Part VI: Summary of the risk management plan

Summary of risk management plan for EQUASYM (Methylphenidate Hydrochloride)

This is a summary of the risk management plan (RMP) for EQUASYM/QUASYM (henceforth referred to as EQUASYM). The RMP details important risks of EQUASYM, how these risks can be minimised, and how more information will be obtained about EQUASYM's risks and uncertainties (missing information).

EQUASYM's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how EQUASYM should be used.

Important new concerns or changes to the current ones will be included in updates of EQUASYM's RMP.

I. The medicine and what it is used for

EQUASYM is authorized for as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient (see SmPC for the full indication). It contains methylphenidate hydrochloride as the active substance, and it is given by oral route of administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of EQUASYM, together with measures to minimise such risks and the proposed studies for learning more about EQUASYM 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of EQUASYM, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of EQUASYM is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of EQUASYM are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of EQUASYM. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been

established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Serious cardiovascular events • Reduced weight gain • Decreased rate of growth • Psychosis/mania • Depression • Aggression • Drug abuse/drug dependence • Seizures • Verbal or Motor Tics • Withdrawal syndrome • Cerebrovascular disorders
Important potential risks	• Suicidality • Sexual maturation delayed
Missing information	• Long-term effects

II.B Summary of important risks

Important Identified Risk: Serious cardiovascular events	
Evidence for linking the risk to the medicine	PRAC recommendation following the final assessment report for the methylphenidate periodic benefit risk evaluation report (June 2019).
Risk factors and risk groups	Bradycardia Most cases of SA node dysfunction are due to idiopathic degeneration or are secondary to pharmacologic agents. Sinus bradycardia is often found. in the elderly as an isolated phenomenon. Specific diseases associated with SA node dysfunction include senile amyloidosis and other conditions associated with infiltration of the atrial myocardium. Sinus bradycardia is associated with hypothyroidism, advanced liver disease, hypothermia, typhoid fever, and brucellosis; it occurs during episodes of vasovagal syncope, severe hypoxia, hypercapnia, acidemia, and acute hypertension [101]. Atrioventricular block may be caused by myocardial infarction (particularly inferior coronary infarcts); coronary

Important Identified Risk: Serious cardiovascular events	
	spasm (usually of the right coronary artery); digoxin, beta, and/or calcium blockers; acute infections such as viral myocarditis, acute rheumatic fever, and infectious mononucleosis; and miscellaneous disorders such as Lyme's disease, sarcoidosis, amyloidosis, and neoplasms, particularly cardiac mesotheliomas. It may also be congenital [101]. Tachycardia Sinus tachycardia is a physiological response to fever, volume depletion, anxiety, exercise, thyrotoxicosis, hypoxemia, hypotension, or congestive heart failure [101]. Atrial fibrillation and atrial flutter can occur due to rheumatic heart disease, nonrheumatic mitral valve disease, hypertensive cardiovascular disease, chronic lung disease, thyrotoxicosis, atrial septal defect, and a variety of miscellaneous cardiac abnormalities [101]. Ventricular tachycardia generally accompanies some form of structural defect like a prior myocardial infarction, surgery, or congenital septal defect. The annual incidence of cardiomyopathy is higher in boys than in girls (0.66 versus 0.47 cases per 100,000), in Blacks than in Whites (0.98 versus 0.46 cases per 100,000), and in infants (less than 1 year of age) than in children (8.34 versus 0.70 cases per 100,000). The majority of children (66%) have idiopathic disease. The most common, known causes are myocarditis (46%) and neuromuscular disease 26% [102]. In adults, hypertrophic cardiomyopathy is a relatively common genetic cardiac disease (1:500 in the general population), caused by a mutation in some of the genes in heart muscle proteins. Hypertrophic cardiomyopathy also can develop over time because of high blood pressure or aging. Other diseases, such as diabetes or thyroid disease, also can cause hypertrophic cardiomyopathy [103]. Risk factors for LQTS that have been identified in children include female gender, age, prior syncopal history, QT-interval duration, and genetic/familial factors [104]. Most research in this area has focused upon the risk factors for serious cardiac events following diagnosis of LQTS. The most common underlying cause of SCD in those up to 30 years of age includes myocarditis, hypertrophic cardiomyopathy, coronary artery disease, congenital coronary artery abnormalities, conduction-system abnormalities, drug abuse, mitral valve prolapse, and aortic dissection, with, again, a higher risk in those with familial history of SCD [105]. Sudden cardiac death is

Important Identified Risk: Serious cardiovascular events	
	more common in males, in African Americans and during the winter months.
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.3, 4.4, 4.5 and 4.8 of the SmPC Sections 2, 3 and 4 of the PIL Prescription only medicine **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	Attention-Deficit Hyperactivity Drugs Use Chronic Effects (ADDUCE) studies.

Important Identified Risk: Reduced weight gain	
Evidence for linking the risk to the medicine	Reduced weight gain is listed as an identified risk of MPH treatment in accordance with the PRAC recommendation (June 2019).
Risk factors and risk groups	Attention-deficit hyperactivity disorder (ADHD) has been found to co- occur frequently with obesity. The prevalence of overweight/obesity observed in ADHD patients was significantly higher than that in the general population, although the reasons for this association are unknown [110]. In a longitudinal study of girls with ADHD, those who developed an eating disorder had significantly higher lifetime prevalence of major depression (95% versus 69%), anxiety disorders (80% versus 53%), and disruptive behavior disorder (85% versus 53%) than those without an eating disorder [12].
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4 and 4.8. Sections 3 and 4 of the PIL Prescription only medicine **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	Attention-Deficit Hyperactivity Drugs Use Chronic Effects (ADDUCE) studies.

Important Identified Risk: Decreased Rate of Growth	
Evidence for linking the risk to the medicine	Decreased rate of growth is listed as an identified risk of MPH treatment in accordance with the PRAC recommendation (June 2019).
Risk factors and risk groups	Factors that restrict final height and weight attained include nutrition, infection (diarrhoea, respiratory tract infections, intestinal parasitic infestations, malaria, HIV infection, schistosomiasis, *Cryptosporidium parvum* infection, and *Helicobacter pylori* infection), psychosocial stress, food contaminants and pollutants (e.g., lead and polychlorinated biphenyls and aflatoxins) and chondrodysplasia. Behavioral toxicants include the use of alcohol, cigarettes, and narcotics. These and hypoxia can affect birth weight. Many of these factors are conditioned by poverty and socioeconomic status [112]. Deficiencies of energy, protein, and zinc have been implicated in growth faltering, while diets high in fat are associated with weight gain and obesity.
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.2, 4.4 and 4.8 of the SmPC Sections 3 and 4 of the PIL Prescription only medicine. **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	Attention-Deficit Hyperactivity Drugs Use Chronic Effects (ADDUCE) studies.

Important Identified Risk: Psychosis/Mania	
Evidence for linking the risk to the medicine	Psychosis/mania is listed as an identified risk of MPH treatment in accordance with the CHMP request (03 Dec 2008); also listed as an identified risk in accordance with the PRAC recommendation (June 2019).
Risk factors and risk groups	Several studies suggest a genetic linkage and current research is focused on the identification of the specific genes responsible for psychotic traits in the general population [115] [116] [117]. Schizophrenia is present in approximately 6.6% of all first- degree relatives of an affected individual; if both parents are affected with the disorder, the risk for offspring is 40%. The concordance rate for monozygotic twins is 50% and 10% for dizygotic twins [118]. There are other studies, however, that suggest an environmental link, associating an urban atmosphere with the development of these disorders.

Important Identified Risk: Psychosis/Mania	
	Furthermore, some researchers propose a gene-environment interaction that may raise the risk for psychotic disorders [116] [119]. These theories are grounded in the increased incidence of psychotic disorders in urban environments. For example, 30%–40% of the homeless, who typically reside in urban areas, have symptoms suggestive of psychotic disorders; however, untreated psychosis is a cause of the dysfunctions that leads to homelessness, not just a consequence of it. Drug use, which is also more common in urban areas, is also a risk factor for psychoses [120,121]. Other risk factors for schizophrenia include a winter birth and increasing parental age [122,123]. In the Massachusetts General Hospital study, children with ADHD and comorbid mania at either the baseline or the follow-up assessment had other clinical predictors expected in the disorder. These correlates included other psychopathology, psychiatric hospitalization, severely impaired psychosocial functioning, and a family history of mood disorders [96].
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.2, 4.3, 4.4, and 4.8 of the SmPC. Sections 2 and 4 of the PIL Prescription only medicine. **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	None

Important Identified Risk: Depression	
Evidence for linking the risk to the medicine	Depression is listed as an identified risk of MPH treatment in accordance with the PRAC recommendation (June 2019).
Risk factors and risk groups	Identified risk factors for depression in adolescents (most often defined as 14-19 years of age) include female gender, family history of depressive episodes, conflict with parents, and elevated symptoms of borderline personality disorder [125].
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.2, 4.3, 4.4, and 4.8 of the SmPC.

Important Identified Risk: Depression	
	Sections 2, 4 and 7 of the PIL Prescription only medicine **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	None

Important Identified Risk: Aggression	
Evidence for linking the risk to the medicine	Aggression is listed as an identified risk of MPH treatment in accordance with the PRAC recommendation (June 2019).
Risk factors and risk groups	Gender is the most common biological component in aggression modeling. In a randomized sample of 722 first graders followed over 2 years, growth mixture modeling showed 3 classes of children with similar developmental trajectories of aggression [130]. Boys were 17.8 times more likely to reside in the most aggressive early-onset group than the other 2 less aggressive categories [130]. In an Australian cross-sectional population study, males were 1.87 times more likely to be diagnosed as aggressive [131]. In a cluster analysis of 406 children, 10% of boys demonstrated physical violence compared to 5.3% of girls [132]. In an Australian population study of toddlers, children, and teens, impulsive-hyperactive ADHD children were 12.63 more likely to be scored as aggressive; inattentive and combination ADHD children were likely to be scored as delinquent or with CD (2.71 and 4.00 and 3.21 and 2.91, respectively) [131].
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.4 and 4.8 of the SmPC. Sections 2 and 4 of the PIL Prescription only medicine. **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	None

Important Identified Risk: Drug Abuse/ Drug Dependence	
Evidence for linking the risk to the medicine	Drug abuse and drug dependence are listed as an identified risk of MPH treatment in accordance with the PRAC recommendation (2019).
Risk factors and risk groups	Identified risk factors for substance abuse in adolescents and young adults include living in poverty, ineffective parenting, having a caregiver who abuses drugs, poor classroom behavior or social skills, academic failure, and association with drug-abusing peers (US National Institute on Drug Abuse 2003).
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.2, and 4.4 of the SmPC. Sections 2, 3 and 4 of the PIL Prescription only medicine. **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	None

Important Identified Risk: Seizures	
Evidence for linking the risk to the medicine	Seizures is listed as an identified risk of MPH treatment in accordance with the PRAC recommendation (June 2019).
Risk factors and risk groups	There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizure, in patients with prior electroencephalogram abnormalities in the absence of seizures, and very rarely, in patients without a history of seizures and no prior electroencephalogram evidence of seizures.
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.4, and 4.8 of the SmPC. Sections 2 and 4 of the PIL Prescription only medicine **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	None.

Important Identified Risk: Verbal or Motor Tics	
Evidence for linking the risk to the medicine	Tics/Tourette's syndrome/dystonias are listed as a potential risk of MPH treatment in accordance with the CHMP request (03 Dec 2008); Verbal or Motor Tics listed as an identified risk in accordance with PRAC recommendation (June 2019).
Risk factors and risk groups	Tics/Tourette's syndrome is 4 times more frequent in males than in females[149] [150]. Support for a genetic association is provided by studies of monozygotic twins, which show an 86% concordance rate for chronic tic disorder compared with 20% in dizygotic twins [151]. Abrupt exacerbation of symptoms at about the same time as a streptococcal infection has led to the identifying label of PANDAS associated with streptococcal infection. Support for PANDAS is derived from the description of additional cohorts, familial studies showing that first-degree relatives of children with PANDAS have higher rates of tic disorders than do those in the general population.
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.4, and 4.8 of the SmPC. Sections 2 and 4 of the PIL Prescription only medicine **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	None

Important Identified Risk: Cerebrovascular Disorders	
Evidence for linking the risk to the medicine	Cerebrovascular disorder is listed as an identified risk of MPH treatment in accordance with the PRAC request (2019).
Risk factors and risk groups	Identified risk factors for stroke in children include gender, race (African Americans) found to be at increased risk; [146] hypertension, diabetes, cardiac disease, sickle cell anaemia and asymptomatic cerebrovascular disease [147].
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.3, 4.4, and 4.8 of the SmPC. Sections 2 and 4 of the PIL

	Prescription only medicine. **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	None

Important Identified Risk: Withdrawal Syndrome	
Evidence for linking the risk to the medicine	Withdrawal syndrome is listed as an identified risk of MPH treatment in accordance with the PRAC recommendation (June 2019).
Risk factors and risk groups	This section is not applicable since the background risk is undefined.
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.4 of the SmPC. Section 7 of the PIL Prescription only medicine **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	None

Important Potential Risk: Suicidality	
Evidence for linking the risk to the medicine	Suicidality is listed as a potential risk of MPH treatment in accordance with the CHMP request (03 Dec 2008); also listed as a potential risk in accordance with the PRAC recommendation (June 2019).
Risk factors and risk groups	Suicidal ideation is a risk factor for suicide attempt and completed suicide. Mental disorders are the most common risk factors for suicide in all age groups. A review of studies of completed suicides estimated that 30.2% of cases were associated with mood disorders, 17.6% with substance-related disorders, 14.1% with schizophrenia, 13.0% with personality disorders, and 16.7% with other disorders; only 2.0% of cases had no associated mental disorders [153]. A study from the National Violent Death Reporting System in the US found a diagnosis of depression in 34.7% of non-Hispanic Whites, 21.6% of non-Hispanic Blacks, 15.6% of Hispanics, and 24.2% of

	other race/ethnic groups [154]. This study, which used reports from family and friends as the primary source of diagnosis information, found a lower prevalence (42.1%) of any mental disorder among suicide victims than the review [153] [154]. An investigation of suicidal ideation and suicide attempts among youth ages 9-17 years obtained a hazard ratio for depression of 8.5 (95% CI: 4.5–15.9) [155]. This study found that alcohol abuse or dependence was highly predictive of suicide attempts (OR: 25.2; 95% CI: 4.6–129.2). Daily use of cigarettes also predicted suicide attempts (OR: 5.0; 95% CI: 1.2-19.4) [155]. By contrast, in a survey from Israel, alcohol abuse was the least predictive of a range of DSM-IV disorders identified as risk factors for the first onset of suicidal behaviors (ORs [95% CI] of 2.0 [1.0–4.2], 4.8 [2.0–11.7], 6.0 [2.2–16.6]) for suicidal ideation, suicide planning or suicide attempt respectively [156]. In this larger study bipolar disorder was most strongly associated with an increased risk of suicidal behaviours (ORs [95% CI] of 13.4 [5.0-36.0], 22.8 [6.2-84.2] and 43.0 [13.0–141.8] for ideation, planning and attempt, respectively), followed by PTSD (ORs [95% CI] of 6.5 [3.3-12.5], 10.0 [4.0–24.7], 16.6 [7.0-39.1]). Among persons with ADHD, CD is another common comorbidity and has been shown to be associated with elevated risk of suicidal behavior. A 15-year follow-up study of children with hyperactivity found those with persistent antisocial behavior to have greater risk of a suicide attempt (31.5% versus 0%, p=0.02) [51]. A case-control study of children with disruptive disorders (ADHD and/or CD) found suicide victims to have a higher prevalence of CD than controls (OR: 2.9; 95% CI: 1.0–8.8). The same study also found family history of mood disorders (OR: 2.3; 95% CI: 1.0–5.5) and substance abuse (OR: 7.4; 95% CI: 1.7-31.4) to be associated with suicide [157]. Amphetamines are among the most commonly prescribed medications to manage ADHD [56]. Three comprehensive reviews of the safety of ADHD pharmacotherapies [57] [58] [59] suggest that ADHD itself is a risk factor for suicide-related events. Impulsive suicidality is observed in children and adolescents with ADHD; however, suicide-related events appear to be rarely reported in association with ADHD pharmacotherapy. A large retrospective cohort study comparing pediatric patients 5 to 18 years age in the US from 2002 to 2006 treated with atomoxetine versus stimulants found no difference in the incidence of suicidal events either with first-line (HR=0.95; 95% CI:0.47-1.92) or second-line (HR=0.71; 95%CI: 0.30-1.67) treatment [60]. After considering the relationship between atomoxetine therapy

	and suicidality, Graham and colleagues (2011) found little or no compelling evidence to suggest that the observed rate of suicide-related events in children treated with ADHD drugs was greater than the expected (background) rate in the general population; an expert opinion reaffirmed by van de Loo-Neus and colleagues [59]. However, as Graham and colleagues [58] prudently point out, patients treated with ADHD drugs should be observed for the emergence of suicide-related events. In a register based longitudinal study in Sweden using within patient design, Chen et al. [61] found that treatment with ADHD drugs seemed to be associated with an increased rate of suicide-related events at the population level. However, these associations were not evident in within patient comparisons. Among those treated with stimulants for ADHD, a reduced rate of suicide-related events (suicide attempt and completed suicide) was seen during treatment periods as compared to non-treatment period. The hazard ratio was 0.81, (95% CI=0.70 to 0.94). Taken together, it suggests that ADHD is associated with a higher risk of suicide-related events, but treatment with stimulants reduced such risk [61]. A self-controlled case-series study conducted with individuals 6 to 25 years of age in Hong Kong from 2001 to 2015 found no difference in the risk of suicide attempt when the risk during the first 90 days of treatment was compared with the 90 days preceding first treatment (IRR=0.78; 95%CI: 0.26-2.35) [158].
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.3, 4.4, and 4.8 of the SmPC. Section 4 of the PIL Prescription only medicine **Additional risk minimisation measures:** Physician's guide to prescribing
Additional pharmacovigilance activities	None

Important Potential Risk: Sexual Maturation Delayed	
Evidence for linking the risk to the medicine	Sexual maturation delayed is listed as a potential risk of MPH treatment in accordance with the CHMP request (03 Dec 2008).
Risk factors and risk groups	Various disorders, such as diabetes mellitus, inflammatory bowel disease, kidney disease, cystic fibrosis, and anaemia, can delay or prevent sexual development. Development may be delayed in adolescents receiving

	radiation therapy or cancer chemotherapy. Adolescents, particularly girls, who lose body weight because of excessive exercise and/or dieting, may have delayed sexual maturation, including an absence of menstruation [161]. Hauspie et al. [162] demonstrated that the onset of pubertal growth spurt in young males with asthma was delayed on average by about 0.75 years and the development of pubic hair by about 2 years [163]. A chronic delay in growth and puberty occurs in asthmatic boys with a prevalence of more than 30% [127]. In children with Type 1 diabetes, retardation in physical growth and pubertal development is positively correlated with the duration of diabetes before the onset of puberty, glycated haemoglobin and is associated with the conventional insulin therapy [128]. Selevan et al. [164], analyzed the relations between blood lead concentration and pubertal development using the data from the third National Health and Nutrition Examination Survey and found blood lead concentrations of 3 µg/dL were associated with significant delays in breast and pubic hair development in African-American and Mexican-American girls. The delays were most marked among African-American girls. In white girls, there were nonsignificant delays in all pubertal measures in association with a lead concentration of 3 µg/dL [164].
Risk minimisation measures	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Attention-Deficit Hyperactivity Drugs Use Chronic Effects (ADDUCE) studies.

Missing Information: Long-term effects	
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.2, and 4.4 of the SmPC. Section 3 of the PIL **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Attention-Deficit Hyperactivity Drugs Use Chronic Effects (ADDUCE) studies.

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of EQUASYM.

II.C.2. Other studies in post-authorisation development plan

Other Studies in the Post-Authorisation Development Plan

Study name	Purpose of the study
ADDUCE Study	To address the long-term safety (cardiovascular, cerebrovascular, and psychiatric effects) of MPH. The study's aim objective includes addressing scientific questions about prevalence, clinical significance, development and moderating and/or mediating factors of 4 specific classes of long-term adverse effects of MPH: growth, neurological, psychiatric and cardiovascular.