A Justification for changing the current wording of the GSL classification of phenylephrine to include a cut-off point for solid dose products containing 10 mg or less of phenylephrine.

Background

Following a company submission to the 30th Meeting of the Medicines Classification Committee (seeking a cut-off point of 10mg or less per dose as general sale and pharmacy-only for doses greater than 10mg), the MCC decided that not only would there be no change to the current classification but a more restrictive classification was proposed.

The Agenda for the 31st Meeting expands this view to state that "Oral preparations containing doses greater than 10 mg should be Prescription Medicines. There should be no oral phenylephrine preparations sold as general sale medicines".

According to the minutes of the last MCC meeting, the Committee accepted that it was technically difficult to convert phenylephrine to methamphetamine and that there was no record of methamphetamine being manufactured illicitly from phenylephrine in Australia. However, no data was presented demonstrating conclusively that conversion to methamphetamine was not possible. Furthermore it was noted that the risk/benefit profile of phenylephrine was generally similar to pseudoephedrine.

While there was agreement that 10 milligrams was an appropriate therapeutic dose, the Committee felt that this should apply as a maximum cut-off point for all over-the-counter oral dose forms of phenylephrine and that all oral dose forms below this cut-off point should be classified as pharmacy-only medicines.

This discussion paper reviews the basic pharmacology, efficacy and safety of phenylephrine as single ingredient preparation and in Cold & Flu combination products. The marketing experience in several countries is also reviewed, with specific emphasis on the United Kingdom, Australia and New Zealand.

This discussion concludes that at therapeutic doses, phenylephrine is a safe and efficacious ingredient. Side effects are predictable and in the majority of cases resolve spontaneously. Where clinical intervention is required, the management is standardised and effective. This data, together with the knowledge that conversion of phenylephrine to illicit drugs is a technically difficult task that has not been reported in any market to date, supports the argument for changing the current wording of the GSL classification of phenylephrine to include a cut-off point for solid dose products containing 10 mg or less of phenylephrine.

Clinical Pharmacology

Phenylephrine is sympathomimetic vasoconstrictor that has been used as a nasal decongestant for many years [1-4]. Phenylephrine has one chiral centre and can exist as either the S(+) or R(-) enantiomer. The R(-) enantiomer is the one used in products containing phenylephrine. It is a relatively selective alpha-adrenoceptor agonist [1-4]. The majority of the sympathomimetic action is due to direct stimulation of the adrenoceptors and relatively little is due to an indirect effect via release of noradrenaline [1]. Its pressor action is weaker than that of noradrenaline but of longer duration [4]. At therapeutic doses, it does not cause significant stimulation of the central nervous system [4].

Sympathomimetic decongestants reduce the nasal congestion due to increased nasal blood flow associated with colds and influenza. This effect forms the therapeutic basis for their use in these conditions [5, 6].

Hypertensive patients should be aware of the possible side effects of nonprescription medications on blood pressure control. For absolute safety no adrenergic agents should be used. However, when required, phenylephrine is the safest of these agents [23]. Studies assessing the hypertensive effect of oral phenylephrine in normotensive volunteers have demonstrated that the minimal dose required to elicit an increase in blood pressure is approximately 50 mg that is five times the therapeutic dose [2]. Doses in excess of 120 mg are required to elicit a significant effect on blood pressure. A recent study in normotensive volunteers demonstrated that following administration of a cold relief product containing phenylephrine 10 mg and caffeine 60 mg, there was a small but statistically significant increase in total peripheral resistance but no consistent effect on other cardiovascular parameters including heart rate and blood pressure [7].

Interactions

The coadministration of Monoamine Oxidase Inhibitors (MAOIs) or tricyclic antidepressants and an indirect or mixed-acting sympathomimetic may result in a hypertensive crisis. Direct-acting sympathomimetics appear to interact minimally, if at all [16 - Drug Interaction Facts. 4th edition]. Such concomitant use is clearly identified as a contra-indication on the labelling of all phenylephrine-containing products and the appropriate warnings are provided. Additionally sympathomimetics may reduce the efficacy of beta-blocking and anti-hypertensive drugs. Conditions where these drugs are used are contra-indicated for the product.

Pregnancy and Lactation

The safety of phenylephrine hydrochloride in pregnancy has not been fully established. Available published data on phenylephrine do not contraindicate breast-feeding.

Clinical Pharmacokinetics

Phenylephrine is readily and completely absorbed from the gastro-intestinal tract after oral administration [1, 8]. It is subject to extensive presystemic metabolism in the gut wall and therefore has a systemic bioavailability of approximately 40% relative to intravenous dosing. Following oral administration, peak plasma concentrations are achieved in 1 - 2 hours. The mean plasma half-life is in the range 2 - 3 hours.

The volume of distribution is large (200 to 500 litres) [1, 8]. Penetration of the brain and excretion in breast milk appear to be minimal. Phenylephrine does not cross the placenta. The extent of protein binding is unknown.

Phenylephrine is extensively metabolised in the gut wall and liver [1, 8]. The principal routes of metabolism are sulphation and glucuronidation of the 3-hydroxyl group and oxidative deamination by monoamine oxidase to 3-hydroxymandelic acid and 3-hydroxyphenylglycol. Sulphate conjugates are formed from the metabolites. Excretion is via the kidneys.

Efficacy

Phenylephrine is a sympathomimetic agent that, similar to other agents in that class such as pseuodephedrine and phenylpropanolamine, relieves the nasal congestion associated with colds and influenza [1-4]. Compared to pseudoephedrine, phenylephrine has a larger range of applications including:

Nasal decongestion
- Nasal drops or sprays (0.25 - 0.5% solution)
- Tablets, capsules or sachets (5 - 12 mg/dose; 40 - 60 mg/day)

Ophthalmology
- Mydriatic (2.5% or 10% solution)
- Conjunctival decongestant (012% solution).

Treatment of varicose veins or inflamed veins (legs; haemorrhoids)
- Ointments & creams (0.25 - 0.5%)
- Suppositories (0.25%)

The main application for pseudoephedrine is nasal decongestion and allergic rhinitis (oral doses of 60 mg, 3 - 4 times daily and sustained release formulations - 120 mg twice daily) [17, 18].

A number of studies show significant relief of nasal congestion and improvement of nasal air flow following oral treatment of patients with phenylephrine [17, 19].

The most comprehensive review of the efficacy of oral phenylephrine, as a nasal decongestant was undertaken in 1976 by an Advisory Panel at the request of the FDA. In undertaking this review, they received and reviewed unpublished clinical data from a number of companies. In their published report [9], they reviewed the available data from a total of 12 studies and concluded that oral phenylephrine 10 mg was an effective decongestant in patients with a common cold.

In one double-blind study [Citation 26 in Reference 9], in 50 patients with a common cold, oral phenylephrine 10 mg led to a statistically significant reduction in nasal airways resistance compared to placebo. The mean falls in nasal airways resistance, at 15, 60 and 120 minutes after dosing, were 11%, 28% and 26%, respectively. Patients also experienced symptomatic relief of nasal congestion, runny nose and sneezing.

In a series of five double-blind, placebo-controlled studies from one laboratory, oral phenylephrine 5-25 mg resulted in a reduction in nasal airways resistance compared to placebo in patients with a cold [Citations 5-9 and 19 of Reference 9]. The onset of action was within 15 to 20 minutes with the effect lasting 2-4 hours. The maximal effect was observed with phenylephrine 25 mg.

As noted in a recent review of nasal decongestants [10], not all studies assessing the efficacy of phenylephrine demonstrated a positive effect. A study quoted by Hendeles [10], failed to demonstrate any difference between phenylephrine 10 mg and placebo. This was one of the 12 studies reviewed by the Advisory Panel in 1976, and the negative findings were noted [Citation 25 of Reference 9].

Since these were unpublished company reports submitted to the FDA, it is not possible to interrogate these data. However, the FDA endorsed the panel's findings in 1985 having further reviewed the data following criticism [11] and a final monograph endorsing the efficacy and safety of oral phenylephrine 10 mg as a nasal decongestant available for non-prescription usage in the USA was issued in 1994 [12].

Overview of Safety

Phenylephrine is a direct acting sympathomimetic agent, unlike pseudoephedrine, which is a mixed acting sympathomimetic and therefore has more side effects than phenylephrine. Furthermore, because of its specificity of action, phenylephrine does not exert significant stimulating effects on the Central Nervous System (CNS). There are minimal cardiovascular effects at recommended doses, and rare side effects include tachycardia, headaches, restlessness and nausea [17, 18, 20]. By comparison pseudoephedrine is a direct and indirect-acting sympathomimetic agent. It acts on both alpha and Beta-adrenergic receptors, causing the release of noradrenaline from adrenergic endings thus stimulating adrenergic receptors indirectly [21]. It enters the

CNS readily, thus commonly causing CNS effects such as anxiety, restlessness, nervousness and irritability. Other common side effects include tachycardia, insomnia, allergic effects on the skin, urinary retention, dry mouth, anorexia, hallucinations, headaches, nausea and upset stomachs [17]. Increased risk of stroke has been associated with the use of pseudoephedrine [22].

There is very extensive marketing experience with phenylephrine, used alone or in combination with other cold & Flu ingredients. Phenylephrine is marketed in non-prescription products in a number of countries worldwide (Appendix 1 - Worldwide Marketing status). It has an excellent and predictable safety profile when used at therapeutic doses.

Extent and Type of Patient Exposure

During the period 1995 to 2004, it is estimated that approximately 64 million individuals have been exposed to phenylephrine- containing formulations sold in 4 regions, namely Central and Eastern Europe, Hong Kong, Spain and the United Kingdom. The breakdown of sales per region is presented in Table 1.

GlaxoSmithKline markets a number of products (predominantly in sachet format) containing phenylephrine (10 mg /dose) in combination with other Cold & Flu ingredients.

Review of Published Safety Reports

As with other nasal decongestants which are sympathomimetic amines, such as pseudoephedrine and phenylpropanolamine, phenylephrine has the potential to cause hypertension and hypertensive crises. However reports of such cases have been extremely rare [1, 2, 4]. A case of hypertensive crises involving the use of oral phenylephrine was reported in the literature [13]. This was a 34-year-old man who presented with hypertension and congestive cardiac failure. Subsequent inquiries determined that he had been ingesting very large quantities of a variety of decongestants including phenylephrine, ephedrine and oxymetazoline on a regular and prolonged basis. As reviewed in the Clinical Phamacology Section, studies in normal subjects have demonstrated that doses of oral phenylephrine 50 mg, fives times the therapeutic level, are required to elicit an increase in blood pressure [2]. Oral phenylephrine 10 mg did not affect blood pressure or heart rate [7].

As a class, sympathomimetic amines may also cause headaches, vomiting, diarrhoea, insomnia, restlessness and palpitations. However, there have been few reports of these with normal doses of phenylephrine [1]. Only one case of significant psychiatric disturbance associated with the use of phenylephrine has been identified in the literature [14]. This was a 42 year old man who developed mania following the use of a non-prescription product for rhinitis containing phenylephrine 80 mg,

hydrocodone 20 mg and diphenylpyriline 8 mg. Although the product may have caused the mania, it is not possible to determine which of the three ingredients caused the mania. The dose of phenylephrine is excessive compared to the standard therapeutic dose. Additionally both hydrocodone, a narcotic derivative of codeine and diphenylpyriline, a histamine H1 antagonist, have known CNS effects and cannot be excluded as a cause.

Rare reports of hypertension and mania have also been reported following the topical use of phenylephrine as a nasal spray [1, 2, 4].

Given the recent concerns about cerebrovascular accidents associated with the use of phenylpropanolamine, another sympathomimetic nasal decongestant, it is pertinent to note that not a single case of cerebrovascular accident has been identified associated with the use of phenylephrine.

Rebound nasal congestion occurs with prolonged use of topical decongestants, a problem not identified with oral decongestants [15].

Reports to UK Licensing Authority for products containing phenylephrine

In the period July 1963 to June 2004, a total of 166 reports involving 227 adverse events (39 for single ingredient products) have been reported to the UK Licensing Authority for products containing phenylephrine (Appendix II). Three reports with a combination product had a fatal outcome. The number of reports in each system organ class is low and unremarkable.

The most frequent reports involved the skin and subcutaneous tissues (59 reports) with urticaria (20 cases), face oedema (7 cases), and rash (6 cases). The other most frequent events ($\geq$ 4 cases) were urinary retention (7 cases), bronchospasm (7 cases), sedation (4 cases) and diarrhoea (4 cases). No cases of cerebrovascular accidents or myocardial infarction were reported. There were two reports of hypertension and one of aggravated hypertension.

Australian Experience - Adverse Events Reported to ADRAC

In the period 1975 - 2004 there have been 37 suspected reactions to phenylephrine, with only 14 cases having phenylephrine as the sole suspected drug (Appendix III). The majority of these adverse events relate to eye drop preparations containing phenylephrine.

The low incidence of adverse event reports as well as the non-serious nature of reactions reflects favourably on the safety of phenylephrine. Furthermore, it is worth noting that in each case the outcome was full recovery.

Overdosage

In overdosage, the principal clinical features are likely to be a rise in blood pressure with an associated reflex bradycardia [1]. Treatment with alpha-adrenoceptor antagonists for the hypertension and atropine for the bradycardia is a standard treatment. Phenylephrine overdosage may also cause irritability, headache and contribute to nausea and vomiting.
The majority of phenylephrine-containing products marketed by GlaxoSmithKline worldwide are in sachet format that is dissolved into a hot drink. The nature of this dosage form places limitations on potential product misuse.

Conclusions

There is extensive experience with the safety of phenylephrine contained in many Cold & Flu preparations. At therapeutic doses, phenylephrine has an excellent and predictable safety profile and there are few adverse events.

The safety of phenylephrine is demonstrated by the low incidence of adverse events reported spontaneously to the company for products containing this active ingredient and to the UK Licensing Authority for products containing phenylepherine..
Following overdosage, phenylephrine is associated with hypertension and a reflex bradycardia that will respond to appropriate clinical management.

APPENDIX 1

WORLDWIDE MARKETING AUTHORISATION STATUS

Country	Trade Name	Strength (paracetamol/ ascorbic acid/ phenylephrine)
Armenia	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
Azerbaijan	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
Belarus	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
Bosnia	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
	COLDREX Maxigrip Lemon	1000mg / 60mg / 10mg
Bulgaria	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
	COLDREX Maxgrip lemon	1000mg/60mg/10mg
Croatia	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
	COLDREX Maxigrip Lemon	1000mg / 60mg / 10mg
Czech Republic	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
	COLDREX Maxgrip lemon	1000mg/60mg/10mg
Estonia	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
	COLDREX Maxgrip lemon	1000mg/60mg/ 10mg
Georgia	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
Hong Kong	BEECHAMS Hot Lemon	600mg / 40mg / 10mg
Hungary	COLDREX Hotrem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
Ireland	BEECHAMS Hot Lemon Decongestant (licence expired Jan 2003)	600mg / 10mg / 40mg
Kazakhstan	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
Kirgizia	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg

Country	Trade Name	Strength (paracetamol/ ascorbic acid/ phenylephrine)
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
Latvia	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
Lithuania	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
	COLDREX Maxgrip lemon	1000mg/60mg/10mg
Macedonia	COLDREX HotRem powders lemon	750mg/60mg/10mg
	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
Poland	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
	COLDREX Maxgrip lemon	1000mg/60mg/10mg
Romania	COLDREX Hotrem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
Russia	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon and Honey	750mg/60mg/10mg
	COLDREX Maxgrip lemon	1000mg/60mg/10mg
Slovak Republic	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
South Africa	BEECHAMS Hot Medication Plus Powder	600mg/40mg/10mg
Spain	BEECHAM lemon	600mg / 40mg / 10mg
Turkmenistan	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg

Country	Trade Name	Strength (paracetamol/ ascorbic acid/ phenylephrine)
United Kingdom	BEECHAMS Hot Lemon (or BEECHAMS Warmers Lemon or BEECHAMS Cold & Flu Hot Lemon)	600mg / 40mg / 10mg
	BEECHAMS Hot Blackcurrant (or BEECHAMS Warmers Blackcurrant or BEECHAMS Cold & Flu Hot Blackcurrant)	600mg / 40mg / 10mg
	BEECHAMS Hot Lemon and Honey (or BEECHAMS Warmers Lemon and Honey or BEECHAMS Cold & Flu Hot Lemon and Honey)	600mg / 40mg / 10mg
	BEECHAMS Flu-Plus Hot Berry Fruits	1000mg / 70mg / 10mg
	BEECHAMS Flu Plus Hot Lemon	1000mg / 40mg / 10mg
Ukraine	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
Uzbekistan	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg
Yugoslavia	COLDREX HotRem Powder Blackcurrant	750mg / 60mg / 10mg
	COLDREX HotRem Powder Lemon	750mg / 60mg / 10mg

APPENDIX II

Adverse Event Reports to UK Licensing Authority for products containing phenylephrine

APPENDIX III

Adverse Event Reports on ADRAC Database (1975 - 2004)

References (available on request)

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MEDDRA VERSION: 6.0
EXTRACT PERIOD: 01/07/63-01/06/04 EARLIEST REACTION DATE: 08/07/64 REACTION: ALL TYPE:SPONTANEOUS ORIGIN: UK

DRUG : PHENYLEPHRINE SUBSTANCE/VARIANT/NPCG: SUBS
ROUTE: ALL
SINGLE-CONSTITUENT PRODS : MINIMS PHENYLEPHRINE, NEOPHRYN, RICHARD DANIEL PHENYLEPHRINE

MULTI-CONSTITUENT PRODS : AURUM PHARMS LIDOCAINE AND PHENYLEPHRINE (LIGNOCAINE)
BEECHAMS 2 (CAFFEINE, PARACETAMOL)
BEECHAMS ALL-IN-ONE (GUAIPHENESIN, PARACETAMOL)
BEECHAMS FLU-PLUS (CAFFEINE, PARACETAMOL)
BETNOVATE RECTAL (BETAMETHASONE, LIGNOCAINE)
BOOTS COLD RELIEF (ASCORBIC ACID, CAFFEINE, PARACETAMOL, SODIUM CITRATE)
BRONCHILATOR (ISOETHARINE)
COLDREX 3 (ASCORBIC ACID, CAFFEINE, PARACETAMOL, TERPIN)
DIMOTANE PLUS ELIXIR (BROMPHENIRAMINE, PHENYLPROPANOLAMINE)
DIMOTANE WITH CODEINE (BROMPHENIRAMINE, CODEINE, GUAIPHENESIN, PHENYLPROPANOLAMINE, PSEUDOEPHEDRINE)
DIMOTAPP (BROMPHENIRAMINE, PHENYLPROPANOLAMINE)
DIMOTAPP P (BROMPHENIRAMINE, PARACETAMOL, PHENYLPROPANOLAMINE)
LEMSIP (ASCORBIC ACID, PARACETAMOL)
LEMSIP JUNIOR (ASCORBIC ACID, PARACETAMOL, SODIUM CITRATE)
LIGNOCAINE WITH PHENYLEPHRINE (LIGNOCAINE)
MEDIHALER-DUO (ISOPRENALINE)
NETHAPRIN DOSPAN (DOXYLAMINE)
SAFEWAYS HOT LEMON POWDERS (ASCORBIC ACID, PARACETAMOL)
STERWIN REAL LEMON COLD POWDERS (ASCORBIC ACID, PARACETAMOL)

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Blood and lymphatic system disorders				
Lymphatic system disorders NEC				
Lymphadenopathy	0	0	1	0
Leukocytoses NEC				
Eosinophilia	0	0	1	0
Neutropenias				
Granulocytopenia	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	3	0
Cardiac disorders				
Cardiac conduction disorders				
Bundle branch block right	1	0	0	0
Rate and rhythm disorders NEC				
Arrhythmia NOS	1	0	0	0
Bradycardia NOS	1	0	0	0
Tachycardia NOS	1	0	1	0
Tachycardia paroxysmal NOS	0	0	1	0
Ventricular arrhythmias and cardiac arrest				
Ventricular arrhythmia NOS	1	0	0	0
Cardiac signs and symptoms NEC				
Cyanosis NOS	0	0	1	0
Palpitations	0	0	1	0
SYS ORGAN CLASS TOTAL:	5	0	4	0
Congenital, familial and genetic disorders				
Non-site specific bone disorders congenital				
Skeleton dysplasia	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	1	0
Ear and labyrinth disorders				
Ear disorders NEC				
Ear pain	0	0	1	0
Hearing losses				
Deafness NOS	1	0	0	0
Inner ear signs and symptoms				
Vertigo	1	0	1	0
SYS ORGAN CLASS TOTAL:	2	0	2	0
Eye disorders				
Anterior chamber structural change, deposit and degeneration				
Anterior chamber disorder NOS	1	0	0	0
Corneal structural change, deposit and degeneration				
Corneal opacity	1	0	0	0
Ocular disorders NEC				
Eye pain	1	0	0	0
Glaucomas (excl congenital)				
Glaucoma NOS	0	0	1	0
Conjunctival infections, irritations and inflammations				

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Conjunctivitis	2	0	0	0
Ocular infections, inflammations and associated manifestations				
Eye redness	1	0	0	0
Retinopathies NEC				
Retinopathy NOS	0	0	1	0
Refractive and accommodative disorders				
Accommodation disorder	0	0	1	0
Visual disorders NEC				
Diplopia	0	0	1	0
Visual disturbance NOS	0	0	1	0
SYS ORGAN CLASS TOTAL:	6	0	5	0
Gastrointestinal disorders				
Acute and chronic pancreatitis				
Pancreatitis NOS	0	0	1	0
Non-site specific gastrointestinal haemorrhages				
Gastrointestinal haemorrhage NOS	0	0	1	0
Haematemesis	0	0	1	0
Melaena	0	0	1	0
Diarrhoea (excl infective)				
Diarrhoea NOS	0	0	4	0
Gastrointestinal atonic and hypomotility disorders NEC				
Constipation	0	0	3	0
Dyspeptic signs and symptoms				
Dyspepsia	0	0	1	0
Gastrointestinal and abdominal pains (excl oral and throat)				
Abdominal pain NOS	1	0	0	0
Gastrointestinal signs and symptoms NEC				
Dysphagia	0	0	1	0
Nausea and vomiting symptoms				
Nausea	2	0	0	0
Vomiting NOS	2	0	0	0
Oesophageal ulcers and perforation				
Oesophageal ulcer	0	0	1	0
Oral dryness and saliva altered				
Dry mouth	0	0	1	0
Tongue signs and symptoms				
Swollen tongue	0	0	3	0
Tongue oedema	0	0	1	0
SYS ORGAN CLASS TOTAL:	5	0	19	0
General disorders and administration site conditions				
Interactions				
Drug interaction NOS	0	0	3	0
Drug interaction inhibition	0	0	1	0
Therapeutic and nontherapeutic responses				
Drug withdrawal syndrome	0	0	3	0
Asthenic conditions				
Asthenia	0	0	2	0
Malaise	1	0	2	0
General signs and symptoms NEC				
Crepitations NOS	1	0	0	0
Hangover	0	0	1	0
Oedema NEC				
Anasarca	0	0	1	0
Oedema NOS	0	0	2	0
Oedema peripheral	0	0	2	0
SYS ORGAN CLASS TOTAL:	2	0	17	0
Hepatobiliary disorders				
Cholestasis and jaundice				
Jaundice NOS	0	0	2	0
Hepatocellular damage and hepatitis NEC				
Hepatitis NOS	0	0	2	1
SYS ORGAN CLASS TOTAL:	0	0	4	1
Immune system disorders				
Allergic conditions NEC				
Hypersensitivity NOS	0	0	1	0
Anaphylactic responses				
Anaphylactic reaction	1	0	2	0
SYS ORGAN CLASS TOTAL:	1	0	3	0
Infections and infestations				
Skin structures and soft tissue infections				
Cellulitis	0	0	1	0
Urinary tract infections				
Urinary tract infection NOS	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	2	0
Investigations				
Blood gas and acid base analyses				
Oxygen saturation decreased	1	0	0	0
Physical examination procedures				
Body temperature increased	0	0	1	0
Respiratory rate decreased	1	0	0	0
SYS ORGAN CLASS TOTAL:	2	0	1	0
Musculoskeletal and connective tissue disorders				
Arthropathies NEC				
Arthritis NOS	0	0	1	0
Joint related signs and symptoms				
Arthralgia	0	0	1	0
Osteoarthropathies				
Osteoarthritis NOS	0	0	1	0
Muscle related signs and symptoms NEC				
Muscle cramp	0	0	2	0
Musculoskeletal and connective tissue signs and symptoms NEC				
Muscle spasms	0	0	1	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Sensation of heaviness	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	7	0
Neoplasms benign, malignant and unspecified (incl cysts and polyp				
Leukaemias NEC				
Leukaemia NOS	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	1	0
Nervous system disorders				
Olfactory nerve disorders				
Anosmia	0	0	1	0
Headaches NEC				
Headache	0	0	4	0
Memory loss (excl dementia)				
Amnesia	0	0	2	0
Mental impairment (excl dementia and memory loss)				
Disturbance in attention	0	0	1	0
Mental impairment NOS	0	0	1	0
Dyskinesias and movement disorders NEC				
Movement disorder NOS	0	0	1	0
Dystonias				
Dystonia	0	0	1	0
Oculogyric crisis	0	0	1	0
Torticollis	0	0	1	0
Paralysis and paresis (excl congenital and cranial nerve)				
Hemiparesis	0	0	1	0
Paresis	0	0	1	0
Tremor (excl congenital)				
Tremor	0	0	1	0
Disturbances in consciousness NEC				
Loss of consciousness	0	0	1	0
Somnolence	0	0	4	0
Syncope	1	0	1	0
Neurological signs and symptoms NEC				
Dizziness	1	0	2	0
Paraesthesias and dysaesthesias				
Burning sensation NOS	0	0	1	0
Hypoaesthesia	0	0	2	0
Paraesthesia	0	0	3	0
Speech and language abnormalities				
Speech disorder	0	0	1	0
Seizures and seizure disorders NEC				
Convulsions NOS	0	0	1	0
Epilepsy NOS	0	0	2	0
SYS ORGAN CLASS TOTAL:	2	0	34	0
Psychiatric disorders				
Anxiety symptoms				
Agitation	0	0	2	0
Anxiety	0	0	1	0
Tension	0	0	1	0
Speech articulation and rhythm disturbances				
Screaming	0	0	2	0
Confusion and disorientation				
Confusional state	0	0	3	0
Perception disturbances				
Hallucination NOS	0	0	1	0
Hallucination, visual	0	0	1	0
Mood alterations with manic symptoms				
Mania	0	0	1	0
Emotional and mood disturbances NEC				
Euphoric mood	0	0	1	0
Behaviour and socialisation disturbances				
Irritability	0	0	3	0
Personality disorders NEC				
Personality disorder NOS	0	0	2	0
Psychiatric symptoms NEC				
Drug dependence	6	0	0	0
Psychotic disorder NEC				
Psychotic disorder NOS	0	0	3	0
Sexual desire disorders				
Libido increased	0	0	1	0
Disturbances in initiating and maintaining sleep				
Insomnia	0	0	2	0
Parasomnias				
Nightmare	0	0	2	0
Sleep walking	0	0	1	0
SYS ORGAN CLASS TOTAL:	6	0	27	0
Renal and urinary disorders				
Renal failure and impairment				
Oliguria	0	0	1	0
Renal failure NOS	0	0	1	1
Bladder and urethral symptoms				
Dysuria	0	0	2	0
Micturition disorder	0	0	2	0
Pollakiuria	0	0	3	0
Urinary retention	0	0	7	0
SYS ORGAN CLASS TOTAL:	0	0	16	1
Reproductive system and breast disorders				
Menstruation and uterine bleeding NEC				
Menstruation irregular	0	0	1	0
Menstruation with increased bleeding				
Metrorrhagia	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	2	0
Respiratory, thoracic and mediastinal disorders				
Bronchospasm and obstruction				
Asthma NOS	0	0	3	1

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Bronchospasm NOS	0	0	6	0
Wheezing	0	0	1	0
Lower respiratory tract inflammatory and immunologic conditions				
Alveolitis allergic	0	0	1	0
Pulmonary oedemas				
Pulmonary congestion	1	0	0	0
Pulmonary oedema NOS	1	0	0	0
Breathing abnormalities				
Dyspnoea	1	0	1	0
Respiratory failures (excl neonatal)				
Respiratory distress	1	0	0	0
Upper respiratory tract signs and symptoms				
Pharyngolaryngeal pain	0	0	1	0
Throat tightness	0	0	1	0
Nasal congestion and inflammations				
Rhinitis NOS	6	0	0	0
Pharyngeal disorders (excl infections and neoplasms)				
Oropharyngeal swelling	0	0	1	0
SYS ORGAN CLASS TOTAL:	10	0	15	1
Skin and subcutaneous tissue disorders				
Angioedemas				
Angioneurotic oedema	1	0	6	0
Face oedema	0	0	3	0
Periorbital oedema	0	0	4	0
Urticarias				
Urticaria NOS	1	0	20	0
Bullous conditions				
Erythema multiforme	0	0	2	0
Dermal and epidermal conditions NEC				
Swelling face	1	0	6	0
Dermatitis and eczema				
Dermatitis NOS	0	0	1	0
Dermatitis allergic	0	0	1	0
Erythemas				
Erythema	0	0	1	0
Rash erythematous	0	0	3	0
Exfoliative conditions				
Dermatitis exfoliative NOS	0	0	1	0
Pruritus NEC				
Pruritus	0	0	1	0
Pruritus generalised	0	0	1	0
Pustular conditions				
Rash follicular	0	0	1	0
Rashes, eruptions and exanthems NEC				
Rash NOS	2	0	7	0
Rash generalised	0	0	1	0
Rash scarlatiniform	0	0	1	0
Panniculitides				
Erythema nodosum	0	0	1	0
Apocrine and eccrine gland disorders				
Cold sweat	1	0	0	0
Sweating increased	1	0	0	0
Purpura and related conditions				
Purpura NOS	0	0	3	0
SYS ORGAN CLASS TOTAL:	7	0	64	0
Vascular disorders				
Vascular hypotensive disorders				
Hypotension NOS	1	0	0	0
Site specific vascular disorders NEC				
Pallor	1	0	0	0
Vascular hypertensive disorders NEC				
Hypertension NOS	2	0	2	0
SYS ORGAN CLASS TOTAL:	4	0	2	0
TOTAL REACTIONS FOR DRUG:	52	0	229	3

TOTAL REPORTS: 166 TOTAL FATAL OUTCOME: 3

*** END OF REPORT ***

THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

PHENYLEPHRINE

	ALL REPORT DATES	
	Causality Unclear Exclud	
	Total	Sole Suspected
- Cases Including Medicine	18	5
- Occurences of Medicine	18	5
- Reactions Related to Medicine	37	14
Anaphylactoid reaction	1	0
Application site reaction	4	1
Asthenia	1	0
Conjunctivitis	2	1
Corneal ulcer	2	0
Dysphagia	1	0
Face oedema	1	1
Flushing	1	1
Headache	1	0
Hyperhidrosis	1	0
Hypertension	5	4
Lacrimal disorder	1	0
Palpitations	1	0
Paraesthesia	1	0
Periorbital oedema	5	2
Rash	2	1
Rash erythematous	1	1
Respiratory disorder	1	1
Supraventricular tachycardia	1	0
Tachycardia	1	1
Urticaria	1	0
Visual disturbance	1	0
Vomiting	1	0