13.2 Part VI.2 Elements for a Public Summary

13.2.1 Part VI.2.1 Overview of disease epidemiology

Chronic pain of moderate to severe intensity occurs in 19% of adult Europeans, seriously affecting the quality of their social and working lives. A large scale computer-assisted telephone survey was undertaken to explore the frequency, severity, treatment and impact of chronic pain in 15 European countries and Israel in adults with chronic pain. 19% of 46,394 respondents had suffered pain for more than 6 months, had experienced pain in the last month and several times during the last week. Their pain intensity was ≥5 on a 10-point Numeric Rating Scale (NRS) (1 = no pain, 10 = worst pain imaginable) during last episode of pain. In-depth interviews with 4839 respondents with chronic pain (about 300 per country) showed: 66% had moderate pain (NRS = 5–7), 34% had severe pain (NRS = 8–10), 46% had constant pain, 54% had intermittent pain. 59% had suffered with pain for two to 15 years, 21% had

been diagnosed with depression because of their pain, 61% were less able or unable to work outside the home, 19% had lost their job and 13% had changed jobs because of their pain (Breivik H, et al. (2006).

13.2.2 Part VI.2.2 Summary of treatment benefits

Therapeutic options to treat chronic pain cover on the one hand non-medication treatments, e.g. massage, physical therapy and acupuncture and on the other hand medication treatments, so called analgesics like NSAIDs, paracetamol, weak opioids, COX-2 inhibitors and strong opioids.

World Health Organization step III opioids are the mainstay of pain treatment for cancer patients and morphine has been the most commonly used for decades. Moreover they are commonly prescribed for chronic non-cancer pain. The role of opioids in neuropathic pain has been under debate in the past but is nowadays more and more accepted (Pergolizzi J, et al. 2008). Buprenorphine is effective and well tolerated for the treatment of chronic pain caused by non-malignant conditions when administered according to the manufacturer's recommendations.

13.2.3 Part VI.2.3 Unknowns relating to treatment benefits

There are no adequate data from the use of Buprenorphine transdermal patch in pregnant women. Data on excretion into human milk are also not available.

13.2.4 Part VI.2.4 Summary of safety concerns

Table 13-4 Important identified risks

Risk	What is known	Preventability
Respiratory depression	The most serious undesirable effect of buprenorphine is respiratory depression, a reduced ability to breathe. Symptoms are that the person breathes abnormally slowly or weakly.	For management of respiratory depression immediate countermeasures should be started, including removing the patch and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone.
Abuse, misuse and diversion	Buprenorphine can be abused in a manner similar to other opioid agonists. Overdosing might occur in subjects who misuse/abuse buprenorphine patches to apply the active substance via the parenteral route.	Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require monitoring for signs of misuse, abuse, or addiction. Used transdermal patches should be folded with the adhesive surfaces inwards and due to safety and environmental reasons,

Risk	What is known	Preventability
		discarded safely or whenever possible returned to the pharmacy. Any unused medicinal product should be discarded safely or returned to the pharmacy.
Drug dependence and withdrawal	Long-term use of buprenorphine can lead to development of tolerance and physical and psychological dependence. Physical dependence is an adaptive state that results from resetting of homeostatic mechanisms to permit normal functioning despite continued presence of the drug and can result due to legitimate therapeutic use. After discontinuation of therapy patients may show opioid withdrawal symptoms (for instance agitation, anxiety, nervousness, insomnia and gastrointestinal disorders).	Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Iatrogenic addiction following opioid administration is rare. Patients with a prior history of drug dependence/alcohol abuse are more at risk to develop dependence and abuse in opioid treatment. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations. In case of withdrawal symptoms it is recommended to treat those with short-acting morphine in low doses.
Accumulation of buprenorphine in patients with hepatic impairment	Patients with severe hepatic impairment may accumulate buprenorphine during treatment.	Consideration of alternate therapy should be considered, and buprenorphine should be used with caution, if at all, in such patients.

Table 13-5 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Accidental exposure	Used patches must be folded over on themselves with the adhesive layer inwards, and discarded safely out of sight and reach of children. They should not be thrown away via wastewater or household waste. These measures will help protect the environment.
Medication errors	Active-substance containing transdermal patches are relatively new and rarely used unconventional dosage forms. Certain conditions for a proper use, which are mandatory for safe and efficacious use, have to be fulfilled. Even though a detailed instruction of use is part of the product information and the labelling is clear and comprehensible, a potential for medication errors cannot be excluded.
Overdose	The most common sign of an overdose is reduced ability to breathe. Symptoms are that the person breathes abnormally slowly or weakly. Other symptoms of an overdose are drowsiness, low body temperature, slow heart rate, decreased muscle tone, deep sedation, loss of muscle

Risk	What is known (Including reason why it is considered a potential risk)
	co-ordination, constriction of the pupils and convulsions.
Off-label use in the treatment of chronic pain in paediatric patients	From the insufficient paediatric data available, it appears that buprenorphine has no higher adverse potential than the more commonly used opioids (Michel, 2011). However, due to insufficient data on safety and efficacy of transdermal burpenorphine in paediatric patients its use is not recommended in this patient population (<18 years of age).

Table 13-6 Missing information

Risk	What is known
Safety and efficacy of use during pregnancy and lactation	There are no data from the use of this product in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Towards the end of pregnancy high doses of buprenorphine may induce respiratory depression in the neonate even after a short period of administration. Long-term administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome in the neonate. Therefore it should not be used during pregnancy and in women of childbearing potential who are not using effective contraception. Studies in rats have shown that buprenorphine may inhibit lactation. Excretion of buprenorphine into the milk in rats has been observed. Data on excretion into human milk are not available. Therefore the use of Buprenorphine transdermal patch system TTSM during lactation should be avoided.
Safety and efficacy in paediatric patients	As Buprenorphine has not been studied in patients under 18 years of age the use of Buprenorphine in patients below this age is not recommended.

13.2.5 Part VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a 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.

13.2.6 Part VI.2.6 Planned post authorisation development plan

None

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

Version	Date	Safety Concerns	Comment
1.1	29.07.2014	The following risk has been added to the section " Missing information": "Safety and efficacy in paediatric patients"	Changes have been made according to RMS Day 70 Preliminary Assessment report date 08/07/2014.
1.2	26.06.2015	N/A	Changes have been made to cover all strengths of Buprenorphine Transdermal patch system TTSM (5mcg/1H, 10mcg/1H, 15mcg/1H, 20mcg/1H, 35mcg/1H, 52.5mcg/1H, 70mcg/1H) in one RMP.