VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Allergic reactions of different origins, including hay fever and hay fever, widespread skin rash/hives, itching and life-threatening allergic emergencies:

Allergic reactions occur when the body produces an exaggerated response to a particular stimulus or allergen which in turn caused troublesome symptoms that range from mild to life-threatening events. These include inflammation of the nose, eyes, skin rashes, tissue swelling (oedema), breathing difficulties (wheezing, chest tightness, and breathlessness), nausea, vomiting etc. Common causes of allergic reactions include pollen, dust mites, animal hair, insect venom, chemicals, medicinal products, certain foodstuff (nuts, eggs). Allergic reactions have been reported quite frequently in the general population thereby affecting 1 in 4 people in the UK.

Sleep disorders/Short term sedation and treatment of insomnia in adults/Short term paediatric sedation:

Insomnia is defined as the inability to fall asleep, failure to maintain sleep or early wakening. Insomnia is a common complaint affecting 1 in 10 people worldwide and if left untreated may pose a great burden on the quality of life and bring about further comorbidities (depression, anxiety, increased risk for accidents etc.). Causes of insomnia include environmental factors (noise, extremes of temperature), poor sleep hygiene (drinking alcohol at night or caffeine-rich products, performing physical exercise before going to bed), lifestyle factors (stress, jet lag), disease (depression, schizophrenia, asthma etc.), drugs (sympathomimetics, oral contraception, certain antidepressants – SSRIs). Management of insomnia involves the use of benzodiazepines, Z-drugs, certain sedating antihistamines, melatonin however these are best recommended for short-term use. (4)

Serious state of anxiety:

Anxiety is an umbrella term that covers a wide range of anxiety disorders including panic disorder with or without panic attacks following adverse life events, obsessive behaviour, social anxiety, fear of open spaces, and other specific phobias (arachnophobia- fear of spiders). Symptoms of anxiety include fear, excessive panic in stressful situations, irregular heartbeat, heart pounding, fast breathing, and feeling sick. Anxiety is more common in women than men and has an early onset in the early 20s. Causes of anxiety include adverse life events, childhood trauma, smoking, undergoing initial treatment with certain antidepressants such as SSRIs, caffeine, undergoing alcohol or drug withdrawal. (5) Management has been successful with certain medication such as beta blockers, benzodiazepines, certain antidepressants, and St John's Wort.

Premendication in surgical and dental practice:

Fear prior to surgical procedure is very common in the general population and there are a wide range of techniques to overcome this issue. These include hypnotherapy, the distraction technique and sedation with certain medicines (anxiolytic medicines, sedating antihistamines, local and general anaesthesia). (6)

Motion sickness/ Prevention or treatment of nausea and vomiting with various causes:

Nausea and vomiting are common phenomena that occur due to various causes such as exposure to bacterial toxins, motion sickness, travel sickness, alcohol use, gut infections, certain medications, renal disease, heart disease, pregnancy, migraine, head trauma. Treatment options include oral rehydration therapy, antiemetics (drugs that suppress vomiting), antihistamines, certain medications that act on the brain and stamp down the vomiting reflex (domperidone, metoclopramide, phenothiazines). In most cases nausea and vomiting settle in 48 hours. However, complications may occur and patients should refer to the doctor immediately if they experience the warning signs:

- Vomiting blood
- Weight loss
- Fever and increased sensitivity to sunlight
- Dizziness, falls (7-8)

Alcoholism and drug addiction:
Substance dependence occurs when a patient develops physical and psychological addiction to a particular stimulus (alcohol, sleeping pills, and drugs) and abstinence results in withdrawal symptoms. Opioid dependence affects nearly 5 million people in the United States and leads to approximately 17,000 deaths annually whereas alcohol contributes to 85000 deaths annually. (9, 10) Symptoms of drug or alcohol dependence include a drug seeking behaviour, social withdrawal, tolerance, self-neglect, loss of pleasure of performing activities, loss of interests, maladaptive behaviour. Treatment of addiction is a very complex process, which comprises both long term drug treatment and psychological support (cognitive behavioural therapy). Drug treatment options for addiction include sedating antihistamines, methadone, lofexidine, naltrexone, benzodiazepines etc. (11)

VI.2.2 Summary of treatment benefits

Promethazine has proven beneficial in the treatment of allergic reactions including urticaria, itching, respiratory allergies, and anaphylaxis in a wide range of studies. Halpern and colleagues demonstrated that out of 123 patients diagnosed with urticaria, 108 showed immediate improvement after treatment with 25mg promethazine. Halpern (1949) investigated the efficacy of promethazine in patients with hay fever. 142 cases were treated during spring with oral doses of promethazine 6-25 mg. According to the results of the study, 98 cases (69%) showed complete disappearance of all signs and symptoms, while 36 cases were only partially settled.
Efficacy of promethazine in anaphylactic reactions (life-threatening allergic reactions) has been shown by Worm and colleagues from data originating throughout Europe.
Promethazine has been used in premedication in surgical procedures due to preoperative sedation and calming effect and postoperative suppression of nausea and vomiting.
Promethazine possessed calming and sedative effects according to Adam and Oswald. 12 patients involved in one study showed improved sleep quality whilst treated with promethazine 20 or 40 mg at night. Its sedative properties were studied in children and researchers concluded that promethazine at a dose of 1mg/kg was equally effective to midazolam 0.5mg/kg.
Estrada and colleagues evaluated that promethazine in combination with caffeine was more effective versus comparative treatment for airsickness/ motion sickness. Promethazine was compared to meclizine (25 mg), scopolamine patch (1.5 mg) and acustimulation wristband. One study (Tarkila et.al) concluded that a combination of oral promethazine and transdermal scopolamine was more effective against comparator in reducing PONV symptoms and also reduced the need for postoperative pain treatment. (12)

VI.2.3 Unknowns relating to treatment benefits

According to the SmPC, there is limited information regarding promethazine use in pregnancy, breast-feeding, children below age of 5. However, based on current knowledge, there is no indication to suggest that treatment results would be different in any subgroup of the target population.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Worsening of pre-existing medical conditions (glaucoma, hyperthyroidism, active gastric or duodenal ulcer, pyloric stenosis, severe cardiovascular disease, liver disease, hypertrophy or adenoma of the prostate gland) due to anticholinergic effects of promethazine.	Patients diagnosed with certain medical conditions (glaucoma, hyperthyroidism, active gastric or duodenal ulcer, pyloric stenosis, severe cardiovascular disease, liver disease, hypertrophy or adenoma of the prostate gland) should refer to the prescriber if they experience dry mouth, dry eyes, blurred vision, rapid heart rate, heart pounding, chest pains, stomach upset, fatigue, constipation, and difficulty in passing water.	Yes, by monitoring for signs of aggravation of pre-existing condition
Heart rhythm abnormalities (QT interval prolongation)	Patients with known cardiovascular disease or patients treated with certain medication (moxifloxacin, erythromycin, methadone, lithium, antidepressants, cisapride) may experience heart rhythm abnormalities. Warning signs to look out for include rapid or uneven heartbeat, pounding and chest pains.	Yes, by monitoring for early symptoms and referring to the prescriber should side effects ensue.
Drowsiness (Residual drowsiness)	Drowsiness is a common die effect of promethazine therapy and it usually settles in a few days from starting treatment. Certain medications may interact with promethazine and potentiate residual drowsiness. These include drugs used for irritable bowel syndrome, asthma or weak bladder (anticholinergic medicines. Patients should refrain from driving whilst feeling drowsy.	Patients are advised to refer to the doctor or pharmacist before taking promethazine if they are experiencing drowsiness, severe dizziness or headache.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Increased risk of stroke in patients with pre-existing factors (Risk of cerebrovascular events in patients with risk factors for stroke)	Patients with increased risk of experiencing a stroke are advised to refer to the doctor or pharmacist prior to commencing treatment with promethazine.
Movement disorders (Extrapyramidal symptoms)	Patients treated with promethazine may be at an increased risk of developing new movement disorders. These include tremor, restlessness, continuous muscle spasms/contractions, jerky muscle movements. Drugs causing these undesirable reactions must be discontinued upon first signs and symptoms of movement disorders.

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

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for promethazine.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	27-07-2015	**Important identified risks:** -Worsening of pre-existing medical conditions (glaucoma, hyperthyroidism, active gastric or duodenal ulcer, pyloric stenosis, severe cardiovascular disease, liver disease, hypertrophy or adenoma of the prostate gland) due to anticholinergic effects of promethazine -QT interval prolongation -Residual drowsiness **Important potential risks** -Risk of cerebrovascular events -Extrapyramidal symptoms (EPS)	