NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Duro-Tuss Cough Liquid Expectorant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 mL of the medicine contains: pholcodine 15 mg and bromhexine hydrochloride 12 mg.

Excipients with known effect:
Methyl hydroxybenzoate, propyl hydroxybenzoate, saccharin sodium and sorbitol.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Clear green, slightly viscous liquid with an odour of grenadine.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clearing chest congestion and relieving coughs.

4.2 Dose and method of administration

For oral administration.

Age	Dosage	How often
Adults & children 12 years & over	10 – 15 mL	Every 6 hours as required (Maximum 4 times a day)
Children 6 – 11 years	5 – 10 mL	
Children under 6 years	Do not use	

4.3 Contraindications

- Children under the age of 6 years.
- Hypersensitivity to pholcodine, bromhexine hydrochloride or any of the excipients listed in section 6.1.
- Patients in, or at risk of, developing respiratory failure or during acute asthma attacks, as it may depress respiration.
- Patients with chronic bronchitis, COPD, bronchiolitis or bronchiectasis due to sputum retention.
- Patients with renal or hepatic failure.
- Patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment (see also section 4.5).

4.4 Special warnings and precautions for use

Use with caution in patients with liver or renal disease.

Duro-Tuss Cough Liquid Expectorant should be used with caution in patients with chronic or persistent cough, asthma, including an acute asthma attack, or where cough is accompanied by excessive secretions.

Use with caution in patients with gastric ulceration.

Concomitant use of Duro-Tuss Cough Liquid Expectorant with other medicines intended to treat the symptoms of the common cold is not recommended.

Patients should be advised to expect an increase in the flow of mucus secretions.

Severe cutaneous adverse reactions (SCARs) including acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in patients treated with pholcodine-containing products, most likely in the first week. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Duro-Tuss Cough Liquid Expectorant should be withdrawn immediately.

Cross-reactivity leading to serious allergic reactions (anaphylaxis) have been reported between pholcodine and Neuromuscular Blocking Agents (NMBAs). A precise at-risk period of time between the exposures of pholcodine and NMBAs has not been determined. Clinicians should be aware of this potential in case of future anaesthetic procedures involving NMBAs.

Use of pholcodine with alcohol or other central nervous system (CNS) depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses.

This product contains sorbitol which may have a laxative effect or cause diarrhoea in some people.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

There have been very few reports of severe skin lesions such as Stevens Johnson Syndrome and toxic epidermal necrolysis (TEN) in temporal association with the administration of expectorants such as bromhexine hydrochloride. Mostly, these could be explained by the severity of the patient's underlying disease and or concomitant medication. In addition, during the early phase of a Stevens-Johnson syndrome or TEN a patient may first experience non-specific influenza-like prodromes like fever, aching body, rhinitis, cough and sore throat. Misled by these non-specific influenza-like prodromes it is possible that a symptomatic treatment is started with a cough and cold medication. Therefore, if new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with bromhexine hydrochloride should be discontinued as a precaution.

4.5 Interaction with other medicines and other forms of interaction

Do not use in patients taking MAOIs or within 14 days of stopping treatment.

Interaction with neuromuscular blocking agents (anaphylaxis) has been reported (see Section 4.4).

The reduction in blood pressure caused by antihypertensives may accentuate the hypotensive effects of pholcodine. Diuretics may have the same effect.

Pholcodine may enhance the sedative effect of CNS depressants including alcohol, barbiturates, hypnotics, narcotic analgesics, sedatives and tranquillisers (phenothiazines and tricyclic antidepressants).

Following the administration of bromhexine, the antibiotic concentrations of amoxycillin, erythromycin and oxytetracycline in the sputum and bronchopulmonary secretions are increased.

Bromhexine pharmacokinetics are not relevantly affected by co-administration of ampicillin or oxytetracycline. There was also no relevant interaction between bromhexine and erythromycin according to a historical comparison. The lack of any relevant interaction reports during the long-term marketing of the drug suggests no substantial interaction potential with these drugs.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy: Category A

The safety of pholcodine during pregnancy has not been established. Risk vs benefit must be considered before using pholcodine during pregnancy or lactation. There is a risk of gastric stasis in the mother during labour which may lead to inhalation pneumonia. Teratogenic effects in humans have not been documented but controlled studies have not been done, nor have studies in animals been documented for pholcodine.

There is limited data from the use of bromhexine in pregnant women.

Use in lactation: It is not known whether pholcodine is excreted in breast milk or whether it has a harmful effect on the breastfeeding infant. Pre-clinical studies have shown excretion of bromhexine and its metabolites in breast milk.

Therefore, Duro-Tuss Cough Liquid Expectorant is not recommended during pregnancy unless it is considered essential by the physician.

4.7 Effects on ability to drive and use machines

This medicine can impair cognitive function and can affect a patient's ability to drive safely or operate machinery.

Patients should therefore exercise caution before driving or use of machinery until they know Duro-Tuss Cough Liquid Expectorant does not adversely affect their performance.

4.8 Undesirable effects

The following side effects may be associated with the use of pholcodine:

Nervous system disorders: Occasional drowsiness, dizziness, excitation, confusion

Respiratory, thoracic and mediastinal disorders: Sputum retention

Gastrointestinal disorders: Vomiting, gastrointestinal disturbances (nausea and constipation)

Skin and subcutaneous tissue disorders: Skin reactions including rash.
Acute generalized exanthematous pustulosis (see section 4.4).

Immune system disorders: Hypersensitivity reactions and anaphylaxis.

The following side effects may be associated with the use of bromhexine hydrochloride:

Immune system disorder: hypersensitivity, anaphylactic reaction, anaphylactic shock.

Skin and subcutaneous tissue disorders: angioedema, rash, urticaria, pruritus.

Respiratory, mediastinal and thoracic disorders: bronchospasm.

Gastro-intestinal disorders: Nausea, vomiting, diarrhoea and abdominal pain upper.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Pholcodine is thought to be of low toxicity, but the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. A toxic dose in children is reported to be about 200 mg.

Symptoms: These include nausea, drowsiness, restlessness, excitement, ataxia and respiratory depression.

No specific overdose symptoms have been reported in humans to date for bromhexine.

Management: Treatment of overdose should be symptomatic and supportive. In cases of severe poisoning the specific narcotic antagonist nalaxone may be used.

Information for children:
Nalaxone has been used successfully to reverse central or peripheral opioid effects in children (0.01mg/kg body weight). Another treatment option is activated charcoal (1g/kg body weight) if more than 4mg/kg has been ingested within 1 hour, provided the airway can be protected.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pholcodine is a cough suppressant with mild sedative but little analgesic or euphorigenic activity. It suppresses the cough reflex by a direct central action, probably in the medulla or pons.

Bromhexine is a synthetic derivative of the herbal active ingredient vasicine.

Pharmacotherapeutic group: R05FA Opium derivatives and expectorants

5.2 Pharmacokinetic properties

Absorption

Following oral administration, bromhexine shows dose linear pharmacokinetics in the dose range of 8-32 mg. It is rapidly and completely absorbed from the gastrointestinal tract. The bioavailability after oral administration is substantially reduced by an extensive first-pass effect in the range of 70-80%. Concomitant food intake tended to increase bromhexine plasma concentrations probably due to partial inhibition of the first pass-effect.

For pholcodine, the maximum plasma concentrations are attained at 4 to 8 hours after an oral dose.

Distribution

After intravenous administrations bromhexine was rapidly and widely distributed throughout the body with a mean volume of distribution (Vss) of up to 1209 ± 206 L (19 L/kg). The distribution into lung tissue (bronchial and parenchymal) was investigated after oral administration of 32 mg and 64 mg bromhexine. Lung-tissue concentrations two hours post dose 1.5 - 4.5 times higher in bronchiolo-bronchial tissues and between 2.4 and 5.9 times higher in pulmonary parenchyma compared to plasma concentrations. Unchanged bromhexine is bound to plasma proteins by 95 % (non-restrictive binding).

Pholcodine is protein bound to the extent of 23.5%.

Metabolism

Bromhexine is almost completely metabolised to a variety of hydroxylated metabolites and to dibromanthranilic acid. All metabolites and bromhexine itself are conjugated most probably in form of N-glucuronides and O-glucuronides. There are no substantial hints for a change of the metabolic pattern by a sulphonamide, oxytetracycline or erythromycin. Thus, relevant interactions with CYP450 2C9 or 3A4 substrates are unlikely.

Pholcodine is metabolised in the liver but undergoes little conjugation. There is little or no metabolism of pholcodine to morphine.

Elimination

Bromhexine is a high extraction ratio drug (CL after intravenous administration is ~843-1073 mL/min) resulting in high inter- and intra-individual variability. Bromhexine is almost completely metabolised to a variety of hydroxylated metabolites and to dibromanthranilic acid. Ambroxol is a metabolite of bromhexine. After administration of radiolabelled bromhexine, about 97.4 ± 1.9 % of the dose was recovered in the urine, with less than 1% as the parent compound. Unchanged bromhexine is 95% bound to plasma proteins. Bromhexine plasma concentrations showed a multi-exponential decline. After administration of single oral doses between 8 and 32 mg, the terminal elimination half-life of bromhexine ranged between 6.6 and 31.4 hours. The relevant half-life to predict the multiple dose pharmacokinetics is about 1 hour. No accumulation was observed after multiple dosing (accumulation factor 1.1).

Pholcodine elimination half-life ranges from 32–43 hours and volume of distribution is 30–49 L/kg.

Linearity/Non-linearity

Bromhexine shows dose proportional pharmacokinetics in the range of 8-32 mg following oral administration.

Special populations

There are no data for bromhexine pharmacokinetics in the elderly or in patients with renal or liver insufficiency. Extensive clinical experience did not give rise to relevant safety concerns in these populations.

5.3 Preclinical safety data

Preclinically, bromhexine has been shown to increase the proportion of serous bronchial secretion. Bromhexine enhances mucus transport by reducing mucus viscosity and by activating the ciliated epithelium (mucociliary clearance). Clinical studies show that bromhexine has a secretolytic and secretomotoric effect in the bronchial tract area, which facilitates expectoration and eases cough.

For pholcodine, there are no preclinical data of relevance which are additional to that already included.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid
Glycerol
Grenadine flavour 053040
Hyetellose
Methyl hydroxybenzoate

Patent blue V
Propyl hydroxybenzoate
Purified water
Quinoline yellow
Saccharin sodium
Sorbitol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

Amber PET bottle with polypropylene CRC tamper evident wadded cap.
Pack size: 100 and 200 mL

6.6 Special precautions for disposal

No special requirements

7 MEDICINE SCHEDULE

S3 – Pharmacist Only medicine

8 SPONSOR

iNova Pharmaceuticals (New Zealand) Limited
C/- Simpson Grierson,
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Telephone: 0508 375 394

9 DATE OF FIRST APPROVAL

16 March 2023

10 DATE OF REVISION OF THE TEXT

16 March 2023

SUMMARY TABLE OF CHANGES

Section changed:	**Summary of new information:**
All	New data sheet