E103500	Paranoid schizophrenia in remission

Clinical Term of Interest from List	Code	Code Description
Schizophrenia	E100400	Acute exacerbation of chronic schizophrenia
Schizophrenia	E10y.00	Other schizophrenia
Schizophrenia	E103000	Unspecified paranoid schizophrenia
Schizophrenia	13L3.12	Schizophrenic child
Schizophrenia	Eu20213	[X]Schizophrenic catatonia
Schizophrenia	E100z00	Simple schizophrenia NOS
Schizophrenia	E103400	Acute exacerbation of chronic paranoid schizophrenia
Schizophrenia	Eu20400	[X]Post-schizophrenic depression
Schizophrenia	Eu20300	[X]Undifferentiated schizophrenia
Schizophrenia	E100500	Schizophrenia in remission
Schizophrenia	E10yz00	Other schizophrenia NOS
Schizophrenia	E14z.11	Childhood schizophrenia NOS
Schizophrenia	212W.00	Schizophrenia resolved
Schizophrenia	Eu20100	[X]Hebephrenic schizophrenia
Schizophrenia	Eu21.15	[X]Prodromal schizophrenia
Schizophrenia	Eu20y00	[X]Other schizophrenia
Schizophrenia	E103300	Acute exacerbation of subchronic paranoid schizophrenia
Schizophrenia	Eu23112	[X]Cycloid psychosis with symptoms of schizophrenia
Schizophrenia	E100300	Acute exacerbation of subchronic schizophrenia

Clinical Term of Interest from List	Code	Code Description
Schizophrenia	Eu20500	[X]Residual schizophrenia
Schizophrenia	Eu20011	[X]Paraphrenic schizophrenia
Schizophrenia	Eu20200	[X]Catatonic schizophrenia
Schizophrenia	Eu20111	[X]Disorganised schizophrenia
Schizophrenia	E102z00	Catatonic schizophrenia NOS
Schizophrenia	Eu20212	[X]Schizophrenic catalepsy
Schizophrenia	Eu20311	[X]Atypical schizophrenia
Schizophrenia	Eu21.16	[X]Pseudoneurotic schizophrenia
Schizophrenia	E100.11	Schizophrenia simplex
Schizophrenia	E100100	Subchronic schizophrenia
Schizophrenia	E103100	Subchronic paranoid schizophrenia
Schizophrenia	E105.00	Latent schizophrenia
Schizophrenia	E105500	Latent schizophrenia in remission
Schizophrenia	Eu21.11	[X]Latent schizophrenic reaction
Schizophrenia	Eu21.12	[X]Borderline schizophrenia
Schizophrenia	Eu21.13	[X]Latent schizophrenia
Schizophrenia	Eu21.14	[X]Prepsychotic schizophrenia
Schizophrenia	Eu23214	[X]Schizophrenic reaction
Schizophrenia	E101000	Unspecified hebephrenic schizophrenia

Clinical Term of Interest from List	Code	Code Description
Schizophrenia	E101500	Hebephrenic schizophrenia in remission
Schizophrenia	E101z00	Hebephrenic schizophrenia NOS
Schizophrenia	E102000	Unspecified catatonic schizophrenia
Schizophrenia	E102100	Subchronic catatonic schizophrenia
Schizophrenia	E105000	Unspecified latent schizophrenia
Schizophrenia	E105200	Chronic latent schizophrenia
Schizophrenia	E10y.11	Cenesthopathic schizophrenia
Schizophrenia	Eu20512	[X]Restzustand schizophrenic
Schizophrenia	ZS7C611	Schizophrenic language
Schizophrenia	***E101400***	***Acute exacerbation of chronic hebephrenic schizophrenia***
Schizophrenia	***E102500***	***Catatonic schizophrenia in remission***
Schizophrenia	***E105z00***	***Latent schizophrenia NOS***
Schizophrenia	***E107.11***	***Cyclic schizophrenia***
Schizophrenia	***E10y100***	***Coenesthopathic schizophrenia***
Schizophrenia	***Eu20214***	***[X]Schizophrenic flexibilatis cerea***
Schizophrenia	***Eu21.17***	***[X]Pseudopsychopathic schizophrenia***

APPENDIX D: COVARIATES

Clinical Outcome of Interest	Confounder and Risk Factor for Outcome of Interest
Extrapyramidal symptoms (EPS) ▪ **Tardive dyskinesia** ▪ **Akathisia** ▪ **Dystonia** ▪ **Parkinsonism**	**Neuroleptic-induced tardive dyskinesia risk factors:** • **Long term treatment with antipsychotics** • **Early onset of EPS** • **Older adult** • **Women** • **Psychiatric diagnosis** • **Cognitive deficits** • **Chemical abuse** • **Brain damage** • **Diabetes mellitus** • **History of mood disorders** **Neuroleptic-induced tardive dyskinesia differential diagnosis:** • **Acute dystonia** • **Acute akathisia** • **Huntington's disease** • **Sydenham's chorea** • **Spontaneous dyskinesia** • **Systemic lupus eythematosus** • **Hyperthyroidism** • **Wilson's disease** • **Treatment with L-dopa, bromocriptine or amantadine** **Neuroleptic-induced akathisia risk factors:** • **Use of other antipsychotics than asenapine** **Neuroleptic-induced akathisia differential diagnosis:** • **Use of certain antidepressants (such as fluoxetine, paroxetine, venlafaxine, triclyclic antidpressants, trazodone)** • **Anti-emetic drugs with dopamine blocking properties, i.e. metoclopramide and prochlorperazine** • **Withdrawal from drugs, such as barbiturates, opioids, benzodiazepines, alcohol, cocaine, amphetamines** • **Agitation during depressive or manic episodes** • **Agitation in ADHD, dementia, delirium, substance intoxication, substance withdrawal** • **Parkinson's disease** • **Iron-deficiency anemia** • **Anxiety**

- **Neuroleptic induced tardive dyskinesia**

Neuroleptic-induced dystonia risk factors:

- **Young age**
- **Antipsychotic-naïve patients**
- **History of neuroleptic-induced dystonia**
- **Male sex**
- **Brain damage**

Neuroleptic-induced dystonia differential diagnosis:

- **Focal/segmental dystonias due to temporal lobe seizures, viral and bacterial infections, trauma, space-occupying lesions in the peripheral or central nervous system and endocrinopathies (e.g. hypoparathyroidism)**
- **Catatonia**

Neuroleptic-induced parkinsonism risk factors:

- **History of neuroleptic-induced parkinsonism**
- **Older age**
- **Coexisting delirium, dementia or amnestic disorder**
- **Children**

Neuroleptic-induced parkinsonism differential diagnosis:

- **Parkinson's disease**
- **Wilson's disease**
- **Familial tremor**
- **Substance withdrawal**
- **Stroke**
- **Neuroleptic malignant syndrome**
- **Major depressive episode**
- **Catatonia**
- **Delirium**
- **Dementia**
- **Anxiety disorders**
- **Conversion disorder**
- **Psychosis**

Somnolence and sedation

Aetiology and risk factors for somnolence/sedation:

- **Anxiety**
- **Depression**
- **Insomnia**
- **Sleep apnoe syndrome**
- **Alcohol use**
- **Use of illicit substances with sedative properties (e.g.**

	cannabis, heroin, GHB, etc.) • **Use of drugs with sedatives properties (antipsychotics, antidepressants, barbiturates, benzodiazepines, non-benzodiazepine sedatives, herbal sedatives, antihistamines, opiates and chloralhydrate)** • **Somatic conditions (exhaustive list of comorbidities, including malignancies, infections, endocrine disorders, electrolyte disorders, autoimmune disease, etc.)**
NMS (Neuroleptic Malignant Syndrome)	**Risk factors for NMS:** • **History of NMS** • **High doses of neuroleptics** • **Intramuscular depot formulations** • **Concomitant use of medications associated with NMS, see below** **NMS differential diagnosis:** • **Central nervous system infection** • **Status epilepticus** • **Subcortical brain lesions (stroke, trauma, neoplasms)** • **Systemic conditions (intermittent acute porphyria, tetanus)** • **Heat stroke** • **Malignant hyperthermia** • **Use of other psychotropic medications: monoamine oxidase inhibitors, monoamine oxidase inhibitor-tricyclic combinations, monoamine oxidase inhibitor-serotonergic agent combinations, monoamine oxidase inhibitor-meperidine combinations, lithium, anticholinergics, amphetamines, fenfluramine, cocaine and phencyclidine** • **Serotonin syndrome by SSRIs** • **Catatonia**
Rhabdomyolysis	**Risk factors for rhabdomyolysis in general:** • **Alcohol abuse** • **Alcohol withdrawal** • **Drug abuse (cocaine)** • **Medications, including antipsychotics, statins** • **Muscle ischemia** • **Polymyositis** • **Drug overdose** • **Recent seizure activity.** • **Metabolic derangements** • **Hypothermia** • **Flulike illness**

- **Sepsis**
- **Gangrene**

Causes of rhabdomyolysis:

- **Rhabdomyolysis may occur after excessive muscular activity, such as the following:**
  - **Status epilepticus**
  - **Status asthmaticus**
  - **Severe dystonia**
  - **Acute psychosis**
  - **Toxin-mediated rhabdomyolysis may result from substance abuse, including abuse of the following:**
  - **Ethanol**
  - **Methanol**
  - **Ethylene glycol**
  - **Isopropanol**
  - **Heroin**
  - **Methadone**
  - **Barbiturates**
  - **Cocaine**
  - **Amphetamine**
  - **Phencyclidine**
  - **3,4-methylenedioxymethamphetamine (MDMA, ecstasy)**
  - **Lysergic acid diethylamide (LSD)**
- **Toxic-mediated rhabdomyolysis may result from prescription and nonprescription medications, including the following:**
  - **Antihistamines**
  - **Salicylates**
  - **Caffeine**
  - **Fibric acid derivatives (eg, bezafibrate, clofibrate, fenofibrate, gemfibrozil)**
  - **Neuroleptics/antipsychotics (Neuroleptic Malignant Syndrome)**
  - **Anesthetic and paralytic agents (the malignant hyperthermia syndrome)**
  - **Amphotericin B**
  - **Quinine**
  - **Corticosteroids**
  - **Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors)**
  - **Theophylline**
  - **Cyclic antidepressants**
  - **Selective serotonin reuptake inhibitors (the serotonin syndrome)**

  - **Aminocaproic acid**
  - **Phenylpropanolamine (recalled from US market)**
  - **Propofol (continuous infusion)**
  - **Protease inhibitors**
- **Environmental causes of rhabdomyolysis include the following:**
  - **Hyperthermia**
  - **Hypothermia**
  - **Metabolic causes of rhabdomyolysis include the following:**
  - **Hyponatremia or hypernatremia**
  - **Hypokalemia**
  - **Hypophosphatemia**
  - **Hypothyroidism or hyperthyroidism**
  - **Diabetic ketoacidosis**
  - **Nonketotic hyperosmolar diabetic coma**
- **Viral infectious disease agents may cause rhabdomyolysis, including the following:**
  - **Influenza types A and B (most common)**
  - **HIV**
  - **Coxsackievirus**
  - **Epstein-Barr virus**
  - **Echovirus**
  - **Cytomegalovirus**
  - **Adenovirus**
  - **Herpes simplex virus**
  - **Parainfluenza virus**
  - **Varicella-zoster virus**
  - **West Nile virus**
- **Bacterial infectious agents may cause rhabdomyolysis, including the following:**
  - ***Francisella tularensis***
  - ***Streptococcus pneumoniae***
  - **Group B streptococci**
  - ***Streptococcus pyogenes***
  - ***Staphylococcus epidermidis***
  - ***Escherichia coli***
  - ***Borrelia burgdorferi***
  - ***Clostridium perfringens***
  - ***Clostridium tetani***
  - **Viridans streptococci**
  - ***Plasmodium* species**
  - ***Rickettsia* species**
  - ***Salmonella* species**
  - ***Listeria* species**

- ***Legionella* species**
- ***Mycoplasma* species**
- ***Vibrio* species**
- ***Brucella* species**
- ***Bacillus* species**
- ***Leptospira* species**

- **Fungal infectious agents may cause rhabdomyolysis, including the following:**
  - ***Candida* species**
  - ***Aspergillus* species**
- **Causative connective tissue diseases that can cause rhabdomyolysis include the following:**
  - **Polymyositis**
  - **Dermatomyositis**
- **Inherited disorders may cause rhabdomyolysis, including the following:**
  - **Enzyme deficiencies of carbohydrate, lipid, or amino acid metabolism**
  - **Myopathies**
- **Rhabdomyolysis also has been reported in patients with sickle cell anemia and has mistakenly been identified as a pain crisis.**

Seizures

Causes of new-onset seizures:

- **Epilepsy**
- **CNS pathologies (stroke, neoplasm, trauma, hypoxia, vascular abnormality)**
- **Metabolic abnormalities (hypoglycemia/hyperglycemia, hypomagnesemia, hyponatremia/hypernatremia, hypocalcemia, hepatic encephalopathy)**
- **Toxicologic etiologies:**
  - **Alcohol intoxication**
  - **Alcohol withdrawal**
  - **Drug abuse (cocain, amphetamines, MDMA)**
- **Infection etiologies (meningitis, encephalitis, brain abscess)**
- **Medications:**
  - **Antipsychotics (clozapine, a.o.)**
  - **Antidepressants (clomipramine, bupropion, a.o.)**
  - **Alprazolam**
  - **Isoniazid**
  - **Xanthine derivatives (aminophylline, theophylline)**
  - **Antimalarials**

Risk factors for patients with a known seizure-disorder:

- **Caffeine use**

Hyperprolactinemia

Causes of hyperprolactinemia:

- **Primary hyperthyroidism**
- **Adrenal insufficiency**
- **Medications: antipsychotics, calcium-channel blockers, methyldopa, tricyclic antidepressants, H2 antagonists, opiates**
- **Pregnancy**
- **Renal failure**
- **Hepatic insufficiency**
- **Polycystic ovarian syndrome**
- **Pituitary adenoma**

Orthostatic hypotension

Risk factors for orthostatic hypotension:

- **Elderly age**
- **Pregnancy**

Causes of orthostatic hypotension:

- **Non-neurogenic etiologies:**
  - **Cardiac pump failure**
  - **Aortic stenosis**
  - **Bradyarrhythmia**
  - **Myocardial infarction**
  - **Myocarditis**
  - **Pericarditis**
  - **Tachyarrhythmia**
  - **Reduced intravascular volume**
  - **Adrenal insufficiency**
  - **Burns**
  - **Diabetes insipidus**
  - **Diarrhea**
  - **Hemorrhage**
  - **Salt-losing nephropathy**
  - **Vomiting**
  - **Venous pooling**
  - **Alcohol consumption**
  - **Fever**
  - **Sepsis**
- **Neurogenic etiologies:**
  - **Spinal cord problems**
  - **Syringomyelia**
  - **Tabes dorsalis**
  - **Transverse myelitis**
  - **Tumors**
  - **Peripheral nervous system problems**
  - **HIV/AIDS**

- **Alcoholic polyneuropathy**
- **Amyloidosis**
- **Diabetes mellitus**
- **Dopamine beta-hydroxylase deficiency**
- **Guillain-Barré syndrome**
- **Paraneoplastic syndrome**
- **Renal failure**
- **Vitamin B12 or folate deficiency**
- **Other neurogenic etiologies**
- **Brain-stem lesions**
- **Brain tumors**
- **Carotid sinus hypersensitivity**
- **Cerebral vascular accidents**
- **Dysautonomias**
- **Multiple sclerosis**
- **Multiple system atrophy**
- **Neurocardiogenic syncope**
- **Parkinson's disease**
- **Pure autonomic failure**
- **Syringobulbia**

- **Medications/drugs:**
  - **Alpha and beta blockers**
  - **Antihypertensives**
  - **Bromocriptine (Parlodel)**
  - **Diuretics**
  - **Insulin**
  - **MAO inhibitors**
  - **Marijuana**
  - **Minor tranquilizers**
  - **Narcotics/sedatives**
  - **Nitrates**
  - **Phenothiazines**
  - **Sildenafil (Viagra)**
  - **Sympatholytics**
  - **Sympathomimetics (with prolonged use)**
  - **Tricyclic antidepressants**
  - **Vasodilators**
  - **Vincristine (Oncovin)**

Neutropenia

Causes of neutropenia:

- **Medications:**
  - **Analgesics**
    - **Acetaminophen**
    - **Aminopyrine**
    - **Dipyrone**
  - **Cardiovascular drugs**
    - **Captopril**

- **Hydralazine**
- **Methyldopa**
- **Pindolol**
- **Procainamide**
- **Propranolol**
- **Quinidine**

- **Antibiotics**
  - **Cephalosporins**
  - **Clindamycin**
  - **Chloramphenicol**
  - **Doxycycline**
  - **Gentamicin**
  - **Griseofulvin**
  - **Isoniazid**
  - **Metronidazole**
  - **Nitrofurantoin**
  - **Penicillins**
  - **Rifampin**
  - **Streptomycin**
  - **Sulfonamides**
  - **Vancomycin**
- **Diuretics**
  - **Acetazolamide**
  - **Bumetanide**
  - **Chlorothiazide**
  - **Hydrochlorothiazide**
  - **Chlorthalidone**
  - **Methazolamide**
  - **Spironolactone**
- **Anticonvulsants**
  - **Carbamazepine**
  - **Mephenytoin**
  - **Phenytoin**
  - **Primidone**
  - **Trimethadione**
- **Hypoglycemic agents**
  - **Chlorpropamide**
  - **Tolbutamide**
- **Antihistamines**
  - **Brompheniramine**
  - **Cimetidine**
  - **Tripelennamine**
  - **Ranitidine**
  - **Thenalidine**
- **Phenothiazines**
  - **Chlorpromazine**

- **Clozapine**
- **Desipramine**
- **Prochlorperazine**
- **Promazine**
- **Thioridazine**
- **Trifluoperazine**
- **Trimeprazine**

- **Anti-inflammatory drugs**
  - **Fenoprofen**
  - **Ibuprofen**
  - **Indomethacin**
  - **Phenylbutazone**
- **Neuropharmacologic agents**
  - **Chlordiazepoxide**
  - **Clozapine**
  - **Desipramine**
  - **Meprobamate**
  - **Metoclopramide**
  - **Prochlorperazine**
  - **Promazine**
- **Antimalarials**
  - **Amodiaquine**
  - **Dapsone**
  - **Hydroxychloroquine**
  - **Pyrimethamine**
  - **Quinine**
- **Miscellaneous drugs**
  - **Allopurinol**
  - **Colchicine**
  - **D-Penicillamine**
  - **Ethanol**
  - **Levamisole**
  - **Levodopa**
- **Antithyroid agents**
  - **Carbimazole**
  - **Methylthiouracil**
  - **Propylthiouracil**

- **Viral infections:**
  - **Epstein-Barr virus**
  - **Hepatitis B virus**
  - **Yellow fever virus**
  - **Cytomegalovirus**
  - **Influenza**
- **Autoimmune neutropenia**
- **Cyclic neutropenia**
- **Kostmann syndrome**

	• **Chronic severe neutropenia** • **Myelokathexis**
Metaboliceffects: Dyslipidemias	**Causes of hypercholesterolemia:** • **Diabetes mellitus** • **Hypothyroidism** • **Nephrotic syndrome** • **Chronic renal insufficiency** • **Obstructive liver disease** • **Cushing's syndrome** • **Obesity** • **Cigarette smoking** • **Excessive alcohol intake** • **Familial hypercholesterolemia** **Causes of low HDL levels not listed above:** • **Elevated serum triglycerides** • **Certain drugs (beta-blockers, anabolic steroids, progestational agents)** **Causes of hypertriglyceridemia not listed above:** • **Chronic renal failure** • **Nephrotic syndrome** • **Lipodystrophy** • **Pregnancy** • **Medications: corticosteroids, protease inhibitors for HIV, beta-adrenergic blocking agents, oral estrogens, retinoids, tamoxifen)** • **Genetic forms of hypertriglyceridemia:** o **Familial combined hyperlipidemia** o **Familial hypertriglyceridemia** o **Familial dysbetalipoproteinemia** o **Polygenic hypertriglyceridemia** o **Familial lipoprotein lipase deficiency** o **Familial apolipoprotein C-II deficiency**
Metabolic effects: Hyperglycemia and diabetes mellitus	**Causes for hyperglycemia:** • **Type I Diabetes mellitus** • **Type II Diabetes mellitus** • **Secondary diabetes mellitus (see below)** • **Stroke** • **Myocardial infarction** • **Infections** • **Medications:** o **Thiazide and loop diuretics** o **Beta-blockers** o **Calcium-channel blockers** o **Central alpha blockers** o **Minoxidil**

- **Diazoxide**
- **Corticosteroids and ACTH**
- **Oral contraceptive**
- **Nicotinic acid**
- **Beta-2 agonists**
- **Cyclosporine**
- **Thyroid hormones**
- **Pentamidine**
- **Isoniazid**
- **Phenytoin**
- **Phenothiazines**
- **Nalidixic acid**
- **Asparaginase**
- **Dapsone**
- **Morphine**
- **Encainide**
- **Lithium**
- **L-Dopa**
- **Theophylline**
- **Acetazolamide**
- **Rifampicin**
- **Indomethacin**
- **Dopamine**
- **Chlordiazepoxide**
- **Amoxapine**
- **Droperidol**
- **Doxapram**
- **Octreotide**
- **Quinathazone**
- **Ethanol**
- **Amiodarone**

Risk factors for type II diabetes mellitus not listed above:

- **Older than 45 years of age**
- **Obesity**
- **Family history of type 2 diabetes**
- **History of previous impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)**
- **Hypertension (>140/90 mm Hg)**
- **Dyslipidemia (high-density lipoprotein [HDL] cholesterol level <40 mg/dL or triglyceride level >150 mg/dL)**
- **History of gestational diabetes mellitus**
- **Polycystic ovarian syndrome**

Secondary causes of diabetes mellitus:

- **Pancreatectomy**

	• **Acute pancreatitis** • **Chronic pancreatitis** • **Hemochromatosis** • **Carcinoma** • **Cystic fibrosis** • **Glucagonoma** • **Somatostatinoma** • **Gastrinoma** • **VIPoma (vasoactive intestinal peptide tumor)** • **Carcinoid syndrome** • **Chronic liver disease and cirrhosis** • **Hepatitis C** • **Acute hepatitis** • **Acromegaly** • **Cushing's syndrome** • **Pheochromocytoma** • **Hyperthyroidism** • **Hyperparathyroidism** • **Hyperaldosteronism** • **Klinefelter's syndrome** • **Turner's syndrome** • **Wolfram's syndrome** • **Friedreich's syndrome** • **Huntington's chorea** • **Lawrence–Moon–Biedl syndrome** • **Myotonic dystrophy** • **Porphyria** • **Prader–Willi syndrome**

Allergic reactions (Immediate hypersensitivity reaction)	**Risk factors for anaphylactic reactions:**
	• **Female sex**
	Most common causes of anaphylactic reactions:
	• **Drugs:**
	  ○ **Antibiotics (especially penicillin)**
	  ○ **Intravenous anaesthetic drugs**
	  ○ **Aspirin**
	  ○ **Non-steroidal anti-inflammatory drugs**
	  ○ **Intravenous contrast media**
	  ○ **Opioid analgesics**

Additional risk factors or confounders

- **Migraine**
- **Treatment for migraine**

- **Charlson comorbidity index**
- **Healthcare resource utilization**
  - **Number of hospitalizations**
  - **Number of prescriptions**
  - **Number of visits to general practitioner's office**
  - **Referral to a pyschiatrist**

ATTACHMENT A: PRODUCT CIRCULAR

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 5 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 5 mg asenapine (as maleate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet
Round, white to off-white, sublingual tablets debossed with "5" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sycrest is indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults

4.2 Posology and method of administration

Posology

Manic episode
The recommended starting dose of Sycrest as monotherapy is 10 mg twice daily. One dose should be taken in the morning and one dose should be taken in the evening. The dose can be reduced to 5 mg twice daily according to clinical assessment. For combination therapy a starting dose of 5 mg twice daily is recommended. Depending on the clinical response and tolerability in the individual patient, the dose can be increased to 10 mg twice daily.

Additional information on special populations

Paediatric population
The safety and efficacy of Sycrest in children aged below 18 years have not been established. Limited safety data with Sycrest are available in adolescent patients. A pharmacokinetic study was performed in adolescent patients. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Elderly patients
Sycrest should be used with care in the elderly. Limited data on efficacy in patients 65 years of age and older are available. Available pharmacokinetic data are described in section 5.2.

Renally impaired patients
No dose adjustment is required for patients with renal impairment. There is no experience with asenapine in severe renal impairment patients with a creatinine clearance less than 15 ml/min.

Hepatic impaired patients
No dose adjustment is required for patients with mild hepatic impairment. The possibility of elevated asenapine plasma levels cannot be excluded in some patients with moderate hepatic impairment (Child-Pugh B) and caution is advised. In subjects with severe hepatic impairment (Child-Pugh C), a

7-fold increase in asenapine exposure was observed. Thus, Sycrest is not recommended in patients with severe hepatic impairment.

Method of administration

The tablet should not be removed from the blister until ready to take it. Dry hands should be used when touching the tablet. The tablet should not be pushed through the tablet pack. The tablet pack should not be cut or torn. The coloured tab should be peeled back and the tablet should be removed gently. The tablet should not be crushed.

To ensure optimal absorption, the Sycrest sublingual tablet should be placed under the tongue and allowed to dissolve completely. The tablet will dissolve in saliva within seconds. Sycrest sublingual tablets should not be chewed or swallowed. Eating and drinking should be avoided for 10 minutes after administration.
When used in combination with other medication, Sycrest should be taken last.

Treatment with Sycrest is not advised in patients who are unable to comply with this method of administration, as the bioavailability of asenapine when swallowed is low (<2 % with an oral tablet formulation).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Elderly patients with dementia-related psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic substances are at an increased risk of death.
Sycrest is not approved for the treatment of patients with dementia-related psychosis and is not recommended for use in this particular group of patients.

Neuroleptic Malignant Syndrome
Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur with antipsychotics, including asenapine. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure.
If a patient develops signs and symptoms indicative of NMS Sycrest must be discontinued.

Seizures
In clinical trials, cases of seizure were occasionally reported during treatment with asenapine. Therefore, Sycrest should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Suicide
The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder and close supervision of high-risk patients should accompany treatment.

Orthostatic hypotension
Asenapine may induce orthostatic hypotension and syncope, especially early in treatment, probably reflecting its α1-adrenergic antagonist properties. Elderly patients are particularly at risk for experiencing orthostatic hypotension (see section 4.8). In clinical trials, cases of syncope were occasionally reported during treatment with Sycrest. Sycrest should be used with caution in elderly patients and in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration and hypovolemia).

Tardive dyskinesia
Medicinal products with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical, involuntary movements, predominantly of the tongue and/or face. In clinical trials, cases of tardive dyskinesia were occasionally reported during treatment with asenapine. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on Sycrest, discontinuation of treatment should be considered.

Hyperprolactinaemia
Increases in prolactin levels were observed in some patients with Sycrest. In clinical trials, there were few adverse reactions related to abnormal prolactin levels reported.

QT interval
Clinically relevant QT prolongation does not appear to be associated with asenapine. Caution should be exercised when Sycrest is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QT interval.

Hyperglycaemia and diabetes mellitus
Hyperglycaemia or exacerbation of pre-existing diabetes has occasionally been reported during treatment with asenapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia or bipolar disorder and the increasing incidence of diabetes mellitus in the general population. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic treatment. Cases of dysphagia were occasionally reported in patients treated with Sycrest.

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. From the clinical trials, it is concluded that clinically relevant body temperature dysregulation does not appear to be associated with asenapine. Appropriate care is advised when prescribing Sycrest for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant medicinal products with anticholinergic activity or being subject to dehydration.

Patients with severe hepatic impairment
Asenapine exposure is increased 7-fold in patients with severe hepatic impairment (Child-Pugh C). Therefore, Sycrest is not recommended in such patients.

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing antipsychotic medicinal products, including Sycrest, to patients with Parkinson's disease or dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary effects of asenapine on the central nervous system (CNS) (see section 4.8), caution should be used when it is taken in combination with other centrally acting medicinal products. Patients should be advised to avoid alcohol while taking Sycrest.

Potential for other medicines to affect Sycrest

Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2). The potential effects of inhibitors and an inducer of several of these enzyme pathways on asenapine pharmacokinetics were studied, specifically fluvoxamine (CYP1A2 inhibitor), paroxetine (CYP2D6 inhibitor), imipramine (CYP1A2/2C19/3A4 inhibitor), cimetidine (CYP3A4/2D6/1A2 inhibitor), carbamazepine (CYP3A4/1A2 inducer) and valproate (UGT inhibitor). Except for fluvoxamine, none of the interacting medicinal products resulted in clinically relevant alterations in asenapine pharmacokinetics.
During combined administration with a single dose of asenapine 5 mg, fluvoxamine 25 mg BID resulted in a 29 % increase in asenapine AUC. The full therapeutic dose of fluvoxamine would be expected to produce a greater increase in asenapine plasma concentrations. Therefore, co-administration of asenapine and fluvoxamine should be approached with caution.

Potential for Sycrest to affect other medicines
Because of its α1-adrenergic antagonism with potential for inducing orthostatic hypotension (see section 4.4), Sycrest may enhance the effects of certain antihypertensive agents.

Asenapine may antagonise the effect of levodopa and dopamine agonists. If this combination is deemed necessary, the lowest effective dose of each treatment should be prescribed.

In vitro studies indicate that asenapine weakly inhibits CYP2D6. Clinical drug interaction studies investigating the effects of CYP2D6 inhibition by asenapine showed the following results:

- Following co-administration of dextromethorphan and asenapine in healthy subjects, the ratio of dextrorphan/dextromethorphan (DX/DM) as a marker of CYP2D6 activity was measured. Indicative of CYP2D6 inhibition, treatment with asenapine 5 mg twice daily resulted in a fractional decrease in DX/DM ratio to 0.43. In the same study, treatment with paroxetine 20 mg daily decreased the DX/DM ratio to 0.032.

- In a separate study, co-administration of a single 75-mg dose of imipramine with a single 5-mg dose of asenapine did not affect the plasma concentrations of the metabolite desipramine (a CYP2D6 substrate).

- Co-administration of a single 20-mg dose of paroxetine (a CYP2D6 substrate and inhibitor) during treatment with 5 mg asenapine twice daily in 15 healthy male subjects resulted in an almost 2-fold increase in paroxetine exposure.

In vivo asenapine appears to be at most a weak inhibitor of CYP2D6. However, asenapine may enhance the inhibitory effects of paroxetine on its own metabolism.
Therefore, Sycrest should be co-administered cautiously with medicinal products that are both substrates and inhibitors for CYP2D6.

To ensure optimal absorption, eating and drinking should be avoided for 10 minutes after administration.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Sycrest in pregnant women. Asenapine was not teratogenic in animal studies. Maternal and embryo toxic effects were found in animal studies (see section 5.3). Sycrest should not be used during pregnancy unless clearly necessary and only if the potential benefit outweighs the potential risk to the foetus.

Breast-feeding
Asenapine was excreted in milk of rats during lactation. It is not known whether asenapine or its metabolites are excreted in human milk. It is recommended that women receiving Sycrest should not breast-feed.

Fertility
No impairment of fertility has been observed in nonclinical studies (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Asenapine may cause somnolence and sedation. Therefore, patients should be cautioned about operating machinery, including motor vehicles, until they are reasonably certain that Sycrest therapy does not affect them adversely.

4.8 Undesirable effects

The most frequently reported adverse drug reactions during treatment with asenapine were somnolence and anxiety. The incidences of the Adverse Drug Reactions (ADRs) associated with asenapine therapy are tabulated below. The table is based on adverse event reporting from clinical trials.
All ADRs are listed by system organ class and frequency; very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare
Blood and lymphatic disorders				Neutropenia
Metabolism and nutrition disorders		Weight increased Increased appetite	Hyperglycaemia	
Psychiatric disorders	Anxiety			
Nervous system disorders	Somnolence	Dystonia Akathisia Dyskinesia Parkinsonism Sedation Dizziness Dysgeusia	Syncope Seizure Extrapyramidal disorder Dysarthria	Neuroleptic malignant syndrome
Eye disorders				Accommodation disorder
Cardiac disorders			Sinus bradycardia Bundle branch block Electrocardiogram QT prolonged	
Vascular disorders			Orthostatic hypotension Hypotension	
Respiratory, thoracic and mediastinal disorders				Pulmonary embolism
Gastrointestinal disorders		Hypoaesthesia oral	Swollen tongue Dysphagia Glossodynia Paraesthesia oral	

Hepatobiliary disorders		Alanine aminotransferase increased		
Musculoskeletal and connective tissue disorders		Muscle rigidity		Rhabdomyolysis
Reproductive system and breast disorders			Sexual dysfunction Amenorrhoea	Gynaecomastia Galactorrhoea
General disorders and administration site conditions		Fatigue		

Description of selected adverse reactions

Extrapyramidal Symptoms (EPS)
In clinical trials, the incidence of extrapyramidal symptoms in asenapine-treated patients was higher than placebo (15.4 % vs 11.0 %).
From the short-term (6 weeks) schizophrenia trials there appears to be a dose-response relationship for akathisia in patients treated with asenapine, and for parkinsonism there was an increasing trend with higher doses.

Weight increase
In the combined short-term and long-term schizophrenia and bipolar mania trials, the mean change in body weight for asenapine was 0.8 kg. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) in the short-term schizophrenia trials was 5.3 % for asenapine compared to 2.3 % for placebo. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) in the short-term bipolar mania trials was 6.5 % for asenapine compared to 0.6 % for placebo.

Orthostatic hypotension
The incidence of orthostatic hypotension in elderly subjects was 4.1 % compared to 0.3 % in the combined phase 2/3 trial population.

Hepatic enzymes
Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (AST) have been seen commonly, especially in early treatment.

Other findings
Cerebrovascular events have been reported in patients treated with asenapine but there is no evidence of any excess incidence over what is expected in adults between 18 and 65 years of age.

Asenapine has anaesthetic properties. Oral hypoaesthesia and oral paraesthesia may occur directly after administration and usually resolves within 1 hour.

4.9 Overdose

Few cases of overdose were reported in the asenapine program. Reported estimated doses were between 15 and 400 mg. In most cases it was not clear if asenapine had been taken sublingually. Treatment-related adverse reactions included agitation and confusion, akathisia, orofacial dystonia, sedation, and asymptomatic ECG findings (bradycardia, supraventricular complexes, intraventricular conduction delay).
No specific information is available on the treatment of overdose with Sycrest. There is no specific antidote to Sycrest. The possibility of multiple medicinal product involvement should be considered. Cardiovascular monitoring is necessary to detect possible arrhythmias and management of overdose

should concentrate on supportive therapy, maintaining an adequate airway oxygenation and ventilation, and management of symptoms. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulations may worsen hypotension in the setting of Sycrest-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medicines should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, antipsychotics, ATC code: N05AH05

Mechanism of action
The mechanism of action of asenapine, as with other medicinal products having efficacy in bipolar disorder, is not fully understood. However, based on its receptor pharmacology, it is proposed that the efficacy of asenapine is mediated through a combination of antagonist activity at D2 and 5-HT2A receptors. Actions at other receptors e.g., 5-HT1A, 5-HT1B, 5-HT2C, 5-HT6, 5-HT7, D3, and α2-adrenergic receptors, may also contribute to the clinical effects of asenapine.

Clinical efficacy

Clinical efficacy in bipolar I disorder
The efficacy of asenapine in the treatment of a DSM-IV manic or mixed episode of bipolar I disorder with or without psychotic features was evaluated in two similarly designed 3-week, randomized, double-blind, placebo- and active controlled (olanzapine) monotherapy trials involving 488 and 489 patients, respectively. All patients met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria for bipolar I disorder, current episode manic (DSM-IV 296.4x), or mixed (DSM-IV 296.6x) and had a Young Mania Rating Scale (Y-MRS) score of ≥ 20 at screening and baseline. Patients with rapid cycling were excluded from these studies. Asenapine demonstrated superior efficacy to placebo in the reduction of manic symptoms over 3 weeks. Point estimates [95 % CI] for the change from baseline to endpoint in YMRS using LOCF analysis in the two studies were as follows:
-11.5 [-13.0, -10.0] for asenapine vs -7.8 [-10.0, -5.6] for placebo and
-10.8 [-12.3, -9.3] for asenapine vs -5.5 [-7.5, -3.5] for placebo.
A statistically significant difference between asenapine and placebo was seen as early as day 2.

Patients from the two pivotal 3 week trials were studied for a further 9 weeks an extension trial. Maintenance of effect during the episode after 12 weeks of randomised treatment was demonstrated in this trial.

In a 12-week, placebo-controlled trial involving 326 patients with a manic or mixed episode of bipolar I disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of asenapine as adjunctive therapy resulted in superior efficacy to lithium or valproate monotherapy at week 3 (point estimates [95 % CI] for the change from baseline to endpoint in YMRS using LOCF analysis-10.3 [-11.9, -8.8] for asenapine and -7.9 [-9.4, -6.4] for placebo) and at week 12 (-12.7 [-14.5, -10.9] for asenapine and -9.3 [-11.8, -7.6] for placebo) in the reduction of manic symptoms.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with asenapine in one or more subsets of the paediatric population in schizophrenia and bipolar I disorder (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Following sublingual administration, asenapine is rapidly absorbed with peak plasma concentrations occurring within 0.5 to 1.5 hours. The absolute bioavailability of sublingual asenapine at 5 mg is 35 %. The absolute bioavailability of asenapine when swallowed is low (<2 % with an oral tablet formulation). The intake of water several (2 or 5) minutes after asenapine administration resulted in decreased (19 % and 10 %, respectively) asenapine exposure. Therefore, eating and drinking should be avoided for 10 minutes after administration (see section 4.2).

Distribution
Asenapine is rapidly distributed and has a large volume of distribution (approximately 1700 l), indicating extensive extravascular distribution. Asenapine is highly bound (95 %) to plasma proteins, including albumin and α1-acid glycoprotein.

Biotransformation
Asenapine is extensively metabolized. Direct glucuronidation (mediated by UGT1A4) and cytochrome P450 (primarily CYP1A2, with contributions of 2D6 and 3A4) mediated oxidation and demethylation are the primary metabolic pathways for asenapine. In an *in vivo* study in humans with radio-labelled asenapine, the predominant drug-related entity in plasma was asenapine N^+-glucuronide; others included N-desmethylasenapine, N-desmethylasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. Sycrest activity is primarily due to the parent compound.
Asenapine is a weak inhibitor of CYP2D6. Asenapine does not cause induction of CYP1A2 or CYP3A4 activities in cultured human hepatocytes. Co-administration of asenapine with known inhibitors, inducers or substrates of these metabolic pathways has been studied in a number of drug-drug interaction studies (see section 4.5).

Elimination
Asenapine is a high clearance compound, with a clearance after intravenous administration of 52 l/h. In a mass balance study, the majority of the radioactive dose was recovered in urine (about 50 %) and faeces (about 40 %), with only a small amount excreted in faeces (5-16 %) as unchanged compound. Following an initial more rapid distribution phase, the terminal half-life of asenapine is approximately 24 h.

Linearity/non-linearity
Increasing the dose from 5 to 10 mg twice daily (a two-fold increase) results in less than linear (1.7 times) increases in both the extent of exposure and maximum concentration. The less than proportional increase of Cmax and AUC with dose may be attributed to limitations in the absorption capacity from the oral mucosa following sublingual administration.
During twice-daily dosing, steady-state is attained within 3 days. Overall, steady-state asenapine pharmacokinetics are similar to single-dose pharmacokinetics.

Pharmacokinetics in special populations

Hepatically impaired patients
The pharmacokinetics of asenapine were similar among subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in asenapine exposure was observed (see section 4.2).

Renally impaired patients
The pharmacokinetics of asenapine following a single dose of 5 mg asenapine were similar among subjects with varying degrees of renal impairment and subjects with normal renal function.
There is no experience with asenapine in severe renal impairment patients with a creatinine clearance less than 15 ml/min.

Elderly

In elderly patients (between 65 and 85 years of age), exposure to asenapine is approximately 30 % higher than in younger adults.

Paediatric population (Adolescents)
At the 5 mg twice daily dose level, asenapine pharmacokinetics in adolescent patients (12 to 17 years of age, inclusive) are similar to those observed in adults. In adolescents, the 10 mg twice daily dose did not result in increased exposure compared to 5 mg twice daily.

Gender
A population pharmacokinetic analysis indicated that there is no evidence of gender-related differences in the pharmacokinetics of asenapine.

Race
In a population pharmacokinetic analysis, no clinical relevant effects of race on the pharmacokinetics of asenapine were found.

Smoking
A population pharmacokinetic analysis indicated that smoking, which induces CYP1A2, has no effect on the clearance of asenapine. In a dedicated study, concomitant smoking during administration of a single 5 mg sublingual dose had no effect on the pharmacokinetics of asenapine.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology. Repeat-dose toxicity studies in rat and dog showed mainly dose-limiting pharmacological effects, such as sedation. Furthermore, prolactin-mediated effects on mammary glands and oestrus cycle disturbances were observed. In dogs high oral doses resulted in hepatotoxicity that was not observed after chronic intravenous administration. Asenapine has some affinity to melanin-containing tissues. However, when tested *in vitro* it was devoid of phototoxicity. In addition, histopathological examination of the eyes from dogs treated chronically with asenapine did not reveal any signs of ocular toxicity, demonstrating the absence of a phototoxic hazard. Asenapine was not genotoxic in a battery of tests. In subcutaneous carcinogenicity studies in rats and mice, no increases in tumour incidences were observed. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Asenapine did not impair fertility in rats and was not teratogenic in rat and rabbit. Embryotoxicity was found in reproduction toxicology studies using rats and rabbits. Asenapine caused mild maternal toxicity and slight retardation of foetal skeletal development. Following oral administration to pregnant rabbits during the period of organogenesis, asenapine adversely affected body weight at the high dose of 15 $mg.kg^{-1}$ twice daily. At this dose foetal body weight decreased. When asenapine was administered intravenously to pregnant rabbits, no signs of embryotoxicity were observed. In rats, embryofoetal toxicity (increased post-implantation loss, decreased foetal weights, and delayed ossification) was observed following oral or intravenous administration during organogenesis or throughout gestation. Increased neonatal mortality was observed among the offspring of female rats treated during gestation and lactation. From a cross-fostering study it was concluded that asenapine induced peri- and postnatal losses are caused by impairment of the pups rather than altered nursing behaviour of the dams.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Mannitol (E421)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Peelable aluminium/aluminium blisters in cartons of 20, 60 or 100 sublingual tablets per carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

N.V. Organon, Kloosterstraat 6, NL-5349 AB Oss, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 10 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 10 mg asenapine (as maleate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet
Round, white to off-white, sublingual tablets debossed with ”10” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sycrest is indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults

4.2 Posology and method of administration

Posology

Manic episode
The recommended starting dose of Sycrest as monotherapy is 10 mg twice daily. One dose should be taken in the morning and one dose should be taken in the evening. The dose can be reduced to 5 mg twice daily according to clinical assessment. For combination therapy a starting dose of 5 mg twice daily is recommended. Depending on the clinical response and tolerability in the individual patient, the dose can be increased to 10 mg twice daily.

Additional information on special populations

Paediatric population
The safety and efficacy of Sycrest in children aged below 18 years have not been established. Limited safety data with Sycrest are available in adolescent patients. A pharmacokinetic study was performed in adolescent patients. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Elderly patients
Sycrest should be used with care in the elderly. Limited data on efficacy in patients 65 years of age and older are available. Available pharmacokinetic data are described in section 5.2.

Renally impaired patients
No dose adjustment is required for patients with renal impairment. There is no experience with asenapine in severe renal impairment patients with a creatinine clearance less than 15 ml/min.

Hepatic impaired patients
No dose adjustment is required for patients with mild hepatic impairment. The possibility of elevated asenapine plasma levels cannot be excluded in some patients with moderate hepatic impairment (Child-Pugh B) and caution is advised. In subjects with severe hepatic impairment (Child-Pugh C), a

7-fold increase in asenapine exposure was observed. Thus, Sycrest is not recommended in patients with severe hepatic impairment.

Method of administration

The tablet should not be removed from the blister until ready to take it. Dry hands should be used when touching the tablet. The tablet should not be pushed through the tablet pack. The tablet pack should not be cut or torn. The coloured tab should be peeled back and the tablet should be removed gently. The tablet should not be crushed.

To ensure optimal absorption, the Sycrest sublingual tablet should be placed under the tongue and allowed to dissolve completely. The tablet will dissolve in saliva within seconds. Sycrest sublingual tablets should not be chewed or swallowed. Eating and drinking should be avoided for 10 minutes after administration.
When used in combination with other medication, Sycrest should be taken last.

Treatment with Sycrest is not advised in patients who are unable to comply with this method of administration, as the bioavailability of asenapine when swallowed is low (<2 % with an oral tablet formulation).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Elderly patients with dementia-related psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic substances are at an increased risk of death.
Sycrest is not approved for the treatment of patients with dementia-related psychosis and is not recommended for use in this particular group of patients.

Neuroleptic Malignant Syndrome
Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur with antipsychotics, including asenapine. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure.
If a patient develops signs and symptoms indicative of NMS Sycrest must be discontinued.

Seizures
In clinical trials, cases of seizure were occasionally reported during treatment with asenapine. Therefore, Sycrest should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Suicide
The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder and close supervision of high-risk patients should accompany treatment.

Orthostatic hypotension
Asenapine may induce orthostatic hypotension and syncope, especially early in treatment, probably reflecting its α1-adrenergic antagonist properties. Elderly patients are particularly at risk for experiencing orthostatic hypotension (see section 4.8). In clinical trials, cases of syncope were occasionally reported during treatment with Sycrest. Sycrest should be used with caution in elderly patients and in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration and hypovolemia).

Tardive dyskinesia
Medicinal products with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical, involuntary movements, predominantly of the tongue and/or face. In clinical trials, cases of tardive dyskinesia were occasionally reported during treatment with asenapine. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on Sycrest, discontinuation of treatment should be considered.

Hyperprolactinaemia
Increases in prolactin levels were observed in some patients with Sycrest. In clinical trials, there were few adverse reactions related to abnormal prolactin levels reported.

QT interval
Clinically relevant QT prolongation does not appear to be associated with asenapine. Caution should be exercised when Sycrest is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QT interval.

Hyperglycaemia and diabetes mellitus
Hyperglycaemia or exacerbation of pre-existing diabetes has occasionally been reported during treatment with asenapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia or bipolar disorder and the increasing incidence of diabetes mellitus in the general population. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic treatment. Cases of dysphagia were occasionally reported in patients treated with Sycrest.

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. From the clinical trials, it is concluded that clinically relevant body temperature dysregulation does not appear to be associated with asenapine. Appropriate care is advised when prescribing Sycrest for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant medicinal products with anticholinergic activity or being subject to dehydration.

Patients with severe hepatic impairment
Asenapine exposure is increased 7-fold in patients with severe hepatic impairment (Child-Pugh C). Therefore, Sycrest is not recommended in such patients.

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing antipsychotic medicinal products, including Sycrest, to patients with Parkinson's disease or dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary effects of asenapine on the central nervous system (CNS) (see section 4.8), caution should be used when it is taken in combination with other centrally acting medicinal products. Patients should be advised to avoid alcohol while taking Sycrest.

Potential for other medicines to affect Sycrest

Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2). The potential effects of inhibitors and an inducer of several of these enzyme pathways on asenapine pharmacokinetics were studied, specifically fluvoxamine (CYP1A2 inhibitor), paroxetine (CYP2D6 inhibitor), imipramine (CYP1A2/2C19/3A4 inhibitor), cimetidine (CYP3A4/2D6/1A2 inhibitor), carbamazepine (CYP3A4/1A2 inducer) and valproate (UGT inhibitor). Except for fluvoxamine, none of the interacting medicinal products resulted in clinically relevant alterations in asenapine pharmacokinetics.
During combined administration with a single dose of asenapine 5 mg, fluvoxamine 25 mg BID resulted in a 29 % increase in asenapine AUC. The full therapeutic dose of fluvoxamine would be expected to produce a greater increase in asenapine plasma concentrations. Therefore, co-administration of asenapine and fluvoxamine should be approached with caution.

Potential for Sycrest to affect other medicines
Because of its α1-adrenergic antagonism with potential for inducing orthostatic hypotension (see section 4.4), Sycrest may enhance the effects of certain antihypertensive agents.

Asenapine may antagonise the effect of levodopa and dopamine agonists. If this combination is deemed necessary, the lowest effective dose of each treatment should be prescribed.

In vitro studies indicate that asenapine weakly inhibits CYP2D6. Clinical drug interaction studies investigating the effects of CYP2D6 inhibition by asenapine showed the following results:

- Following co-administration of dextromethorphan and asenapine in healthy subjects, the ratio of dextrorphan/dextromethorphan (DX/DM) as a marker of CYP2D6 activity was measured. Indicative of CYP2D6 inhibition, treatment with asenapine 5 mg twice daily resulted in a fractional decrease in DX/DM ratio to 0.43. In the same study, treatment with paroxetine 20 mg daily decreased the DX/DM ratio to 0.032.

- In a separate study, co-administration of a single 75-mg dose of imipramine with a single 5-mg dose of asenapine did not affect the plasma concentrations of the metabolite desipramine (a CYP2D6 substrate).

- Co-administration of a single 20-mg dose of paroxetine (a CYP2D6 substrate and inhibitor) during treatment with 5 mg asenapine twice daily in 15 healthy male subjects resulted in an almost 2-fold increase in paroxetine exposure.

In vivo asenapine appears to be at most a weak inhibitor of CYP2D6. However, asenapine may enhance the inhibitory effects of paroxetine on its own metabolism.
Therefore, Sycrest should be co-administered cautiously with medicinal products that are both substrates and inhibitors for CYP2D6.

To ensure optimal absorption, eating and drinking should be avoided for 10 minutes after administration.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Sycrest in pregnant women. Asenapine was not teratogenic in animal studies. Maternal and embryo toxic effects were found in animal studies (see section 5.3). Sycrest should not be used during pregnancy unless clearly necessary and only if the potential benefit outweighs the potential risk to the foetus.

Breast-feeding
Asenapine was excreted in milk of rats during lactation. It is not known whether asenapine or its metabolites are excreted in human milk. It is recommended that women receiving Sycrest should not breast-feed.

Fertility
No impairment of fertility has been observed in nonclinical studies (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Asenapine may cause somnolence and sedation. Therefore, patients should be cautioned about operating machinery, including motor vehicles, until they are reasonably certain that Sycrest therapy does not affect them adversely.

4.8 Undesirable effects

The most frequently reported adverse drug reactions during treatment with asenapine were somnolence and anxiety. The incidences of the Adverse Drug Reactions (ADRs) associated with asenapine therapy are tabulated below. The table is based on adverse event reporting from clinical trials.
All ADRs are listed by system organ class and frequency; very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare
Blood and lymphatic disorders				Neutropenia
Metabolism and nutrition disorders		Weight increased Increased appetite	Hyperglycaemia	
Psychiatric disorders	Anxiety			
Nervous system disorders	Somnolence	Dystonia Akathisia Dyskinesia Parkinsonism Sedation Dizziness Dysgeusia	Syncope Seizure Extrapyramidal disorder Dysarthria	Neuroleptic malignant syndrome
Eye disorders				Accommodation disorder
Cardiac disorders			Sinus bradycardia Bundle branch block Electrocardiogram QT prolonged	
Vascular disorders			Orthostatic hypotension Hypotension	
Respiratory, thoracic and mediastinal disorders				Pulmonary embolism
Gastrointestinal disorders		Hypoaesthesia oral	Swollen tongue Dysphagia Glossodynia Paraesthesia oral	

Hepatobiliary disorders		Alanine aminotransferase increased		
Musculoskeletal and connective tissue disorders		Muscle rigidity		Rhabdomyolysis
Reproductive system and breast disorders			Sexual dysfunction Amenorrhoea	Gynaecomastia Galactorrhoea
General disorders and administration site conditions		Fatigue		

Description of selected adverse reactions

Extrapyramidal Symptoms (EPS)
In clinical trials, the incidence of extrapyramidal symptoms in asenapine-treated patients was higher than placebo (15.4 % vs 11.0 %).
From the short-term (6 weeks) schizophrenia trials there appears to be a dose-response relationship for akathisia in patients treated with asenapine, and for parkinsonism there was an increasing trend with higher doses.

Weight increase
In the combined short-term and long-term schizophrenia and bipolar mania trials, the mean change in body weight for asenapine was 0.8 kg. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) in the short-term schizophrenia trials was 5.3 % for asenapine compared to 2.3 % for placebo. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) in the short-term bipolar mania trials was 6.5 % for asenapine compared to 0.6 % for placebo.

Orthostatic hypotension
The incidence of orthostatic hypotension in elderly subjects was 4.1 % compared to 0.3 % in the combined phase 2/3 trial population.

Hepatic enzymes
Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (AST) have been seen commonly, especially in early treatment.

Other findings
Cerebrovascular events have been reported in patients treated with asenapine but there is no evidence of any excess incidence over what is expected in adults between 18 and 65 years of age.

Asenapine has anaesthetic properties. Oral hypoaesthesia and oral paraesthesia may occur directly after administration and usually resolves within 1 hour.

4.9 Overdose

Few cases of overdose were reported in the asenapine program. Reported estimated doses were between 15 and 400 mg. In most cases it was not clear if asenapine had been taken sublingually. Treatment-related adverse reactions included agitation and confusion, akathisia, orofacial dystonia, sedation, and asymptomatic ECG findings (bradycardia, supraventricular complexes, intraventricular conduction delay).
No specific information is available on the treatment of overdose with Sycrest. There is no specific antidote to Sycrest. The possibility of multiple medicinal product involvement should be considered. Cardiovascular monitoring is necessary to detect possible arrhythmias and management of overdose

should concentrate on supportive therapy, maintaining an adequate airway oxygenation and ventilation, and management of symptoms. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulations may worsen hypotension in the setting of Sycrest-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medicines should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, antipsychotics, ATC code: N05AH05

Mechanism of action
The mechanism of action of asenapine, as with other medicinal products having efficacy in bipolar disorder, is not fully understood. However, based on its receptor pharmacology, it is proposed that the efficacy of asenapine is mediated through a combination of antagonist activity at D2 and 5-HT2A receptors. Actions at other receptors e.g., 5-HT1A, 5-HT1B, 5-HT2C, 5-HT6, 5-HT7, D3, and α2-adrenergic receptors, may also contribute to the clinical effects of asenapine.

Clinical efficacy

Clinical efficacy in bipolar I disorder
The efficacy of asenapine in the treatment of a DSM-IV manic or mixed episode of bipolar I disorder with or without psychotic features was evaluated in two similarly designed 3-week, randomized, double-blind, placebo- and active controlled (olanzapine) monotherapy trials involving 488 and 489 patients, respectively. All patients met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria for bipolar I disorder, current episode manic (DSM-IV 296.4x), or mixed (DSM-IV 296.6x) and had a Young Mania Rating Scale (Y-MRS) score of ≥ 20 at screening and baseline. Patients with rapid cycling were excluded from these studies. Asenapine demonstrated superior efficacy to placebo in the reduction of manic symptoms over 3 weeks. Point estimates [95 % CI] for the change from baseline to endpoint in YMRS using LOCF analysis in the two studies were as follows:
-11.5 [-13.0, -10.0] for asenapine vs -7.8 [-10.0, -5.6] for placebo and
-10.8 [-12.3, -9.3] for asenapine vs -5.5 [-7.5, -3.5] for placebo.
A statistically significant difference between asenapine and placebo was seen as early as day 2.

Patients from the two pivotal 3 week trials were studied for a further 9 weeks an extension trial. Maintenance of effect during the episode after 12 weeks of randomised treatment was demonstrated in this trial.

In a 12-week, placebo-controlled trial involving 326 patients with a manic or mixed episode of bipolar I disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of asenapine as adjunctive therapy resulted in superior efficacy to lithium or valproate monotherapy at week 3 (point estimates [95 % CI] for the change from baseline to endpoint in YMRS using LOCF analysis-10.3 [-11.9, -8.8] for asenapine and -7.9 [-9.4, -6.4] for placebo) and at week 12 (-12.7 [-14.5, -10.9] for asenapine and -9.3 [-11.8, -7.6] for placebo) in the reduction of manic symptoms.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with asenapine in one or more subsets of the paediatric population in schizophrenia and bipolar I disorder (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Following sublingual administration, asenapine is rapidly absorbed with peak plasma concentrations occurring within 0.5 to 1.5 hours. The absolute bioavailability of sublingual asenapine at 5 mg is 35 %. The absolute bioavailability of asenapine when swallowed is low (<2 % with an oral tablet formulation). The intake of water several (2 or 5) minutes after asenapine administration resulted in decreased (19 % and 10 %, respectively) asenapine exposure. Therefore, eating and drinking should be avoided for 10 minutes after administration (see section 4.2).

Distribution
Asenapine is rapidly distributed and has a large volume of distribution (approximately 1700 l), indicating extensive extravascular distribution. Asenapine is highly bound (95 %) to plasma proteins, including albumin and α1-acid glycoprotein.

Biotransformation
Asenapine is extensively metabolized. Direct glucuronidation (mediated by UGT1A4) and cytochrome P450 (primarily CYP1A2, with contributions of 2D6 and 3A4) mediated oxidation and demethylation are the primary metabolic pathways for asenapine. In an *in vivo* study in humans with radio-labelled asenapine, the predominant drug-related entity in plasma was asenapine N^+-glucuronide; others included N-desmethylasenapine, N-desmethylasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. Sycrest activity is primarily due to the parent compound.
Asenapine is a weak inhibitor of CYP2D6. Asenapine does not cause induction of CYP1A2 or CYP3A4 activities in cultured human hepatocytes. Co-administration of asenapine with known inhibitors, inducers or substrates of these metabolic pathways has been studied in a number of drug-drug interaction studies (see section 4.5).

Elimination
Asenapine is a high clearance compound, with a clearance after intravenous administration of 52 l/h. In a mass balance study, the majority of the radioactive dose was recovered in urine (about 50 %) and faeces (about 40 %), with only a small amount excreted in faeces (5-16 %) as unchanged compound. Following an initial more rapid distribution phase, the terminal half-life of asenapine is approximately 24 h.

Linearity/non-linearity
Increasing the dose from 5 to 10 mg twice daily (a two-fold increase) results in less than linear (1.7 times) increases in both the extent of exposure and maximum concentration. The less than proportional increase of Cmax and AUC with dose may be attributed to limitations in the absorption capacity from the oral mucosa following sublingual administration.
During twice-daily dosing, steady-state is attained within 3 days. Overall, steady-state asenapine pharmacokinetics are similar to single-dose pharmacokinetics.

Pharmacokinetics in special populations

Hepatically impaired patients
The pharmacokinetics of asenapine were similar among subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in asenapine exposure was observed (see section 4.2).

Renally impaired patients
The pharmacokinetics of asenapine following a single dose of 5 mg asenapine were similar among subjects with varying degrees of renal impairment and subjects with normal renal function.
There is no experience with asenapine in severe renal impairment patients with a creatinine clearance less than 15 ml/min.

Elderly

In elderly patients (between 65 and 85 years of age), exposure to asenapine is approximately 30 % higher than in younger adults.

Paediatric population (Adolescents)
At the 5 mg twice daily dose level, asenapine pharmacokinetics in adolescent patients (12 to 17 years of age, inclusive) are similar to those observed in adults. In adolescents, the 10 mg twice daily dose did not result in increased exposure compared to 5 mg twice daily.

Gender
A population pharmacokinetic analysis indicated that there is no evidence of gender-related differences in the pharmacokinetics of asenapine.

Race
In a population pharmacokinetic analysis, no clinical relevant effects of race on the pharmacokinetics of asenapine were found.

Smoking
A population pharmacokinetic analysis indicated that smoking, which induces CYP1A2, has no effect on the clearance of asenapine. In a dedicated study, concomitant smoking during administration of a single 5 mg sublingual dose had no effect on the pharmacokinetics of asenapine.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology. Repeat-dose toxicity studies in rat and dog showed mainly dose-limiting pharmacological effects, such as sedation. Furthermore, prolactin-mediated effects on mammary glands and oestrus cycle disturbances were observed. In dogs high oral doses resulted in hepatotoxicity that was not observed after chronic intravenous administration. Asenapine has some affinity to melanin-containing tissues. However, when tested *in vitro* it was devoid of phototoxicity. In addition, histopathological examination of the eyes from dogs treated chronically with asenapine did not reveal any signs of ocular toxicity, demonstrating the absence of a phototoxic hazard. Asenapine was not genotoxic in a battery of tests. In subcutaneous carcinogenicity studies in rats and mice, no increases in tumour incidences were observed. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Asenapine did not impair fertility in rats and was not teratogenic in rat and rabbit. Embryotoxicity was found in reproduction toxicology studies using rats and rabbits. Asenapine caused mild maternal toxicity and slight retardation of foetal skeletal development. Following oral administration to pregnant rabbits during the period of organogenesis, asenapine adversely affected body weight at the high dose of 15 $mg.kg^{-1}$ twice daily. At this dose foetal body weight decreased. When asenapine was administered intravenously to pregnant rabbits, no signs of embryotoxicity were observed. In rats, embryofoetal toxicity (increased post-implantation loss, decreased foetal weights, and delayed ossification) was observed following oral or intravenous administration during organogenesis or throughout gestation. Increased neonatal mortality was observed among the offspring of female rats treated during gestation and lactation. From a cross-fostering study it was concluded that asenapine induced peri- and postnatal losses are caused by impairment of the pups rather than altered nursing behaviour of the dams.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Mannitol (E421)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Peelable aluminium/aluminium blisters in cartons of 20, 60 or 100 sublingual tablets per carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

N.V. Organon, Kloosterstraat 6, NL-5349 AB Oss, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Organon (Ireland) Ltd.
Drynam Road, Swords, Co. Dublin
Ireland

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 7 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version INT00137451 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (5 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 5 mg sublingual tablets
asenapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 5 mg asenapine (as maleate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 sublingual tablets
60 sublingual tablets
100 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Sublingual use
Peelable blister. Do not crush, chew or swallow.
Keep the tablet under your tongue until it dissolves.
Do not eat or drink for 10 minutes after taking the tablet.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
NL- 5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/001 20 sublingual tablets
EU/0/00/000/002 60 sublingual tablets
EU/0/00/000/003 100 sublingual tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

sycrest 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (5 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 5 mg sublingual tablets
asenapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (10 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 10 mg sublingual tablets
asenapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 10 mg asenapine (as maleate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 sublingual tablets
60 sublingual tablets
100 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Sublingual use
Peelable blister. Do not crush, chew or swallow.
Keep the tablet under your tongue until it dissolves.
Do not eat or drink for 10 minutes after taking the tablet.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
NL- 5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/001 20 sublingual tablets
EU/0/00/000/002 60 sublingual tablets
EU/0/00/000/003 100 sublingual tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

sycrest 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (10 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 10 mg sublingual tablets
asenapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Sycrest 5 mg sublingual tablets
Sycrest 10 mg sublingual tablets
asenapine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Sycrest is and what it is used for
2. Before you take Sycrest
3. How to take Sycrest
4. Possible side effects
5. How to store Sycrest
6. Further information

1. WHAT SYCREST IS AND WHAT IT IS USED FOR

Sycrest belongs to a group of medicines called antipsychotics and is used to treat moderate to severe manic episodes associated with bipolar I disorder. Antipsychotic medicines affect the chemicals that allow communication between nerve cells (neurotransmitters). Illnesses that affect the brain, such as bipolar I disorder, may be due to certain chemicals in the brain, such as dopamine and serotonin, being out of balance and these imbalances may cause some of the symptoms you may be experiencing. Exactly how Sycrest works is unknown, however, it is believed to adjust the balance of these chemicals.
Manic episodes associated with bipolar I disorder is a condition with symptoms such as feeling “high”, having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability.

2. BEFORE YOU TAKE SYCREST

Do not take Sycrest
If you are allergic (hypersensitive) to asenapine or any of the other ingredients (listed in section 6 Further information).

Take special care with Sycrest
Sycrest has not been studied in elderly patients with dementia. However, elderly patients with dementia, who are treated with other similar types of medicine, may have an increased risk of stroke or death. Sycrest is not approved for the treatment of elderly patients with dementia and is not recommended for use in this particular group of patients.

Sycrest may cause low blood pressure. In the early stages of treatment, some people may faint, especially when getting up from a lying or sitting position. This will usually pass on its own but if it does not, tell your doctor. Your dose may need to be adjusted.

Sycrest may cause weight gain.

Tell your doctor immediately if you experience

- involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of Sycrest may be needed.
- fever, severe muscle stiffness, sweating or a lowered level of consciousness (a disorder called "neuroleptic malignant syndrome"). Immediate medical treatment may be needed.

Check with your doctor or pharmacist before taking Sycrest:

- if you have ever been diagnosed with a condition whose symptoms include high body temperature and muscle stiffness (also known as Neuroleptic Malignant Syndrome).
- if you have ever experienced abnormal movements of the tongue or face (tardive dyskinesia). You should be aware that both of these conditions may be caused by this type of medicine.
- if you have a heart disease or a treatment for heart disease that makes you prone to low blood pressure
- if you are diabetic or prone to diabetes
- you have Parkinson's disease or dementia
- if you have epilepsy (seizures)
- if you experience any difficulty in swallowing (dysphagia)
- if you have severe liver problems. If you do, you should not take Sycrest
- if you have difficulty controlling core body temperature
- if you have thoughts of suicide

Be sure to tell your doctor if you meet any of these conditions as he/she may want to adjust your dose or monitor you for a while. Also contact your doctor immediately if any of these conditions develops or worsens while using Sycrest.

Children and adolescents
Use of Sycrest below the age of 18 years is not recommended due to lack of information on whether it is safe and effective in this age group.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Some medicines may reduce the effect of Sycrest.

If you are taking other medicines, Sycrest should be taken last.

You should tell your doctor if you are taking antidepressant medicines (specifically fluvoxamine, paroxetine or fluoxetine), as it may be necessary to change your Sycrest or antidepressant medicine dose.

You should tell your doctor if you are taking medicines for Parkinson's disease (such as levodopa), as Sycrest may make them less effective.

Since Sycrest works primarily in the brain, interference from other medicines (or alcohol) that work in the brain could occur due to an additive effect on brain function.

Since Sycrest can lower blood pressure, care should be taken when Sycrest is taken with other medicines that lower blood pressure.

Taking Sycrest with food and drink
Do not eat or drink for 10 minutes after taking the tablet.
You should avoid drinking alcohol when taking Sycrest.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Do not take Sycrest while you are pregnant, unless your doctor tells you so. If you are taking Sycrest and you become pregnant or you plan to get pregnant, ask your doctor as soon as possible whether you may continue taking Sycrest.

Do not breast-feed when taking Sycrest.

Driving and using machines
Sycrest may affect your concentration or alertness. Make sure these abilities are not affected before you drive or operate machinery.

3. HOW TO TAKE SYCREST

Always take Sycrest exactly as your doctor or pharmacist has told you. Sycrest is not advised if you are unable to take the tablet as described below.You should check with your doctor or pharmacist if you are not sure. If you are unable to take Sycrest as is described below, the treatment may not be effective for you.
The usual dose is a tablet of 5 mg or 10 mg two times a day. One dose should be taken in the morning and one dose should be taken in the evening.

Instructions for use
- Do not remove a tablet from the blister until ready to take it.
- Use dry hands when touching the tablet.
- Do not push the tablet through the blister. Do not cut or tear the blister.
- Peel back the colored tab (Figure 1).
- Gently remove the tablet (Figure 2). Do not crush the tablet.
- To ensure optimal absorption, place the tablet under the tongue and wait until it dissolves completely (Figure 3). The tablet will dissolve in saliva within seconds.
- Do not swallow or chew on the tablet.
- Do not eat or drink for 10 minutes after taking the tablet.

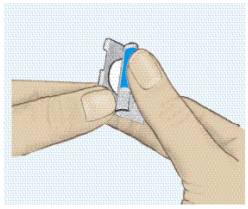
Figure 1

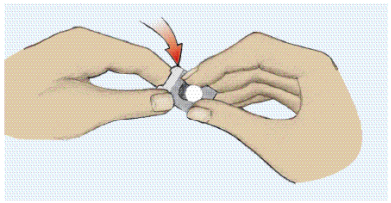
Figure 2

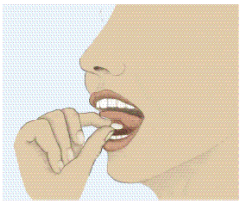
Figure 3

If you take more Sycrest than you should
If you take too much Sycrest, contact a doctor straight away. Take the medicine pack with you. In case of overdose you may feel sleepy or tired, or have abnormal body movements, problems with standing and walking, feel dizzy due to low blood pressure and feel agitated and confused.

If you forget to take Sycrest
Do not take a double dose to make up for a forgotten dose. If you miss one dose, take your next dose as usual. If you miss two or more doses, contact your doctor.

If you stop taking Sycrest
If you stop taking Sycrest, you will lose the effects of this medicine. You should not stop taking this medicine, unless your doctor tells you as your symptoms may return.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Sycrest can cause side effects, although not everybody gets them.

Very common side effects (affects more than 1 user in 10)
- anxiety
- sleepiness

Common side effects (affects 1 to 10 users in 100)
- weight gain
- increased appetite
- slow or sustained muscle contractions
- restlessness
- involuntary muscle contractions
- slow movements, tremor
- sedation
- dizziness
- change in taste
- numb feeling of the tongue or in the mouth
- muscle tightness
- fatigue
- increase in the level of liver proteins

Uncommon side effects (affects 1 to 10 users in 1,000)
- high blood sugar
- fainting episode
- convulsion
- abnormal muscle movements: a collection of symptoms known as extrapyramidal symptoms (EPS) which may include one or more of the following: abnormal movements of muscles, tongue, or jaw, slow or sustained muscle contractions, muscle spasms, tremor (shaking), abnormal movements of the eyes, involuntary muscle contractions, slow movements, or restlessness
- speech problems
- abnormal slow heartbeat
- middle heart block
- abnormal electrocardiogram (prolongation of the QT interval)
- low blood pressure upon standing
- low blood pressure
- tingling of the tongue or in the mouth
- swollen or painful tongue
- difficulty in swallowing
- sexual dysfunction
- lack of regular menstrual periods

Rare side effects (affects 1 to 10 users in 10,000)
- changes in the levels of white blood cells
- neuroleptic malignant syndrome (confusion, reduced or loss of consciousness, high fever, and severe muscle stiffness)
- difficulties in focusing with the eyes
- blood clots in blood vessels to the lungs causing chest pain and difficulty in breathing
- muscle disease presenting as unexplained aches and pains
- male breast enlargement
- leakage of milk or fluid from the breast

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE SYCREST

Keep out of the reach and sight of children.

Do not use Sycrest after the expiry date which is stated on the blister and on the carton. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.

This medicinal product does not require any special temperature storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Sycrest contains
- The active substance is asenapine. Each Sycrest tablet contains either 5 mg or 10 mg of the active substance. The exact amount is shown on your Sycrest tablet pack.
- The other ingredients are gelatin and mannitol (E421).

What Sycrest looks like and contents of the pack
The 5 mg sublingual tablets are round white to off-white tablets marked with "5" on one side.
The 10 mg sublingual tablets are round white to off-white tablets marked with "10" on one side.

The sublingual tablets are provided in peelable blisters containing 10 tablets each. Packs may contain 20, 60 or 100 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
N.V. Organon
Kloosterstraat 6
NL-5349 AB Oss
The Netherlands

Manufacturer
Organon (Ireland) Ltd.
Drynam Road, Swords
Co. Dublin, Ireland

This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

TABLE SHELLS

Table 1

Rate Ratios of Health Outcomes of Interest by Diagnostic Category*

	Risk Period N = xxxxx		Comparison Period N = xxxxx			
Health Outcome of Interest	n / person-years	Incidence per person-year	n / person-years	Incidence per person-year	Rate Ratio (95% CI)†	FDR-adjusted p-value‡
Cardiovascular diseases						
Myocardial infarction	x / xxxx	x.x	x / xxxx	x.x	x.x (x.x - x.x)	x.xx
Acute angina pectoris	x / xxxx	x.x	x / xxxx	x.x	x.x (x.x - x.x)	x.xx
Cardiac failure	x / xxxx	x.x	x / xxxx	x.x	x.x (x.x - x.x)	x.xx

* Similar table will be generated for different settings (e.g. ER, outpatient) and strata (e.g. length of exposure).
† Confidence intervals calculated using the mid-probability exact method.
‡ FDR-adjusted p-value provided only for significantly elevated relative risks (i.e., lower bound of the 95% confidence interval of the relative risk >1) to partially adjust for multiple comparisons.