VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Opioid dependence, notably heroin addiction is a worldwide problem. There is an estimated 1.4 million problem opioid users in Europe. Opiates suppress pain, reduce anxiety, and at sufficiently high doses produce euphoria. Most opiates can be taken by mouth, smoked, snorted or injected. In regular long-time opiates users, nerve receptors likely adapt and begin to resist the drug, causing the need for higher doses. On removal of the drug, a physical withdrawal reaction occurs and receptors must readapt to its absence. Some of the risk factors for opioid abuse include a personal/family history of substance abuse, young age, mental disease, social patters of drug use, polysubstance abuse, psychologic stress, and poor social support. Pharmacologic therapy for opiate addiction focuses on ameliorating withdrawal symptoms and reducing cravings by replacing street opiate with legally obtained opioid agonists. Treatment options included methadone, the standard of care, buprenorphine and Buprenorphine with naloxone.

VI.2.2 Summary of treatment benefits

Buprenorphine-Naloxone 2/0.5 mg, 8/2 mg, sublingual tablets are generic products of the European reference product Suboxone® 2/0.5 mg, 8/2 mg, sublingual tablets registered and marketed by Indivior UK Limited in European countries.

These products are indicated in the substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse.

VI.2.3 Unknows relating to treatment benefits

None information available.

VI.2.4 Summary of safety concerns

The oral fixed combination of prolonged-release buprenorphine and naloxone has a well-established safety profile.
The safety concerns defined with the reference product apply to Buprenorphine-Naloxone 2/0.5 mg, 8/2 mg, sublingual tablets.

Important identified risks

Risk	What is known	Preventability
Fatal overdose	Buprenorphine-Naloxone Ethypharm SmPC mentions that overdose can be caused by misuse/abuse of the medication. The SmPC also contains a section on symptoms and management of Buprenorphine-Naloxone Ethypharm overdose. When Buprenorphine-Naloxone Ethypharm is taken with alcohol or other opioids or sedatives, death may occur due to respiratory depression.	Preventable through routine risk minimisation
Respiratory failure / respiratory depression	Buprenorphine-Naloxone Ethypharm SmPC enlists severe respiratory insufficiency as a contraindication to the usage of Buprenorphine-Naloxone Ethypharm.	Preventable through routine risk minimisation
Misuse and/or abuse (injection/intranasal)	Buprenorphine-Naloxone Ethypharm SmPC enlists misuse, abuse and diversion under the special warnings and precautions for use. While Buprenorphine-Naloxone Ethypharm may be misused like other most other opioids, overdose caused through misuse/abuse may lead to respiratory depression. If Buprenorphine-Naloxone Ethypharm is misused by intravenous route, a component in Buprenorphine-Naloxone Ethypharm causes precipitation of withdrawal syndrome and thus prevents misuse to a certain extent.	Preventable through routine risk minimisation
Paediatric intoxication	Buprenorphine-Naloxone Ethypharm SmPC enlists the risk of paediatric intoxication. The SmPC mentions that severe, possibly fatal, respiratory depression can occur in children and nondependent persons in case of accidental or deliberate ingestion.	Preventable through routine risk minimisation
Hepatitis, hepatic events, use in patients with hepatic failure	Buprenorphine-Naloxone Ethypharm SmPC enlists severe hepatic impairment as a contraindication to the usage of Buprenorphine-Naloxone Ethypharm.	Preventable through routine risk minimisation
Dependence	Buprenorphine-Naloxone Ethypharm SmPC enlists dependence under the special warnings and precautions for use. The opioid component in Buprenorphine-Naloxone Ethypharm may cause dependence. Hence Buprenorphine-	Preventable through routine risk minimisation

Risk	What is known	Preventability
	Naloxone Ethypharm treatment should not be abruptly discontinued.	
Drug withdrawal syndrome	Buprenorphine-Naloxone Ethypharm SmPC enlists drug withdrawal syndrome under the special warnings and precautions for use. Drug withdrawal syndrome may occur while switching to Buprenorphine-Naloxone Ethypharm. Patients should be monitored during this period.	Preventable through routine risk minimisation
Use during pregnancy and lactation (effects on newborn and infant)	Buprenorphine-Naloxone Ethypharm SmPC enlists fertility, pregnancy, and lactation under the special warnings and precautions for use. Studies in pregnant animals have shown reproductive toxicity, but risk in humans is unknown. Depending on how long Buprenorphine-Naloxone Ethypharm was administered to a pregnant mother, the newborn can experience respiratory depression, opioid withdrawal syndrome. Buprenorphine/naloxone should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus. Buprenorphine-Naloxone Ethypharm may get secreted in breast milk. Therefore, breastfeeding should be discontinued during treatment with Buprenorphine-Naloxone Ethypharm. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Buprenorphine-Naloxone Ethypharm Sublingual Tablet and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.	Preventable through routine risk minimisation
CNS depression	Buprenorphine-Naloxone Ethypharm SmPC enlists CNS depression under the special warnings and precautions for use. Buprenorphine-Naloxone Ethypharm causes drowsiness and it further worsens if taken with other agents that cause the same effect e.g. alcohol, other sleep inducing agents.	Preventable through routine risk minimisation
Allergic reactions	Buprenorphine-Naloxone Ethypharm SmPC enlists allergic reactions in contraindications. Buprenorphine-Naloxone Ethypharm should not be taken if a person is allergic to any component of Buprenorphine-Naloxone Ethypharm.	Preventable through routine risk minimisation
Differences in posology between Buprenorphine-Naloxone and Buprenorphine	Buprenorphine-Naloxone Ethypharm SmPC lists differences in posology between Buprenorphine-Naloxone Ethypharm and Buprenorphine while switching in the posology and administration section of published SmPC. Baseline liver function should be measured before the induction and during induction proper dosage regimen and administration method should be followed to avoid precipitation of withdrawal syndrome.	Preventable through routine risk minimisation

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use in patients with head injury	Buprenorphine-Naloxone Ethypharm SmPC lists the use in patients with head injury and increased intracranial pressure under general warnings.

Risk	What is known (Including reason why it is considered a potential risk)
and increased intracranial pressure	The association of Buprenorphine-Naloxone Ethypharm with the incidences is that opioids may elevate cerebrospinal fluid pressure, which may cause seizures, so opioids should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure.
Peripheral edema	Buprenorphine-Naloxone Ethypharm SmPC lists peripheral oedema in Section 4.8 as a common adverse effect under general disorders and administration site conditions

Missing information

Risk	What is known
Limited information on use in elderly patient	The safety and efficacy of buprenorphine/naloxone in elderly patients over 65 years of age have not been established. The general warnings state that opioids should be administered with caution to elderly or debilitated patients. No pharmacokinetic data in elderly patients are available. Ethypharm makes no recommendation on posology in elderly patients.
Limited information on use in pediatric patient	Buprenorphine/naloxone may cause severe, possibly fatal, respiratory depression in children and nondependent persons in case of accidental or deliberate ingestion. The safety and efficacy of buprenorphine/naloxone in children below the age of 15 years have not been established. No data are available.

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 always provided in the form of the package leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Buprenorphine-Naloxone 2/0.5 mg, 8/2 mg, sublingual tablets can be found in the Buprenorphine-Naloxone 2/0.5 mg, 8/2 mg, sublingual tablets' EPAR page.

There were 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

Not applicable.