VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Motion sickness is the uncomfortable dizziness, nausea, and vomiting that people experience whe n sense of balance and equilibrium is disturbed by constant motion.

According to transport surveys, individual susceptibility to motion sickness is developed sometim e during childhood, peak at around the age of puberty, and thereafter slightly decline through adul thood. Although the impact of motion sickness on activities of daily life has not been surveyed ext ensively, probably about one-third of people experience significant symptoms when riding in vehi cles. In extreme cases of individuals with the highest levels of susceptibility, moderate motions m ay induce severe motion sickness that causes incapacitating malaise including nausea, dizziness, a nd headache, which may last throughout motion and for hours afterwards. Women are more susce ptible to motion sickness than men; women show a higher incidence of vomiting and nausea's sy mptoms. About 33% of people are susceptible to motion sickness even in mild circumstances such as being on a boat in calm water, although nearly 66% of people are susceptible in more severe co nditions.

VI.2.2 Summary of treatment benefits

Dimenhydrinate dissociates to diphenhydramine and 8-chlorotheophylline upon administration. Diphenhydramine is an active metabolite and is well absorbed from the gastrointestinal tract with a bioavailability of 42 to 62%. Maximum plasma concentrations (Cmax) of diphenhydramine are reached in humans within 2 to 3 hours. Duration of activity is between 4 and 8 hours.

These pharmacokinetic properties complementary to the formulation of the product that allows to the patient to intake it without water, result in a quick, easy and effective management of the motion sickness

VI.2.3 Unknowns relating to treatment benefits

Dimenhydrinate is a non-prescription ethanolamine, consisting of 53% to 56% diphenhydramine and 44% to 47% 8-chlorotheophylline, a caffeine derivative. A 5-mg/kg dose of dimenhydrinate includes 2.2 to 2.4 mg/kg of 8-chlorotheophylline. Thus, in a 30-kg child, the amount of 8-chlorotheophylline can reach 66 to 71 mg.
By comparison, a 355-mL can of Coca-Cola or 240 mL of coffee contains 104 to 192 mg of caffeine. The effects of 8-chlorotheophylline not been studied. Therefore, [Dimenhydrinate] 50mg, sublingual tablet should be administered in children aged > 12 years old.

There are inconsistent reports about the safe use of dimenhydrinate during pregnancy, as there are contradictory studies concerning congenital malformations in new-borns.
Animal studies have failed to reveal evidence of teratogenicity. In addition, there are no human data that indicate dimenhydrinate is a carcinogen or mutagen or that it impairs fertility
Dimenhydrinate is excreted into human milk in small amounts. Due to the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

VI..2.4 Summary of safety concerns

Important identified risks

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Allergic reactions *(Hypersensitivity to antihistaminic agents)*	Dimenhydrinate may cause rarely an allergic reaction in some people. Allergic reaction symptoms differ on severity. They range from unpleasant and inconvenient to life threatening. These include rash, red or purple discolorations on the skin (purpura), itching of the skin oedema (swelling of the face or neck which could involve difficulty breathing) anaphylactic shock	People who experience an allergic reaction whilst taking the tablets dimenhydrinate and seek advice from a doctor. People who have previously had an allergic reaction to anticholinergic agents should not take dimenhydrinate tablets
Increased pressure of the eye *(Risk of closed angle glaucoma)*	Closed angle glaucoma is been reported as adverse even under the term of vision problems Closed angle glaucoma is a severe potential hazard with high plausibility. Antihistamines, such as dimenhydrinate, often have anticholinergic activity, to which elderly patients are particularly sensitive. Therapy with antihistamines should be administered cautiously, if at all, in patients with preexisting conditions that are likely to be exacerbated by anticholinergic activity, such as angle-closure	. [Dimenhydrinate] should administer carefully in patients with preexisting conditions and discontinuation of the treatment if adverse event occurs. Asking for consultation to doctor or pharmacist before initiate [Dimenhydrinate] intake

	glaucoma, untreated intraocular hypertension, or uncontrolled primary open-angle glaucoma.	
Do not take [Dimenhydrinate] if you have difficult or painful urination due to an enlargement of the prostate gland *(Risk of urinary retention due to urethral-prostate disorders)*	Difficult urinating is been reported as side effect. Antihistamines, such as dimenhydrinate, often have anticholinergic activity, to which elderly patients are particularly sensitive. This anticholinergic effect is a severe potential hazard with high plausibility that applies to urinary tract retention. Therefore, therapy with antihistamines should be administered cautiously, if at all, in patients with preexisting difficulty or painful urination	Dimenhydrinate due to it anticholinergic properties relax the bladder and can cause constipation (impaction) which can result in retention with overflow and difficult or painful urination. In patients with an enlargement of the prostate gland [Dimenhydrinate] should administer carefully
Talk to your doctor or pharmacist before taking [Dimenhydrinate] if you have asthma Asthma *(Administration in cases of bronchial asthma)*	Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction and bronchospasm. Common symptoms include wheezing, coughing, chest tightness, and shortness of breath	[Dimenhydrinate] should be administered with precaution in patients with bronchial asthma or chronic obstructive pulmonary disease. .Asking for consultation to doctor or pharmacist before initiate [Dimenhydrinate] intake
Elderly people with an history of constipation, dizziness or drowsiness and prostate problems *(Elderly with greater susceptibility to orthostatic hypotension, dizziness and sedation; chronic constipation (risk of paralytic ileus) or potential prostatic hypertrophy)*	Orthostatic hypotension, dizziness and drowsiness; chronic constipation (risk of paralytic ileus) or potential prostatic hypertrophy are adverse events that may be revealed with [Dimenhydrinate] treatment. They may be increased if [Dimenhydrinate] is administered in elderly people already suffering from orthostatic hypotension, prostate problems, nervous	[Dimenhydrinate] should be carefully administer in patients with gastrointestinal obstruction, and urinary retention problems and discontinuation of the treatment if adverse event occurs. Asking for consultation to doctor or pharmacist before initiate [Dimenhydrinate] intake

	system disorders	
Use in patients with liver or kidney problems *(Aggravation of hepatic and/or severe renal insufficiency (due to risk of accumulation)*	Dimenhydrinate is metabolized in the liver and the metabolites are eliminated through the kidneys. Patients with renal and/or liver disease may be at greater risk for adverse effects from antihistamines due to drug and metabolite accumulation.	Patient with liver or kidney problems should advise physician about [Dimenhydrinae] administration. Lower initial dosage may be appropriate.
Co-administration with antibiotics induce toxicity in the ear *(Combined administration with ototoxic antibiotics (since dimenhydrinate can mask ototoxicity symptoms)*	Co-administration of dimenhyndrinate with certain antibiotics which may cause ototoxicity (toxic effects on the nerves of the ear) may be resulted, since dimenhydrinate is capable of masking ototoxic symptoms and an irreversible state may be reached.	Co-administration of [Dimenhydrinate] with ototoxic antibiotics should take in consideration. In case of treatment with such antibiotis asking consultation to doctor or pharmacist before initiate [Dimenhydrinate] intake
Co-administration with alcohol beverage or other medicines containing alcohol *(Increase of drowsiness of H_1 antihistamines when co administered with drink alcoholic beverages or taking alcohol)*	This medicine may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol. Patients should be warned not to drive a motor vehicle, operate dangerous machinery or climb dangerous heights as impaired decision making could lead to accidents.	Alcohol should not be consumed during [Dimenhydrinate] administration
Co-administration with atropine and/or other atropinic substances *(Increased anticholinergic effects of atropine and other atropinic substances (tricyclic antidepressants, antiparkinsonians anticholinergic, atropinic antispasmodics, disopyramide, phenothiazine neuroleptics))*	This medicine may lead to supraventricular or ventricular tachycardia, dizziness, nausea, blurred vision, loss of balance, dilated pupils, dry mouth and potentially extreme confusion, dissociative hallucinations and excitation	[Dimenhydrinate] should not be co-administered with atropine and/or other atropinic substances

Co-administration with depressor agents of the central nervous system *(Increased CNS adverse events when dimenhydrinate is co-administered with morphine derivatives (analgesics, antitussives and substitution treatment); benzodiazepines; barbiturates; anxiolytics other than benzodiazepines; hypnotics; neuroleptics; sedative antidepressants; central antihypertensives; baclofen; thalidomide)*	Dimenhydrinate directly inhibits the stimulation of certain nerves in the brain and inner ear to suppress nausea, vomiting, dizziness, and vertigo. Therefore, co administration with other depressor agents may increase adverse effects such as drowsiness, feeling less alert, balance problems	[Dimenhydrinate] should not be co-administered with depressor agents of the central nervous system

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Change in electrical activity of the heart seen on ECG *(QTc prolongation)*	Dimenhydrinate is a combination of two drugs: diphenhydramine and 8-chlorotheophylline, a chlorinated derivative of theophylline. There are several levels of evidence strongly indicating diphenhydramine (similar to chlorpheniramine) can block the delayed rectifier potassium channel and, as a consequence, prolong the QT interval, leading to cardiac arrhythmias such as torsades de pointes. QTc prolongation might be a potential class effect adverse reaction.
Use in patients with pheochromocytoma	Pheochromocytoma is a rare tumor of adrenal gland tissue. It results in the release of too much epinephrine and norepinephrine, hormones that control heart rate, metabolism, and blood pressure. Administration of dimenhydrinate is contraindicated in patients with pheochromocytoma

Important missing information	
Risk	**What is known**
Limited data on use in pregnancy and lactation	<u>*Pregnancy*</u> There are inconsistent reports about the safe use of dimenhydrinate during pregnancy. A prospective study on

	pregnant women did not reveal any evidence for a relationship between dimenhydrinate treatment and malformations. Another study described an association between cardiovascular defects or inguinal hernia with dimenhydrinate exposition during pregnancy. A case-control study included 38,151 new-borns without congenital malformations and 22,843 with congenital malformations of whom a total of 2,640 children were exposed to dimenhydrinate. Dimenhydrinate showed no evidence of teratogenic potential. There are no indications that dimenhydrinate application leads to a higher abortion rate during the first trimester of pregnancy. Dimenhydrinate can stimulate preterm uterine contractions and increases the risk for premature labour. Animal studies with dimenhydrinate are insufficient with respect to reproductive toxicity [Dimenhydrinate] should only be used during pregnancy if a therapy without medication or a treatment with other, safe medicinal products were not effective. [Dimenhydrinate] should not be used during the third trimester because it can trigger preterm uterine contractions. Dimenhydrinate must not be taken during 1st trimenon of pregnancy. Epidemiological data in a small group of pregnant women (599) who took diphenhydraminchloride during the first trimenon showed a possible increase in palatine cleft. For the rest of pregnancy there is a low risk. *Breastfeeding* Dimenhydrinate is excreted into human breast milk. There are no data about the use of dimenhydrinate during breast feeding. Because undesirable effects on a nursing infant such as increased irritability cannot be excluded, either [Dimenhydrinate] treatment should be discontinued or breast feeding should be discontinued.
No studies on fertility	No data available.
Local tolerance	No data 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 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	Change
1.0	29.05.2013	NA	Initial version
2.0	06.06.2014	**Important identified risks** •Hypersensitivity to antihistaminic agents •Risk of closed angle glaucoma •Risk of urinary retention due to urethral-prostate disorders •Administration in cases of bronchial asthma •Elderly with greater susceptibility to orthostatic hypotension, dizziness and sedation; chronic constipation (risk of paralytic ileus) or potential prostatic hypertrophy •Aggravation of hepatic and/or severe renal insufficiency (due to risk of accumulation). •Combined administration with ototoxic antibiotics (since dimenhydrinate can mask ototoxicity symptoms).	Implementation of Day 70 assessor comments

		•Increase of drowsiness of H1 antihistamines when co administered with drink alcoholic beverages or taking alchohol •Increased anticholinergic effects of atropine and other atropinic substances (tricyclic antidepressants, antiparkinsonians anticholinergic, atropinic antispasmodics, disopyramide, phenothiazine neuroleptics) •Increased CNS adverse events with co-administration of dimenhydrinate with morphine derivatives (analgesics, antitussives and substitution treatment); benzodiazepines; barbiturates; anxiolytics other than benzodiazepines; hypnotics; neuroleptics; sedative antidepressants; central antihypertensives; baclofen; thalidomide **Important potential risks** •QTc prolongation •Use in patients with pheochromocytoma	

		Missing information •Limited data on use in pregnancy and lactation •No studies on fertility •Local tolerance	
3.0	24.10.2014	**Important identified risks** •Hypersensitivity to antihistaminic agents •Risk of closed angle glaucoma •Risk of urinary retention due to urethral-prostate disorders •Administration in cases of bronchial asthma •Elderly with greater susceptibility to orthostatic hypotension, dizziness and sedation; chronic constipation (risk of paralytic ileus) or potential prostatic hypertrophy •Aggravation of hepatic and/or severe renal insufficiency (due to risk of accumulation). •Combined administration with ototoxic antibiotics (since dimenhydrinate can mask ototoxicity symptoms). •Increase of drowsiness of H1 antihistamines when co administered with drink alcoholic beverages or taking	Some changes in the p roposed indications ha ve been made based o n the comments receiv ed on SmPC at day 16 0 of the procedure. The safety concerns re main the same as in th e previous version (v2 -060614 being approv ed - day 120 assessm ent report of the proce dure). However, corre ctions have been mad e in the sections relati ve to product indicatio ns

		alchohol •Increased anticholinergic effects of atropine and other atropinic substances (tricyclic antidepressants, antiparkinsonians anticholinergic, atropinic antispasmodics, disopyramide, phenothiazine neuroleptics) •Increased CNS adverse events with co-administration of dimenhydrinate with morphine derivatives (analgesics, antitussives and substitution treatment); benzodiazepines; barbiturates; anxiolytics other than benzodiazepines; hypnotics; neuroleptics; sedative antidepressants; central antihypertensives; baclofen; thalidomide **Important potential risks** •QTc prolongation •Use in patients with pheochromocytoma **Missing information** •Limited data on use in pregnancy and lactation •No studies on fertility	

		•Local tolerance	
4.0	29.11.2014	No changes in the risks. They remained as proposed and approved in RMP DIMENH-v3-241014	Some changes in the proposed indications have been made based on the comments received on SmPC at day 180 of the procedure. The safety concerns remain the same as in the previous version (v3-241014 being approved - day 180 assessment report of the procedure). However, corrections have been made in the sections relative to product indications
5.0	10.12.014	No changes in the risks. They remained as proposed and approved in RMP DIMENH-v4-291114	Some changes in the proposed indications have been made based on the comments received on SmPC at day 208 of the procedure. The safety concerns remain the same as in the previous version (v4-191114 being approved - day 180 assessment report of the procedure). However, corrections have been made in the sections relative to product indications