7.2 Part VI.2 Elements for a Public Summary

7.2.1 Part VI.2.1 Overview of disease epidemiology

Opioid dependence, often characterized as a chronic relapsing disorder, affects millions of people worldwide (Tkacz, Severt, Cacciola, & Ruetsch, 2012). There were 15.5 million opioid-dependent people globally in 2010. Males were more often affected than females, and peaked at 25-29 years. The proportion of a population found to be opioid dependent was higher in Australasia, western Europe and North America than in the rest of world (global pooled prevalence). Opioid dependence was estimated to account for 9.2 million DALYs (the number of years lost due to ill-health, disability or early death) globally (0.37% of global DALYs) in 2010, a 73% increase on DALYs estimated in 1990. Regions with the highest opioid dependence DALY rates were North America (292.1 per 100 000), eastern Europe (288.4 per 100 000), Australasia (278.6 per 100 000) and southern sub-Saharan Africa (263.5 per 100 000). The contribution of YLLs (Years of potential Life Lost) to opioid dependence burden was particularly high in North America, eastern Europe and southern sub-Saharan Africa. Opioid dependence is a substantial contributor to the global disease burden; its contribution to premature mortality varies geographically, with North America, eastern Europe and southern sub-Saharan Africa most strongly affected (Degenhardt et al., 2014).

7.2.2 Part VI.2.2 Summary of treatment benefits

There is an excellent evidence base supporting the efficacy of methadone and buprenorphine or the combination of buprenorphine and naloxone for the treatment of opioid withdrawal, with clonidine and lofexidine as secondary or adjunctive medications. Opioid maintenance with methadone and buprenorphine is the best-studied and most effective treatment for opioid dependence, with heroin and naltrexone as second-line medications (Soyka et al., 2011). Buprenorphine is a safe and effective treatment for opioid dependence, and has very low potential for abuse (Collins & McAllister, 2007).

7.2.3 Part VI.2.3 Unknowns relating to treatment benefits

There are limited data on the use of buprenorphine 0.4 mg, 2 mg, 8 mg, sublingual tablets in pregnant and lactating women. Buprenorphine should not be used in children less than 2 years of age or in children weighing less than 16 kg. No data are available in children less than 15 years of age; therefore, buprenorphine should not be used in children under the age of 15. Buprenorphine should be used only with particular caution in elderly and debilitated patients.

7.2.4 Part VI.2.4 Summary of safety concerns

Table 5-5 Important identified risks

Risk	What is known	Preventability
Increase in dose causing death (severe breathing failure due to increase in dose) and use in patients with alcohol intake/ delirium tremens (a state of confusion of rapid onset that is usually caused by withdrawal from alcohol) [Fatal overdose: Severe respiratory failure (mechanism for death by overdose) and use in	Alcohol increases the sedative (sleep inducing effect) effect of buprenorphine. Some cases of death due to breathing failure have been reported, particularly when used in combination with acting substances or when buprenorphine was not used according to labelling. Massive serious poisoning can	Buprenorphine is not meant to be used in patients with severe respiratory insufficiency (difficulty in breathing) and should be used only under close monitoring and with particular caution. The patient must be informed on the possible deadly risk of combining centrally acting depressants like alcohol, illegal opiates, benzodiazepines,

Risk	What is known	Preventability
patients with alcoholism/delirium tremens]	induce breathing arrest, circulatory failure heart arrest and result in death. The patient must be informed on the possible risks of i.v. misuse which leads to breathing arrest.	hypnotics with buprenorphine. In case of overdose, the heart and breathing status of the patient must be closely monitored and appropriate supportive measures should be initiated. The doctor should be informed if the patient experience reduced breathing function such as asthma.
Abuse (injection/intranasal), misuse and diversion	Abuse of the medicinal product buprenorphine for doping purposes can risk the health. Buprenorphine should be used only with particular caution in acute alcoholism or delirium tremens (a state of confusion of rapid onset that is usually caused by withdrawal from alcohol). It has been demonstrated in studies in humans and animals that buprenorphine has a lower dependency possible than pure opioid agonists. Minor euphoric (feelings of well-being) effects of buprenorphine have been observed in humans. This could result in abuse of the substance to some extent. Prolonged use of buprenorphine can result in development of physical dependence. Diversion of buprenorphine has been reported. Diversion refers to the introduction of buprenorphine into the illicit market either by patients or by individuals who obtain the medicinal product through theft from patients or pharmacies. This diversion may lead to new addicts using buprenorphine as the primary drug of abuse, with the risks of overdose, spread of blood borne viral infections and respiratory depression.	Buprenorphine is not meant to be used in patients who are opioid-dependent, for drug-substitution treatment and known or suspected history of drug abuse. The doctor should consider the risk of abuse misuse and diversion. The dose of buprenorphine should be increased progressively according to the clinical effect of the individual patient. Depending upon the findings of liver injuries, the medicinal product may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to drug addiction. The doctor should be consulted for advice on adequate treatment for problems like depression, anxiety or inability to sleep.

Risk	What is known	Preventability
	The patient must be informed on the possible risks of i.v. misuse: breathing arrest, shock, thrombophlebitis (vein inflammation relate to blood clot), embolism (obstruction in a blood vessel due to a blood clot), endocarditis (infection of the inner lining of heart), infection, liver damage. Serious cases of acute liver injury have been reported in the context of misuse, especially by intravenous route. Some users died from breathing failure after misusing buprenorphine or combining it with brain acting substances, such as: • alcohol • medicines which calm, induce sleep or relax muscles with active substance names ending with “azepam”, such as diazepam, temazepam • other opioids	
Inflammation of liver, liver events, use in patients in liver failure (Hepatitis, hepatic events, use in patients with hepatic failure)	Buprenorphine is metabolised in the liver. The degree and duration of its effects in patients with abnormal liver function may therefore be altered. Serious cases of acute liver injury have been reported in a context of misuse, especially by intravenous route. The symptoms include severe tiredness, itching and yellow skin or eyes.	Buprenorphine is not meant to be used in patients with liver failure. Liver function test is recommended prior to start therapy to rule out any liver disease and regular monitoring of liver function is advised. It is advised to appropriately adjust the dose of buprenorphine in this patient group. Depending upon the findings of liver injuries, the medicinal product may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to drug addiction. The doctor should be consulted if patient experience symptoms

Risk	What is known	Preventability
		of liver problem.
Drug dependence and drug Withdrawal Syndrome	Prolonged use of buprenorphine can result in development of physical dependence. Withdrawal symptoms (abstinence syndrome) are mild, start after 2 days and may persist for up to 2 weeks. Withdrawal symptoms include excitation, anxiety states, nervousness, inability to sleep, muscle contraction, involuntary shaking of the body or limbs (tremor) and digestive tract complaints. Before starting buprenorphine therapy, the dose of methadone should be reduced to a maximum of 30 mg/day. Buprenorphine may increase symptoms of withdrawal in patients dependent upon methadone, therefore buprenorphine should not be administered less than 24 hours after the last dose of methadone.	To avoid unexpected withdrawal, treatment with buprenorphine should be started with initial dose of 0.8 mg to 4 mg, administered as a single daily dose. The dose should not be stopped as it will lead to withdrawal symptoms. The dose of buprenorphine should be increased progressively according to the clinical effect of the individual patient by the doctor. The majority of patients will not require doses exceeding 16 mg/day. Buprenorphine should not be used in patients taking naltrexon.
Use during Pregnancy, and lactation (effects on newborn and infant)	There are insufficient data on the use of buprenorphine during pregnancy and the lactation period. The administration of high doses of buprenorphine towards the end of pregnancy, even if only over the short term, may induce respiratory depression (breathing problem) in the new born. Chronic use of buprenorphine during the final trimester of pregnancy may be responsible for withdrawal symptoms in newborn.	Buprenorphine is not recommended for use during pregnancy. Buprenorphine is not recommended during pregnancy. Tell your doctor before taking buprenorphine if you are pregnant, trying or become pregnant during treatment Breast-feeding should be discontinued during treatment with buprenorphine.
CNS depression (effects on driving ability)	Some users died from breathing failure after misusing buprenorphine or combining it with brain acting substances, such as: • alcohol • medicines which calm, induce sleep or relax muscles with active substance names ending with “azepam”, such as diazepam, temazepam	Buprenorphine should be used only under close monitoring and with particular caution. The patient must be informed on the possible deadly risk of combining centrally acting depressants like alcohol, illegal opiates, benzodiazepines, hypnotics with buprenorphine.

Risk	What is known	Preventability
	• other opioids Buprenorphine may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants.	Patients should be warned on the risk of driving or operating machinery. The doctor should be informed by the patient of any breathing problems or any other history of alcohol and medication.
Allergic reactions	Buprenorphine is not meant to be used in patients who are allergic to any of the composition of the medicinal product.	Buprenorphine is not meant to be used in patients who are allergic to medication, pain killers (centrally acting) or to any of the composition of the medicinal product. The doctor should be informed if the patient is on any other medication.
Hypotension (fall in blood pressure)	Buprenorphine can cause fall in blood pressure when standing up quickly. Massive serious poisoning can induce breathing arrest, circulatory failure heart arrest and result in death.	The doctor has to be informed by the patient if he has low blood pressure. Buprenorphine should be used with caution in patients having low blood pressure.
A group of problems that occur in a newborn who was exposed to addictive opiate drugs while in the mother's womb. (Neonatal Abstinence Syndrome)	In humans, there is currently not sufficient data to evaluate harmful effects of buprenorphine on the newborn baby when administered during pregnancy. At the end of pregnancy, high doses, even for a short duration of time, may induce breathing problem (respiratory depression) in neonates (newborn baby). During the last three months of pregnancy, prolonged use of buprenorphine may be responsible for a withdrawal syndrome in neonates.	The use of buprenorphine is not recommended during second and third trimester of pregnancy
Use in patients with head injury and increased intracranial pressure (the pressure of the fluid in the space between the skull and the brain)	Buprenorphine should be used with extra care in patients having head injury and increased cranial pressure (increase in pressure around the brain).	The doctor should be informed if the patient had any head injury before treatment.