

**SUBMISSION FOR THE
RECLASSIFICATION OF A MEDICINE**

Guaiphenesin 600 mg and 1200mg modified
release tablets

January 2009

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EXECUTIVE SUMMARY

Reckitt Benckiser is planning to introduce a modified release formulation of guaiphenesin in two strengths; 600mg and 1200mg for adults and children over 12 years of age. The indication will be as an expectorant to thin and loosen mucus and to relieve chest congestion. The expectorant properties for guaiphenesin are well accepted and it has been a common ingredient in cough and cold preparations since at least the 1960's. Modified release tablets are a new dosage form that have not previously been registered or sold in New Zealand.

Currently guaiphenesin in oral liquid and divided preparations containing less than 2% or 200mg guaiphenesin are classified "General Sale". Hence the modified release dosage forms, containing a total of 600mg or 1200mg guaiphenesin will be, "Prescription Medicines", however the maximum daily dose from these formulations is within the current GSL range. We submit that this is an inappropriate classification for the modified release tablets.

Clinical trials have shown that the extent of exposure (AUCs) of guaiphenesin after single or multiple dosing of the modified release tablets 600 -1200mg twice daily (daily doses of 1200 - 2400mg) is comparable to AUC's after administration of an immediate release guaiphenesin product (200mg - 400mg), every four hours.

This modified release dosage form is able to reduce the frequency of dosing compared to immediate release preparations, thereby ensuring that the optimal dose is being used. The OTC access would benefit consumers by:

- lowering the risk of dosing errors,
- improving compliance, and
- providing easy access to a safe and effective sustained cough relief product,
- providing prolonged night-time cough relief facilitating rest and consequently recovery,
- providing an easier to use product for older consumers who can be confused by complex or frequent dosing regimens.

The classification of guaiphenesin as a general sale item also extends to Australia, UK, USA and Canada. In the United States of America (USA) guaiphenesin in modified release dosage forms of 600mg and 1200mg are classified as OTC and may be sold in grocery and other outlets.

The safety of the modified release guaiphenesin dosage form is supported by six years post-marketing data from the USA. It is estimated that between July 2002 to April 2008, over 53 million packs, a total of about 1.5 million tablets of modified release guaiphenesin were sold. A total of 2010 reports (2836 adverse events), regardless of whether they were medically confirmed or not, have been identified. These could be attributed to a daily dose of 1200mg or

2400mg. During this period, only five medically confirmed cases of serious events were received for modified release tablets.

Recovery with no sequelae was recorded for three patients while for two patients, the effects resolved after administration was stopped. There was no evidence that suggests a causal relationship between guaiphenesin and the serious AEs.

Safety in the OTC setting can be considered to be well established with use for over thirty years in key countries e.g. New Zealand, Australia, UK, Canada and USA with a total estimated population base of 400 million (taking into account that there may be underreporting). The reports of adverse events to guaiphenesin are very low and there have been no serious unexpected adverse events reported to date.

Cases of abuse and overdose are infrequent and are found when guaiphenesin is taken in combination with other actives, eg ephedrine, phenylpropanolamine, dextromethorphan. Kidney stones have been noted in patients who admitted to taking up to 24g per day of guaiphenesin, in combination with other actives. In another case a woman presenting with apparent acute psychoses reportedly took 800mL of Vicks Formula 44 (12.5 mg phenylpropanolamine, 15 mg dextromethophan and 100 mg guaiphenesin per 5 mL) for 18 months. The authors surmised that her psychosis was most likely the result of the phenylpropanolamine in the medication. If the patient's history is accurate, she consumed 16g of guaiphenesin per day for 18 months.

One fatality has been reported from a combination overdose with guaiphenesin, diphenhydramine and chlorpheniramine. The concentration of guaiphenesin found in the blood was 27.4mg/L (~ 20 times higher than peak blood concentrations after a single oral dose of 600mg (~1.g mg/L at 15 minutes)) which the authors believed to be the highest reported concentration associated with an acute intoxication.

To date, there is no indication of any abuse potential with guaiphenesin as a single active.

There are few risks associated with the use of guaiphenesin. The risks to modified release guaiphenesin are not expected to be any higher than for existing immediate release guaiphenesin products.

Guaiphenesin falls into Australian Pregnancy Category A which is defined as "Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed."

Conclusion

Guaiphenesin is the only substance that is approved as an expectorant in Australian Regulatory Guidelines for OTC Medicines

<http://www.tga.gov.au/docs/pdf/argom.pdf>http://www.fda.gov/cder/otcmonographs/Cold&cough/cold_cough_allergy_bronchodilator_antiasthmatic_expectoant_FR_19890228.pdf) and the US FDA monograph “Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-counter Human Use; Expectorant Drug Products for Over-the-Counter Human Use (http://www.fda.gov/cder/otcmonographs/Cold&cough/cold_cough_allergy_bronchodilator_antiasthmatic_expectoant_FR_19890228.pdf). It has a wide therapeutic index and is already readily available from pharmacy and grocery outlets in cold and flu preparations.

Cough and cold sufferers are familiar with self-medicating for their symptoms and have been doing so with Guaiphenesin for at least the past 30 years. The symptoms are self-limiting and usually last between 7 to 21 days.

Reckitt Benckiser considers a “General Sale” classification as the most appropriate for the proposed 600mg and 1200mg modified release tablets to facilitate availability to consumers and considers it justified on the basis of:

- the long OTC history of the use of the immediate release dosage forms in New Zealand (since early 60s) and overseas,
- the well known safety profile for guaiphenesin at doses up to 2400mg per day, including no known pattern of misuse or abuse, infrequent and generally mild adverse reactions, a wide therapeutic index such that deliberate or accidental ingestion is unlikely to be fatal,
- no known contraindications. Possible interactions with laboratory tests can be managed by withholding guaiphenesin,
- the equivalence of the modified release formulations of guaiphenesin 600mg and 1200mg to 4 hourly doses of immediate release 200mg and 400mg oral doses,
- no dose-dumping effects when administered with food,
- six years of post-marketing data from the USA on the modified release tablets to support its safety,
- delivering an optimum dose which can help to reduce the increasing pressure on medical services for the relief of minor ailments by promoting self-care,
- the availability of the medicine to populations living in rural or remote areas where access to scheduled medicines may be difficult,
- reducing the frequency of dosing thereby lowering the risk of dosing errors and improving compliance,
- providing prolonged night-time cough relief facilitating rest and consequently recovery,
- providing an easier to use product for older consumers who can be confused by complex or frequent dosing regimens.

PART A

1. *International Non-proprietary Name (or British Approved Name or US Adopted Name) of the Medicine*

Guaiphenesin (British Approved Name); guaifenesin (US adopted name). Also known as glyceryl guaicolate, guaiphenesin, guaicol glycerol.

2. *Proprietary Name*

MUCINEX®

3. *Name of company/organisation/individual requesting reclassification*

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4. *Dose form (s) and strength(s) for which a change is sought*

Modified release tablets of 600mg or 1200mg guaiphenesin.

5. **Pack size and other qualifications**

2, 20, 40, 60, 100 tablets

6. **Indications for which change is sought**

Expectorant – thins and loosens mucus (phlegm) to help relieve chest congestion¹.

7. **Present classification of medicine**

Currently the classification is:

Classification	Conditions (if any)
General Sale	Guaiphenesin for oral use in medicines containing 2% or less or 200 milligrams or less per dose form
Prescription	Guaiphenesin for oral use in medicines containing more than 2% or 200 milligrams per dose form

Hence, a modified release tablet with a total guaiphenesin content of 600 mg or 1200mg would be classified a Prescription Medicine even though the release rate of Guaiphenesin is within current general sale dosing guidelines.

8. **Classification sought**

Ingredient	Conditions (if any)	Classification
Guaiphenesin;	for oral use in medicines containing 2% or less or 200 milligrams or less per dose form; in modified release dose forms containing 600 or 1200 milligrams per dosage form.	General Sale
Guaiphenesin;	for oral use in medicines containing more than 2% or 200 milligrams per immediate release dose form or more than 600 and 1200mg per modified release per dose form	Prescription

¹ Copy of Mucinex label

9. Classification status in other countries (especially Australia, UK, USA, Canada)

COUNTRY	CURRENT CLASSIFICATION	COMMENTS
AUSTRALIA	OTC (Unscheduled) when in oral liquid or divided preparation containing 2% or 200mg or less of guaiphenesin per dosage unit.	National Drug and Poisons Schedule Classification (NDPSC) switch application has been submitted to allow for modified release dosage forms
	Prescription Medicine in all other cases	Schedule 4: except (a) in oral liquid preparations containing 2% or less of guaiphenesin; or (b) in divided preparations containing 200mg or less of guaiphenesin per dosage unit
UNITED KINGDOM	OTC (General sales) with a maximum dose of 200mg	List B: Consolidated list of substances in authorised medicines for General Sale - Guaiphenesin with a maximum dose of 200 mg from 18/12/90
UNITED STATES OF AMERICA	OTC (includes modified release preparations)	OTC since 1989 http://www.fda.gov/cder/otc_monographs/category_sort/expectorant.htm . Modified release MUCINEX [®] guaiphenesin tablet was switched from Rx-to-OTC in Dec 2002)
CANADA	OTC	Recommended dosing for guaiphenesin single ingredient products is 200-400 mg every 6 hours. Regulated as an 'old drug' and is sold over-the-counter.

Guaiphenesin is available as a general sales item in New Zealand, Australia, UK, Canada and the USA when presented as an oral liquid up to 2% or as divided solid oral dose preparations containing up to 200mg. In the United

States guaiphenesin, in modified release dosage forms of 600mg and 1200mg, is also classified as OTC.

10. **Extent of usage in NZ and elsewhere (e.g. sales volumes) and dates of original consent to distribute**

A database search on products containing guaiphenesin was performed on the Medsafe website. A total of 29 products are currently marketed (see Table 1)².

Table 1: Products currently approved in New Zealand

Guaiphenesin	Other Ingredients	Brands
Guaiphenesin 13.33 to 20mg/mL		<i>Actifed CC Chesty Cough Syrup, Tussinol Chesty Cough, Dimetapp Chest Congestion Drops Syrup, Dimetapp Chest Congestion Drops, Robitussin Chesty Cough oral solution, Robitussin Ex Cough Syrup, Robitussin Ex Paediatric Drops, Robitussin Paediatric Chesty Cough, Strepsils Chesty Cough Syrup, Vicks Formula 44 for Chesty Coughs, Vicks Formula 44 Honey for Chesty Coughs, Lemsip Chesty Cough Medicine</i>
Guaifenesin 20mg/mL	Pseudoephedrine hydrochloride 6 mg/mL	Benadryl Chesty Cough & Nasal Congestion Syrup, Robitussin PS
Guaiphenesin 20mg/mL	Bromhexine hydrochloride 0.6mg/mL	Benadryl Chesty Forte Oral Solution, Codral Chesty Cough Liquid Oral Solution, Duro-Tuss Chesty Forte , Duro-Tuss Junior Chesty
Guaiphenesin 20mg/mL	Bromhexine hydrochloride 0.8mg/mL	Dimetapp Chesty Cough Elixir, Robitussin ME Chesty Cough Forte
Guaiphenesin 7.5mg/mL	Choline theophyllinate 15mg/mL	Broncelix Expectorant Syrup, Amcal Expectorant Syrup
Guaiphenesin 5mg/mL	Choline theophyllinate 10mg/mL	Brondecon Expectorant Syrup ¹
Guaiphenesin 100mg	Paracetamol 250mg, Phenylephrine hydrochloride 5mg	<i>Coldrex PE Phenylephrine Cough Cold & Flu tablet</i>
Guaiphenesin 200mg	Paracetamol 1000mg, Phenylephrine hydrochloride 12.2mg	<i>Lemsip Max Cold & Flu + Chesty Cough, Lemsip Max Cold & Flu + Chesty Cough Lemon & Menthol, Lemsip Max Cold & Flu + Chesty Cough Wild Berry & Hot Orange</i>
Guaiphenesin 20mg/mL	Dextromethorphan hydrobromide monohydrate 3mg/mL	Robitussin DM
Guaiphenesin 10mg/mL	Dextromethorphan hydrobromide monohydrate 0.7 mg/mL	<i>Vicks Formula 44 Expectorant & Cough Suppressant Syrup</i>
Products in italics are classified "General Sales"		

² <http://www.medsafe.govt.nz/regulatory/DbSearch.asp>

12 of the 29 products on the market contain guaiphenesin as the single active ingredient at concentrations ranging from 10 to 20 mg/mL and maximum daily doses up to 2400 mg and all are classified “General Sale”. All of these products are liquid preparations and the frequency of dosing ranges from 4-6 hourly (see Table 2)

Table 2: Information from CMI or label regarding dosage & frequency

Products	dates of original consent to distribute	Guaiphenesin	Labelled Dose – Adults & Children over 12 years (Max daily dose)
Benadryl Chesty Cough & Nasal Congestion	28/1/98	10 mg/mL	10 mL every 4-6 hours (800 mg)
Lemsip Chesty Cough Medicine	10/2/2000	10mg/mL	20 mL 3-4 times a day (800 mg)
Robitussin Ex Cough Syrup	18/4/1996	20mg/mL	10-20 mL every 4 hours (1200-2400 mg)
Strepsils Chesty Cough Syrup	1/9/2005	20mg/mL	10 mL every 4 hours. (800 mg)
Vicks Formula 44 for Chesty Coughs	8/4/2004	13.33 mg/mL	15 mL every 4 hours. (1200 mg)

Most of the remaining guaiphenesin products are combined with other active ingredients which changes their classification to “Pharmacy Only” or “Class 3 Controlled Drug”.

There is currently no solid oral dosage preparation of guaiphenesin as a single active ingredient registered in New Zealand.

Modified release dosage forms of guaiphenesin are not yet registered or available in New Zealand.

In the USA, the modified release guaiphenesin 600mg tablet was approved in July 2002 and the higher strength 1200mg tablet was approved in December 2002. The reclassification of modified release guaiphenesin 600 and 1200mg tablets was approved by the FDA in December 2002.

11. Labelling of draft labelling for the proposed new presentation (s)

Please refer to a copy of a label attached for Mucinex 600 mg¹.

12. *Proposed warning statements if applicable*

Guaiphenesin has no required warnings. The following general warnings for Cough & Cold products are proposed:

“KEEP OUT OF THE REACH OF CHILDREN

Do not exceed the stated dose. Seek medical advice if your cough worsens or does not go away after a few days. Do not use if cap seal is broken or missing.”

13. *Other products containing the same active ingredient(s) and which would be affected by the proposed change.*

The proposed change in scheduling will not affect the classification of any other currently registered guaiphenesin medicines.

Part B

Reasons for requesting classification changes

This section should be supported where relevant by the following:

1. *A statement of the benefits to both the consumer and to the public expected from the proposed change*

Cough is a normal voluntary or reflex attempt to clear an irritant from the airways. In productive coughs, the irritant can be mucus secretions that are often the thick mucus or phlegm. Expectorants help to thin and loosen this mucus and so aid with its removal making coughing more effective in clearing the irritant.

As can be seen from Part A, point 10, most of the current cough and cold preparations containing Guaiphenesin are in liquid form and have to be taken every four hours.

Guaiphenesin is a common ingredient in 29 medicines registered with Medsafe and at least 80 cough mixtures registered with the TGA. At least a quarter of these products contain guaiphenesin as a single active ingredient and are already in the “unscheduled” category that can be sold in supermarkets, health food stores and other retailers. This indicates its safety profile at doses up to 2400mg per day is acceptable to Medsafe and the TGA.

The modified release formulation of guaiphenesin 600mg or 1200mg taken twice a day is equivalent to taking one or two immediate release tablets of guaiphenesin 200mg six times a day (every four hours). The benefits to the consumer are as follows:

- convenient dosage form that reduces the frequency of dosing and can ensure delivery of an optimal dose as an expectorant,
- improves compliance and lowers the risk of dosing errors,
- provides prolonged night-time cough relief facilitating rest and consequently recovery,
- provides an easier to use product for older consumers who can be confused by complex or frequent dosing regimens and lowers the risk of dosing errors,

- the tablet format makes the medicine more portable and easier to dose without need for measuring devices.

A “General Sale” classification will provide ready access to a proven effective sustained cough relief product without the need to visit a doctor for a prescription. This will reduce the strain on the healthcare system while promoting self-care.

2. *Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated*

Colds are one of the most common illnesses. An average person will have at least one cold per year³. The flu is similar, and sometimes has the same symptoms as a cold but is often much more severe and lasts longer. Cold and flu viruses attack the upper respiratory tract including the nose, nasal sinuses, throat, trachea and bronchi. They invade the moist lining of these structures and can cause a runny nose, sinus congestion, sneezing, sore throat and cough. Other typical symptoms include malaise and tiredness.

Since cold and flu are quite common, the symptoms are easily diagnosed by either the sufferer or a pharmacist. A productive cough may be the last symptom left after a cold or flu. Coughs are often worse when waking and when talking. Patients may feel congested and breathless, with the cough bringing up mucus or phlegm⁴.

Statistics from the UK⁵ presented at the recent Australian Self-Medication Industry Annual Conference in November 2008 by Fabian Dwyer, General Manager IMS Australia & New Zealand support that coughs and colds are considered minor ailments and comprise only 3.4% of the visits in a general practice. Since 50.5% of these patients do not receive a prescription for treatment, most patients with coughs are left to either seek advice from the pharmacies or self-medicate.

The symptoms have been adequately managed by the patients with rest, adequate hydration and self-selected decongestants and cough medicines⁵.

3. *Relevant comparative data for like compounds*

In 1990, the US FDA considered all expectorant ingredients used in cough mixtures ie antimony, potassium tartrate, chloroform, iodides

³ <http://quickcare.org/resp/colds.html>

⁴ <http://www.mydr.com.au/respiratory-health/cough-productive-or-wet-cough>

⁵ Fabian Dwyer. Driving the Self Care Agenda: Minor Ailment Workload in General Practice, Presentation ASMI Conference 19 November 2008.

(calcium iodide, anhydrous hydriodic acid syrup, iodised lime, potassium iodide), ipecac fluid extract, squill preparations, turpentine oil, ammonium chloride, beechwood, creosote, benzoin preparations, camphor, eucalyptol/eucalyptus oil, horehound, ipecac syrup, menthol/peppermint oil, pine tar preparations, potassium guaiailfulfonate, sodium citrate, terpin hydrate preparations and tolu preparations. It was concluded that guaiphenesin was the only monographed ingredient for expectorant use⁶.

Guaiphenesin is the only substance listed under Expectorants in the Australian Regulatory Guidelines for OTC Medicines (<http://www.tga.gov.au/docs/pdf/argom.pdf> pp. 111 of 159).

There are a number of cough & cold products registered with Medsafe containing ammonium salts, most of which are available as general sales medicines. A few older cough mixtures, such as Baxters Lung Preserver are still registered which contain ipecacuanha, however this active is no longer primarily used as an expectorant.

Table 3: Products containing ammonium salts as an active ingredient

Ingredient	Active	Other Active	Product/Classification/Year registered
Ammonium carbonate	Yes	Camphor, capsicum tincture, carrageenan, menthol, potassium bicarbonate	Buckleys Canadiol Mixture Linctus, (General sale) (1969)
Ammonium carbonate	Yes	Dextrometorphan, camphor, menthol	Buckley's DM Oral solution, . (General sale) (1998)
Ammonium chloride	Yes	Diphenhydramine, sodium citrate	Benadryl Original Cough Medicine Syrup**, (Restricted) (1969), Chesty Mucus Cough Mixture (Pharmacy Health) Syrup**, (Restricted) (2001)
Ammonium chloride	Yes	Diphenhydramine	Diphenhydramine Cough Mixture Syrup, (PSM) (Restricted) (1999), Diphenacough Syrup, 2.5mg/mL (Restricted); Diphenhydramine Cough Mixture Syrup, (PSM) (Restricted)

⁶ US FDA monograph "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-counter Human Use; Expectorant Drug Products for Over-the-Counter Human Use
http://www.fda.gov/cder/otcmonographs/Cold&cough/cold_cough_allergy_bronchodilator_antiasthmatic_expectorant_FR_19890228.pdf

** these products also contain sodium citrate as active ingredients.

Bromhexine is a mucolytic agent used to decrease the viscosity of secretions. There are 13 products registered with Medsafe. All are either Pharmacy Medicines or Controlled Drugs due to the presence of pseudoephedrine.

4. Local data or special considerations relating to NZ

The proposed reclassification would allow consumers ready access to a convenient, portable and long-lasting form of treatment for chesty coughs.

Guaiphenesin's expectorant properties are well accepted. It is already a common ingredient in cough and cold preparations and has been used for over 30 years at 200 - 400 mg every four hours = 1200 – 2400 mg per day

The modified release 600mg or 1200mg is delivering a maximum daily dose at a similar rate to currently registered immediate release guaiphenesin products for general sale:

Modified release 600 -1200mg twice a day = 1200 - 2400mg per day

equivalent to a dose of

200 - 400mg every four hours = 1200 – 2400mg per day

A general sales classification for the modified release tablets would benefit New Zealand consumers by:

- providing easy access to an effective sustained release cough relief product,
- providing prolonged night-time cough relief facilitating rest and consequently recovery,
- reducing the frequency of dosing compared to immediate release preparations and thereby ensuring that the optimal dose is being used,
- lowering the risk of dosing errors,
- improving compliance,
- providing an easier to use product for older consumers who can be confused by complex or frequent dosing regimens.

5. Interactions with other medicines

There are no reported interactions with other medicines.

6. Contraindications

Guaiphenesin is contraindicated for use in persons with known hypersensitivity or idiosyncratic reaction to guaiphenesin (or any of the other ingredients in the product).

Guaiphenesin has been shown to be porphyrinogenic in animals and should not be used in persons with porphyria.

Guaiphenesin should not be used for chronic or persistent cough associated with chronic lower respiratory tract diseases such as asthma, bronchitis, chronic obstructive pulmonary disease (COPD), emphysema or smoker's cough.

7. Possible resistance

Not applicable

8. Adverse events – nature, frequency etc

According to Martindale 35th Edition⁷, occasional adverse events with guaiphenesin are gastrointestinal discomfort, nausea and vomiting. However this is more often noted when large doses have been taken.

Other possible adverse effects associated with guaiphenesin include interference of plateletlet adhesiveness and bleeding time, lowering of serum uric acid due to uricosuric uricosuric effect⁸.

According to Martindale 35th Edition⁷, guaiphenesin is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals.

Post Marketing (Spontaneous) Reports Modified Release Formulations - USA

In the USA, the modified release guaiphenesin 600 mg tablet was approved in July 2002 and the higher strength modified release guaiphenesin 1200 mg tablet was approved in December 2002. These preparations are sold without a prescription at most food, drug and mass – merchandise stores. It is estimated that between July 2002 and March, 2008, over 53 million packs, a

⁷ Martindale, 35th Edition by Pharmaceutical Press, Coughs Suppressants Expectorants Mucolytics and Nasal Decongestants, pp: 1408

⁸ Australian NDPSC Submission

total of about 1.5 million tablets of modified release guaiphenesin were sold in the USA. A total of 2010 cases (2836 adverse events) have been reported for guaiphenesin modified release, regardless of whether they were medically confirmed or not. The breakdown per seriousness and expectedness is described (see Table 4).

Table 4: Number of spontaneous AE cases reported for modified release guaiphenesin up to 31st March, 2008.

	Serious		Non-serious	
	Expected	Unexpected	Expected	Unexpected
Mucinex®	-	5	560	1445

The adverse events are summarised by body system (MedDRA) and seriousness. The most commonly reported events were classified as:

- Gastrointestinal disorders (739 adverse events (AEs), mainly diarrhoea (156 AEs), nausea (125 AEs) and stomach discomfort (101 AEs))
- General disorders and administration site conditions (583 AEs), mainly drug ineffective (403 AEs)
- Nervous system disorders (482 AEs), mainly dizziness (145 AEs), headache (108 AEs) and insomnia (82 AEs).

During this period, only five medically confirmed reports were received. Recovery with no sequelae was recorded for three of the patients while for two patients the effects resolved after administration was stopped. These are listed below in Table 5:

Table 5: Summary of Medically Confirmed Serious AEs

Date Received	Guaiphenesin	MeDRA Term & Outcome
15/10/02	600 mg	Otorrhoea, haemoptysis, headache, International Normalised Ratio decreased. The patient required hospitalisation and recovered with no sequelae.
12/9/06	600 mg	Haemorrhagic stroke, oedema peripheral, abdominal distension. The patient required hospitalisation and recovered with no sequelae.
10/9/07	600 mg	Asthma. This was deemed serious. The event abated after the drug was stopped.
26/11/07	600 mg	Hallucination, dysarthria, gait disturbance, disorientation. The patient required hospitalisation and the events resolve after a few days.
16/3/08	600 mg	Asthenia, nervousness, dizziness, vomiting, blood pressure decreased, heart rate decreased, dizziness. The patient required

Date Received	Guaiphenesin	MeDRA Term & Outcome
		hospitalisation and recovered with no sequelae.

There is no evidence that suggest a causal relationship between modified release guaiphenesin and serious AEs⁸.

Pharmacovigilance data of other guaiphenesin products⁸

Guaiphenesin in various dosage forms has been available in New Zealand, Australia, the USA, Canada and the United Kingdom for many years. Spontaneous reports form a substantial body of evidence supporting a well characterised safety profile for guaiphenesin at single oral doses of 200mg-400mg and maximum daily doses of up to 2400mg are associated with a low incidence of adverse effects and no significant contra-indications.

Most spontaneous adverse event reports are for combination products or in situations where guaiphenesin has been co-administered with other actives. There are few AEs reported for single active guaiphenesin. This combined with the fact there has been a large quantity of guaiphenesin containing products sold globally over many years provides considerable reassurance that the safety profile has been well documented.

CARM Reports from New Zealand

There were 15 case reports from the Centre for Adverse Reactions Monitoring Medsafe from 1971 to September 2008. There were no reports in which guaiphenesin was listed as the only suspect medication. All adverse events were to guaiphenesin combined with other actives or co-administered with other drug products and consisted of diarrhoea (1), abdominal pain (1), skeletal pain (1), rash pruritic (1), headache (2), palpitation (2), vasoconstriction (1), tremor (2), brand switch (1), palpitation (2), convulsion (1), fever (1), vomiting (1), arrhythmia (1), jaundice (1), salivary gland enlargement (1), abdominal pain (2), confusion (1), tachycardia (1), pallor (1), granulocytopenia (1), and hearing impairment aggravated (1).

ADRAC reports - Australia

There are over 80 products in the ARTG that contain guaiphenesin as an active ingredient. Of these about 20 products contain guaiphenesin as a single active ingredient. Adverse events data on guaiphenesin were extracted from the 4 ADRAC searches on the different brand names from 1973 to August 2008. The results are tabulated in

Table 6: No of AE cases Reported for Products Containing guaiphenesin

Products containing guaiphenesin	Not co-administered	Co-administration with Other Products	Total
Actifed CC Chesty (& pseudoephedrine)	5	1	6
Amcal Chesty	1	0	1
Benadryl Chesty Forte (& pseudoephedrine)	2	1	3
Coldguard Chesty Mucus Medicines	1	0	1
Dimetapp Chesty Cough (& bromhexine)	1	0	1
Dimetapp Cold Cough & Flu caps	23	10	33
Logicin Mixture for Congested Chesty Coughs	1	1*	2
Orthoxicol Expectorant	4	0	4
Pharmacist Expectorant (& bromhexine)	0	1	1
Robitussin DM (& dextrometorphan)	8	10	18
Robitussin DM-P (& pseudoephedrine & dextrometorphan)	2	1	3
Robitussin ME (& bromhexine)	10	1	11
Robitussin PS (& pseudoephedrine)	2	0	2
Brondecon (& choline theophyllinate)	21	58#	79
Guaiphenesin	0	2	2
TOTAL	81	86	167
* 1 death # 2 deaths			

Among a total of 167 reports, there were only two in which guaiphenesin was listed as the only active ingredient in the product. Both cases showed that the product was coadministered with other active drug products. One report of adverse events included urticaria, while the other included facial oedema, pruritus, oedema peripheral. Of the remaining 167 reports, 81 were for guaiphenesin combined with other actives e.g. bromhexine, pseudoephedrine, dextrometorphan or choline theophyllinate and 86 reports had co-administration with other multiple active drug products.

There were 2 cases of deaths (ADRAC Case numbers 12558 and 100420) where Brondecon was coadministered with other products and 1 death attributed to Logicin Mixture for Congested Chesty Coughs coadministered with an antibiotic. The causality is rated as possible. These adverse events are summarised (Table 7).

Table 7: Adverse events with guaiphenesin from ADRAC

Guaiphenesin product	No of Reports	Adverse Events
Only active ingredient	2	4: Urticaria (1), face oedema (1), pruritus (1), oedema peripheral (1)
Combined with other actives but not co-administered with other drug products	81	155: Dyspnoea (9), dizziness (9), vomiting (8), nausea (7), diarrhoea (5), periorbital oedema (4), rash (4), insomnia (5), tremor (3), somnolence (3), oedema peripheral (3), face oedema (3), chest pain (3), anaphylactic reaction (3), angioedema (2), vision blurred (2), tachycardia (2), stomach discomfort (2), rash erythematous (2), pyrexia (2), paraesthesia (2), palpitations (2), muscle spasms (2), hyperkinesia (2), hypersensitivity (2), hypotension (2), loss of consciousness (2), urticaria (2), abdominal pain (2 drug ineffective (2), dry mouth (1), lip swelling (1), agitation (1), bronchospasm (1), conjunctivitis (1), convulsion (1), cough (1), cyanosis (1), depersonalisation (1), dermatitis (1), dyskinesia (1), dysphagia (1), dystonia (1), feeling abnormal (1), feeling hot (1),), eye disorder (2), gingivitis (1), hyperhidrosis (1), nervousness (1), nightmare (1), opisthotonos (1), orthostatic hypotension (1), pallor (1), pharyngitis (1), pruritus (1), rash generalised (1), rash macula-papular (1), rash pustular (1), regurgitation (1), stridor (1), throat irritation (1), hypoaesthesia (1), visual disturbance (1), anaphylactoid reaction (1), circulatory collapse (1), delirium (1), dysuria (1), erectile dysfunction (1), fatigue (1), hallucination (1), headache (1), heart rate irregular (1), hypertension (1), lethargy (1), malaise (1), medication error (1), mydriasis (1), paranoia (1), pain (1), pharmaceutical product complaint (1), restless leg syndrome (1), swollen tongue (1), syncope (1), urinary retention (1), visual impairment (1), convulsion (1), choking (1), accidental overdose (1).

Yellow Card System in the United Kingdom

An online search on the Drug Analysis Prints Report of suspected adverse drug reactions (ADRs) to guaiphenesin reported to the MHRA through the Yellow Card Scheme by healthcare professionals and patients in the United Kingdom from July 1963 to June 2008 yielded a total of 407 reactions in a total number of 194 reports. Of the 407 adverse events, 108 (in 54 reports) were to products where guaiphenesin is a single active ingredient. These are summarised below Table 8.

Table 8: UK Spontaneous ADR Reporting Guaiphenesin

No of AEs	System Organ Class	Adverse Event
20	Psychiatric disorders	Drug abuse (3), drug dependence (3), insomnia (2), hallucination (2), paranoia (2), confusional state (2), anxiety (1), aggression (1), disorientation (1), depression (1), sleep disorder (1), screaming (1).
16	Skin disorders	Urticaria (4), dermatitis allergic (2), angioedema (1), periorbital oedema (1), hyperhidrosis (1),

No of AEs	System Organ Class	Adverse Event
		erythema multiforme (1), pain of skin (1), eczema (1), rash erythematous (1), pruritus (1), purpura (1), rash generalised (1)
12	Nervous system disorders	Tremor (3), ataxia (2), hyperflexia (1), lethargy (1), somnolence (1), stupor (1), movement disorder (1), psychomotor hyperactivity (1), peripheral neuropathy (1)
10	Cardiac disorders	Tachycardia (5), Palpitations (1), cardiac failure (1), arrhythmia (1), atrial fibrillation(1), ventricular tachycardia (1)
10	Gastrointestinal disorders	Diarrhoea (1), abdominal pain (1), abdominal pain upper (1), abdominal pain lower (1), nausea (1), vomiting (1), haematemesis(1) , lip swelling (1), mouth ulceration (1), swollen tongue (1)
7	Immune system disorders	Hypersensitivity (4), anaphylactic reaction (1), anaphylactoid reaction (2)
6	Eye disorders	Eye swelling (1), photophobia (1), miosis (1), mydriasis (1), retinal artery spasm (1), scotoma (1)
6	General disorders	Asthenia (1), condition aggravated (1), irritability (1), drug interaction (1), face oedema (1), chest pain (1)
5	Respiratory disorders	Dyspnoea (1), respiratory depression (1), tachypnoea (1), asthma (1), cough (1)
4	Investigations	Blood glucose increased (3), international normalised ratio increased (1)
3	Renal and urinary disorders	Micturition disorder (1), renal failure (1), haematuria (1)
2	Blood disorders	Aplastic anaemia (1), thrombocytopenia (1)
2	Injuries	Expired drug administered (1), accidental overdose (1)
2	Muscle & tissue disorders	Backpain (1), rhandomyolysis (1)
1	Metabolic disorders	Hypoglycaemia (1)
1	Social circumstances	Pharmaceutical product complaint (1)
1	Vascular disorders	Hypertension (1)
108		TOTAL

MedEffect in Canada

An online search was conducted on the Canadian Adverse Reactions to Drug and Other Health Products “MedEffect Canada” on guaiphenesin. A total of 147 reports were found from 1963 to September 2008. None of these reports were attributed to guaiphenesin single ingredient product. All products contained guaiphenesin in combination with other actives.

Conclusion

Guaiphenesin has a long OTC history of use in immediate release oral solid and liquid dosage forms worldwide. It is mainly used in combination with other active in coughs and cold preparations. It has a well established safety profile at doses up to 2400 mg per day.

Six years of post-marketing data from the USA on the modified release tablets are now available and support its safety.

Other safety monitoring data from key regulatory agencies have shown that the incidence of adverse effects to guaiphenesin as a single active ingredient is relatively low compared to guaiphenesin combination products (see *Table 9*).

Table 9: Pharmacovigilance Data from Key Regulatory Agencies

Country	Population (million) 2008	No of Reports	No of reports to Guaiphenesin as a single active
Australia - ADRAC (1973 – Sep 08)	20	167	2
UK (1963 to 06/08)	60	194	108
New Zealand (1971-08/08)	4	15	0
Canada (1963-08/08)	33	147	0
Total	417	618	113

The evidence collected to date demonstrated that it is highly unlikely that the 600mg or 1200mg guaiphenesin modified release tablets will lead to an increase in ADRs since maximum daily doses of 1200 mg and 2400 mg have already been used in existing unscheduled/general sale products.

Overdosage⁸

Acute overdoses with guaifenesin are infrequently reported. The drug is not recognised to produce clinically important adverse effects even at doses several times those recommended therapeutic doses.

Overdose with guaifenesin is unlikely to produce toxic effects since its toxicity is low. An LD50 of 2553 mg/kg calculated during a study investigating the pharmacological activity of guaiphenesin administered by stomach tube to anaesthetised rabbits. Guaifenesin, when administered by stomach tube to test animals in doses up to 5 g/kg, produced no signs of toxicity. Hence, the data indicate a large margin of safety over the guaiphenesin 600-1200 mg (0.85-17 mg/kg) provided by the recommended dose of modified release guaiphenesin even if a dose-dumping rather than the expected sustained release was to occur.

In severe cases of overdose, treatment should be aimed at reducing further absorption of the drug, e.g. activated charcoal if given one to two hours after ingestion.

Overdose may cause gastrointestinal discomfort and very large doses may result in nausea and vomiting.

In a single case report reported by Wogoman and co-workers a 48-year old woman found dead in her residence. The toxicologic analysis performed post mortem indicated a combination overdose with guaifenesin, diphenhydramine and chlorpheniramine. The concentration of guaifenesin found in her blood was 27.4 mg/L (~ 20 times higher than peak blood concentrations after a single oral dose of 600 mg (~1.g mg/L at 15 minutes)) which the authors believed to be the highest reported concentration associated with an acute intoxication.

Chronic overdose⁸

Chronic overdosage of guaifenesin- sympathomimetic amine combination products has been reported in patients seeking to abuse the sympathomimetic component.

In one report, a 25-year old woman reportedly had a daily ingestion of 800 mL of Vicks Formula 44 (12.5 mg phenylpropanolamine, 15 mg dextromethophan and 100 mg guaifenesin per 5 mL) for 18 months. On presentation she was described as exhibiting symptoms consistent with an acute psychosis. She recovered uneventfully and her psychosis resolved within three days without symptoms of withdrawal. The authors surmised that her psychosis was most likely the result of the phenylpropanolamine in the medication. If the patient's history is accurate, she consumed 16 g of guaifenesin per day for 18 months.

Kidney stones have been noted in patients who admitted to taking large doses of guaifenesin of up to 24 g per day. Analysis of the stones revealed that they were largely composed of a carboxylate salt of the guaifenesin metabolite beta-(2-methoxyphenoxy) lactic acid. In a study by Ramsdell and Kelley, 6629 uric acid measurements were taken from a general hospital population and 64 of these were found to be hypo uric. Of these, six had been taking guaifenesin and there was some speculation that the drug may have caused the modest hypouricaemia, though it was not known to alter uric acid metabolism.

No other effects attributed to the guaifenesin have been described in these reports even though the reported ingestions in some cases were in excess of 100 tablets (12.5 mg ephedrine and 200 mg guaifenesin) per day. This would simply over 20 g of guaifenesin ingested per day. The reports of an increased frequency of renal stone disease were subsequent to the FDA's removal, in 1994, of mono component ephedrine from OTC availability.

9. Potential for abuse or misuse

Guaifenesin is not recognised to have any abuse potential.

The drug may, however, have central nervous system effects. At intravenous doses of 110 mg/kg, guaifenesin is used as a muscle relaxant during

anaesthesia in horses and other large animals for short-term surgical procedures. There is no approved parenteral formulation of guaifenesin for humans and the dose recommended for animals is approximately 20-fold higher on a per kilogram basis than the maximum adult dose recommended for oral use (400 mg or 6 mg/kg).

The mechanism of action for the muscle relaxation is not known, though it is thought the agent may act centrally.

There has been one report of chronic abuse where high doses of guaiphenesin were taken in combination with ephedrine. Doses of up to 24g of guaiphenesin have been taken without fatality (see Part B, 8).

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