VI.2.1 Overview of disease epidemiology

The United Nations Office on Drugs and Crime (UNODC) estimates that there are 25 million problem drug users all over the world, of whom 15.6 million are problem opioid users and 11.1 million problem heroin users (approximately 0.3% of the global population) **(***WHO***,** *2009***)**

According to the "Österreichische Gesellschaft für Arzneimittelgestützte Behandlung von Suchtkranken (ÖGABS)" around 30.000 persons in Austria are estimated to show "problematic" opioid consumption practices (***ÖGABS***, ***2012***).

VI.2.2 Summary of treatment benefits

This Medicine is used to treat dependence on opioid (narcotic) drugs such as heroin or morphine in drug addicts who have agreed to be treated for their addiction.
Maintenance therapy is one of the most effective types of pharmacological therapy of opioid dependence. There is consistent evidence from numerous controlled trials, large longitudinal studies and pr ogram evaluations, that maintenance treatment of opioid dependence is generally associated with substantial reductions in illicit opioid use, criminal activity, deaths due to overdose, and behaviour with a high risk of HIV transmission (***World Health Organization et al.***, ***2004)***.
Buprenorphine is used in the treatment of opioid dependence. It has a lower potential for dependence and a lower risk of respiratory depression in overdose than other drugs used for the treatment of opioid dependence. Buprenorphine can be used as substitution therapy in patients with moderate opioid dependence for the acute management of withdrawal and in maintenance treatment as an alternative to methadone.
Naloxone is included in opioid formulations used for the treatment of opioid dependence in order to reduce the potential for parenteral abuse (injecting into blood vessels), or to counteract opioid-induced constipation.
Medicines with the active substance combination buprenorphine+naloxone have a w ell established use in the treatment of opioid dependence. The originator product (Suboxone®/Indivior) has been available in Europe and many other countries since 2006. In 2002, the US FDA approved two sublingual formulations of a buprenorphine fixed-combination product with naloxone for the treatment of opioid addiction. Therefore the safety profile of buprenorphine in combination with naloxone is well known.

VI.2.3 Unknowns relating to treatment benefits

The safety and beneficial effect has not been studied in children below the age of 15 years.
The safety and beneficial effect has not been studied in elderly patients above the age of 65 years. There are not enough data available to evaluate harmful effects of combined buprenorphine and naloxone during pregnancy. There are not enough data available to evaluate harmful effects of combined buprenorphine and naloxone in patients with liver or kidney impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Fatal overdose - Severe respiratory failure (mechanism for death by overdose) - Use in patients with alcoholism/delirium tremens	Opioids like buprenorphine or naloxone (the active substances combined in this medicine) can have negative effects on respiration. This is usually associated with overdose and in combination with other medicines that have an effect on respiration (e.g. alcohol or tranquilisers like benzodiazepines). The main sign of opioid overdose is disturbed breathing (respiratory depression), which could even lead to breathing arrest and death. There have been isolated reports of fatal outcomes.	Risk factors for respiratory depression are overdose and the use of other drugs (e.g. alcohol or benzodiazepines), Patients with underlying diseases affecting respiration should be monitored closely. Patients suffering from alcoholism and/or delirium tremens must not take this medicine.
Misuse and/or abuse (injection/intranasal/pediatric use) (injecting buprenorphine in blood vessels/intentionally taking to much buprenorphine)	Opioids like buprenorphine or naloxone (the active substances combined in this medicine), have the potential to be abused (e.g. injected into blood vessels or sniffed) or misused (e.g. intake of high single doses). The potential for such actions is lower compared to other opioid drugs. Dissolution and injection of the tablets may lead to severe side effects with possible fatal course (breathing problems, severe liver damage) and to severe reactions or infections at the injection site.	Prescription of buprenorphine/naloxone should be carried out by physicians with experience in the treatment of drug addicts and specialised in treatment of drug addiction. To reduce the misuse potential it is recommended to have the daily intake supervised in the doctor's office or in the pharmacy. Misuse may be prevented by dispensing small packages.
Hepatitis, hepatic events, use in patients with hepatic failure (severe damage to the liver)	Cases of severe liver damage after use of buprenorphine/naloxone (especially when injected into blood vessels) have been reported. Life threatening conditions may result from liver	Physicians should be aware that liver damage may occur. Patients are advised to talk to their physician if they have problems with their liver. To reduce the misuse

Risk	What is known	Preventability
	damage.	potential it is recommended to have the daily intake supervised in the doctor's office or in the pharmacy.
Dependence (addiction to buprenorphine)	Opioids like buprenorphine or naloxone (the active substances combined in this medicine), have the potential to induce addiction when consumed continuously over a prolonged period of time. However the potential for the development of addiction, physical and/or psychological dependence is lower when compared to other opioid drugs. Nonetheless physical and psychological dependence as well as tolerance may develop. Withdrawal symptoms may develop if the medication is withdrawn abruptly. Withdrawal symptoms may also develop upon initiation of buprenorphine/naloxone treatment after stopping the use of illegal opioids (e.g. heroin). Babies exposed to buprenorphine during pregnancy may also experience withdrawal syndrome.	Prescription of and supervision of treatment with buprenorphine/ naloxone should be carried out by physicians with experience in the treatment of drug addicts and specialised in treatment of drug addiction.
Drug withdrawal syndrome (Physical and psychological problems after sudden withdrawal of buprenorphine)	Withdrawal symptoms may develop if the medication is withdrawn abruptly. Withdrawal symptoms may also develop upon initiation of buprenorphine/naloxone treatment after stopping the use of illegal opioids (e.g. heroin) Babies exposed to buprenorphine/naloxone during pregnancy may also experience withdrawal syndrome.	Prescription of and supervision of treatment with buprenorphine/naloxone should be carried out by physicians with experience in the treatment of drug addicts and specialised in treatment of drug addiction.
Use during pregnancy and lactation (effects on the newborn and infant)	There are not enough data available to evaluate harmful effects of combined	Prescribing physicians should be aware of the risks associated with the

Risk	What is known	Preventability
	buprenorphine and naloxone during pregnancy. High doses at the end of pregnancy may cause breathing problems in the newborn. The long-term intake of buprenorphine and naloxone combined, during the last three months of pregnancy may cause a withdrawal syndrome in the newborn. Via breast milk, buprenorphine is ingested by the baby. It is not known if naloxone is excreted into breast milk	use of buprenorphine/ naloxone in pregnant and lactating women. If treated patients are pregnant or plan to become pregnant they are advised to talk to their physician. They also should contact their physician if there is anything wrong with their babies.
CNS Depression (effects on driving ability) (effects on the nervous system e.g. drowsiness)	Opioids like buprenorphine or naloxone (the active substances combined in this medicine), may affect your consciousness and perception, especially when combined with alcohol or other drugs. Therefore caution is advised when driving or operating machinery.	Patients are advised to exercise caution when driving a car or operating machinery. Persons who for medical reasons receive addictive substances or medicinal products potentially affecting the ability to drive, may be granted permission to drive on an individual basis subject to medical confirmation.
Allergic reactions	Buprenorphine and naloxone (the active substances combined in this medicine) may induce hypersensitivity reactions like facial swelling or allergic shock.	Patients should tell their doctors if they have experienced any allergic reactions in the past.

Important potential risks

Risk	What is known (including reasons why it is considered a potential risk)
Use in patients with head injury and increased intracranial pressure	Some opioids potentially induce elevated pressure in the head that may lead to damage of the brain or even death. There are no data indicating that this effect is induced by combined buprenorphine

Risk	What is known (including reasons why it is considered a potential risk)
(high blood pressure in the head)	and naloxone. Nonetheless caution is advised when treating patients with head injury or increased head pressure.
Peripheral oedema (swelling of the limbs)	There have been reports of swelling of the limbs in connection with combination therapy using buprenorphine and naloxone.

Missing information

Risk	What is known
Elderly patients >65 years old	No information on harmful effects regarding elderly patients is available.
Children <15 years old (Use in children younger than 15 years)	The safety and beneficial effect of combined buprenorphine and naloxone use in children and adolescents below the age of 15 has not been studied.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures. This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety concerns	Comment
10.02.2017 Version 01	➢ Version 01	Important identified risks ➢ Fatal overdose - *Severe respiratory failure* - *Use in patients with alcoholism/delirium tremens* ➢ Misuse and/or abuse (injection/intranasal/pediatric use) ➢ Hepatitis, hepatic events, use in patients with hepatic failure ➢ Dependence ➢ Drug withdrawal syndrome ➢ Use during pregnancy and lactation (effects on newborn and infant) ➢ CNS Depression (effects on driving ability ➢ Allergic reactions Important potential risks ➢ Use in patients with head injury and increased intracranial pressure ➢ Peripheral oedema Missing information ➢ Elderly patients >65 years old ➢ Children <15years old	First version
Version 02	02.10.2017	Important identified risks ➢ Fatal overdose - *Severe respiratory failure* - *Use in patients with*	Update as requested by the RMS in the Day 70 PrAR of procedures DE/H/5111,

		alcoholism/delirium tremens ➢ Misuse and/or abuse (injection/intranasal/pediatric use) ➢ Hepatitis, hepatic events, use in patients with hepatic failure ➢ Dependence ➢ Drug withdrawal syndrome ➢ Use during pregnancy and lactation (effects on newborn and infant) ➢ CNS Depression (effects on driving ability ➢ Allergic reactions ➢ Differences in posology between Buprenorphine+Naloxone s.l.-tablets and Buprenorphine s.l.-tablets <u>Important potential risks</u> ➢ Use in patients with head injury and increased intracranial pressure ➢ Peripheral oedema <u>Missing information</u> ➢ Elderly patients >65 years old ➢ Children <15years old	DE/H/5112, DE/H/5113, DE/H/5117