Scheduling Evaluation Report

Application to amend the Poisons Standard with respect to amygdalin and hydrocyanic acid for human therapeutic use

Chinese Medicine Industry Council of Australia Ltd (CMIC)

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1. EXECUTIVE SUMMARY

The Chinese Medicine Industry Council requests:

a) A rescheduling of amygdalin from Schedule 10 to Schedule 4 except when included in or expressly excluded from Schedule 4;

b) A new Schedule 4 entry for amygdalin when included as a natural component in traditional Chinese medicines for oral use in adults with an exclusion to 'unscheduled' when the maximum recommended daily dose is equivalent to no greater than 5 mg of amygdalin; and

c) A change to the Schedule 4 entry for hydrocyanic acid with an exclusion when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults.

Amygdalin (D-mandelonitrile-β-D-glucoside-6-β-glucoside) is a cyanogenic glycoside found naturally in plants including seeds of the Prunus genus. It is metabolised in mammalian gut by enzymes in the gut wall and gut flora to hydrogen cyanide. Amygdalin is currently prohibited from use in therapeutic goods in Australia even at very low levels.

Studies have found the oral single dose that is lethal to 50% of animals (LD_{50}) is in the range 522 to 880 mg/kg for amygdalin and 3 to 22 mg cyanide ion/kg for cyanide in rats. In mice the single dose lethal to 10% of animals (LD_{10}) is approximately 450 mg/kg for orally administered amygdalin, and 4.2 mg/kg in intraperitoneally administered cyanide.

In longer term studies (13 weeks) no observable toxic effects were observed after oral exposure to 4.5 mg/kg/d cyanide in rats and 26 mg/kg/d in mice. After 12 months on a diet containing 50% cassava (containing a different cyanogenic glycoside to amygdalin and resulting in exposure to approximately 0.102 mg cyanide per day) rats displayed impaired motor coordination and cellular changes in liver and pancreas. Amygdalin and cyanide are not observed to be carcinogenic in animal studies. Amygdalin has been shown to be genotoxic in some but not all test systems. Cyanide has been found to be negative in genotoxicity tests systems at non-cytotoxic doses.

Amygdalin has been shown to produce foetal abnormalities at close to materno-toxic doses in hamsters when administered in a single dose. The effects of amygdalin from ground apricot kernels on reproduction in rats is unclear. In rabbits cyanide at 5 g/100 g in the diet produced impaired fertility. A diet of raw cassava resulted in impairments in fertility and some reproductive and developmental parameters at materno-toxic doses, but no effects when the cassava content in the diet was 45% or less.

Case reports suggest that toxicity in adults can occur with oral amygdalin/laetrile in single doses ranging from 3 g to 10.5 g (but this could be as low as 0.6g) and daily

doses from 0.42 g to 1.5 g, with fatality at doses of 3g and 10.5g in adults and 0.5-2.5 g in infants. Toxicity in adults has been reported after ingestion of single doses of apricot or peach kernels containing the equivalent of 25 mg to 1384 mg amygdalin or after ingestion of other seed containing preparations (bitter almonds plus laetrile tablets, apple seeds, or chokecherries) with a total estimated amygdalin content ranging from 60 mg to 4 g. However, little evidence of toxicity has been observed in clinical studies using a combination of IV amygdalin treatment plus oral amygdalin in doses of 1.5 g or 2g daily. Based on the average lethal dose of cyanide, which is reported to be in the range 0.5 to 3.5 mg/kg, the lethal dose of amygdalin in adults is estimated to be 9 to 60 mg/kg (540 to 3600 mg for a 60 kg adult).

This suggests that there is significant variability in the toxic response to amygdalin ingestion. The severity of cyanide toxicity is known to be influenced by a range of factors which affect the metabolism and detoxification of amygdalin to cyanide, including the amygdalin content of the herbal ingredient, which may vary depending on varietal differences, seasonal effects on growth, freshness, and processing; the β-glucosidase content of the herbal ingredient, which aids the conversion of amygdalin to cyanide; the route of administration, e.g. oral administration results in higher cyanide levels compared to IV administration, which bypasses the gut β-glucosidase enzymes; chewing or processing (e.g. grinding) of the herbal ingredient, which can release the β-glucosidase in the herbal ingredient, increasing the conversion to cyanide; co-administration with other substances (e.g. other herbal ingredients) that may influence either the metabolism of amygdalin to cyanide or the detoxification of cyanide; and inter-individual variability with respect to gut microbial flora and nutritional status.

On the basis of animal studies, regulatory authorities have concluded that oral intake of 5 to 20 µg/kg/d of cyanide is not of toxicological concern over the long term, and Food Standards Australia New Zealand have established an acute reference dose for cyanide of 0.8 mg/kg bw for short term intake. Assuming complete hydrolysis of amygdalin to cyanide, the amount of amygdalin producing 5 to 20 µg hydrogen cyanide is 84 to 338 µg. Thus, a daily oral intake of 5.1 to 20.3 mg amygdalin for a 60 Kg adult and 1.7 to 6.8 mg for a 20 kg child is considered to present no appreciable risk. A dose of 5 mg amygdalin is also lower than the permitted quantity in some foods and drinks.

However, there is less evidence for the safety of higher doses of amygdalin, especially considering the wide variability on cyanide toxicity observed following oral administration of amygdalin-containing substances.

The safety data may support the exclusion from Schedule 10 for medicines containing a maximum daily dose of less than 5 mg amygdalin but do not support the proposed exclusion from Schedule 10 when included as a natural component in traditional Chinese medicines for oral use in adults and inclusion in Schedule 4 at a maximum daily adult dose of more than 5 mg).

2. PURPOSE OF APPLICATION

Regulatory background issues

The Submission included information provided by the Medicines Scheduling Secretariat Team (23 November 2017) relating to the available scheduling history of amygdalin, which is summarised as follows:

Date	Amygdalin Scheduling	Reason for decision
November 1974	A new entry for '*amygdalin including defatted kernels of bitter almonds, apricots and peaches containing amygdalin*' was created in the prohibited list of the Uniform Poisons Standard	On the basis of its supply as a new drug for the treatment of cancer (Laetrile)
May 1975	No apparent action regarding the scheduling of amygdalin	Evidence provided by the Australian Drug Evaluation Committee which indicated that there was no evidence that amygdalin had any effect against cancer and no evidence of its safety
November 1977	The PSSC considered a proposal to amend the scheduling of amygdalin to Schedule 7 and recommended that the production of amygdalin in Australia under proper supervision, and its distribution under strict controls, as proposed in Victoria, free of charge, should be investigated as a matter of urgency.	To allow compassionate use in Victoria in certain cancer patients, to eliminate the exploitation of cancer patients. Although new toxicity data were considered adequate, in making this statement the PSSC in no way implies the admission of efficacy or any therapeutic value of amygdalin.
August 1986	The DPSC noted that amygdalin was still being imported on an individual patient usage basis despite the opinion that there is no evidence of its efficacy in the treatment of advanced cancer. The scheduling of amygdalin at this time was noted to be Schedule 7 and it is assumed that this recommendation occurred in November 1977.	No information is available regarding the wording of the Schedule 7 nor reasons for its inclusion
August 1992	Included amygdalin for therapeutic use in Appendix C of the SUSDP (now Schedule 10)	Due to concerns about its serious toxicity profile and lack of efficacy data

November 1999	NDPSC clarified that the SUSDP entry for amygdalin acid does not apply to sweet almond oil	
February 2000	NDPSC recommended to the NZ Minister Of Health that amygdalin be moved into Part 1 of the Medicines Regulations (Prescription medicines)	This recommendation relates to the harmonisation of scheduling of 'medicines banned from human therapeutic use' in Australia (listed in Appendix C to the SUSDP) and New Zealand. It appears that no new efficacy or safety data were considered by the NDPSC. At the time, amygdalin was not scheduled in NZ2005. The NZ MCC agreed that amygdalin should be classified as a prescription medicine at all strengths to harmonise with the Australian Appendix C scheduling. [1]
February 2005	When considering the availability of certain substances for therapeutic use listed in Appendix C, the NDPSC agreed that no action should be taken at the time to limit availability of amygdalin	Amygdalin for the treatment of terminal cancers appeared to be the Appendix C substance most often accessed through the Special Access Scheme (SAS) (under Category A notification for "life threatening conditions"). The committee did express concern however over the apparent contradiction that certain substances which had been included in Appendix C on the grounds that they present such danger to health as to warrant prohibition should be made available for therapeutic use under special circumstances.

This information indicates that in 1974, amygdalin was included in the prohibited list of the Uniform Poisons Standard on the basis of its supply as a new drug for the treatment of cancer (Laetrile). At a later date (presumably in November 1977), the scheduling of amygdalin was amended to Schedule 7 of the SUSDP to allow compassionate use in Victoria in certain cancer patients, despite the lack of efficacy data for this use but taking into account the adequacy of the toxicity data. The scheduling of amygdalin was last amended in August 1992 to include amygdalin for therapeutic use in Appendix C of the SUSDP (now Schedule 10), due to concerns about its serious toxicity profile and lack of efficacy data. As part of the harmonisation of the scheduling of Appendix C medicines, the NDPSC recommended

[1] https://medsafe.govt.nz/profs/class/Agendas/agen htm

to the NZ Minister Of Health in 2000 that amygdalin be moved into Part 1 of the Medicines Regulations (Prescription medicines), which ensures that the regulatory process will prevent their being granted consent to market. In order to prevent their use in even very low concentrations, the New Zealand schedule includes the words "at all strengths".

The scheduling of amygdalin was not considered again until 2005, when the NDPSC agreed that no action should be taken at the time to limit its availability for therapeutic use, despite concerns that substances of such danger to health as to warrant prohibition of sale, supply and use but expressed concern over the apparent contradiction that certain substances which had been included in Appendix C on the grounds that they present such danger to health as to warrant prohibition should be made available for therapeutic use under special circumstances.

Current entries in SUSMP

AMYGDALIN for therapeutic use is included in Schedule 10 (substances of such danger to health as to warrant prohibition of sale, supply and use).

HYDROCYANIC ACID is included in Schedules 4 and 7 and in Appendices F, G and J, as follows:

- HYDROCYANIC ACID for therapeutic use is included in Schedule 4
- HYDROCYANIC ACID is included in Schedule 7 **except**:
  a) when included in Schedule 4; or
  b) its salts and derivatives other than cyanides separately specified in this Schedule.
- HYDROCYANIC ACID, when included in Schedule 7, is required to be labelled with the following Appendix F Warning Statements and Safety Directions:
  - Warning Statement 13: 'May be fatal if inhaled, swallowed or absorbed through skin'.
  - Safety Directions 4: 'Avoid contact with skin' and 8: 'Avoid breathing dust (or) vapour (or) spray mist'.
- Appendix G (Dilute preparations): The requirements of this Standard do not apply to HYDROCYANIC ACID at a concentration not more than 1 microgram per litre or kilogram.
- Appendix J (Schedule 7 poisons requiring additional controls on availability and use): HYDROCYANIC ACID AND CYANIDES: Poisons marked with 'p' have been identified as representing a significant risk to public health. Additional restrictions on their possession and use must be applied through an authorisation or licensing process which includes a case by case assessment of risks to public health.

Proposed changes

The Chinese Medicine Industry Council requests:

d) A rescheduling of amygdalin from Schedule 10 to Schedule 4 except when included in or expressly excluded from Schedule 4;

e) A new Schedule 4 entry for amygdalin when included as a natural component in traditional Chinese medicines for oral use in adults with an exclusion to 'unscheduled' when the maximum recommended daily dose is equivalent to no greater than 5 mg of amygdalin; and

f) A change to the Schedule 4 entry for hydrocyanic acid with an exclusion when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults.

The suggested amended scheduling is as follows (changes underlined):

Schedule 10

AMYGDALIN for therapeutic use except when included in or expressly excluded from Schedule 4.

Schedule 4

AMYGDALIN when included as a natural component in traditional Chinese medicines for oral use in adults **except** when the maximum recommended daily dose is equivalent to no greater than 5 mg of amygdalin.

HYDROCYANIC ACID for therapeutic use except when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults.

Schedule 7

HYDROCYANIC ACID **except**:

a) when included in Schedule 4; or

b) its salts and derivatives other than cyanides separately specified in this Schedule.

No changes to the Appendix F, G or J entries are proposed.

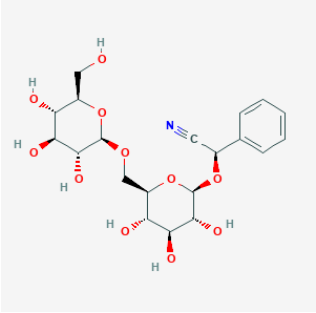
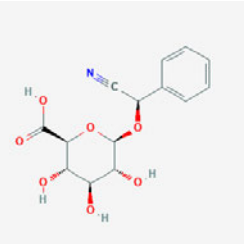
3. SUBSTANCE

Description of the substance

Amygdalin is a cyanogenic glycoside found naturally in bitter almonds, apricot kernels and seeds of other plants in the *Prunus* genus. It is also referred to as Vitamin B17, although it is not a vitamin, and often as laetrile, although laetrile and amygdalin are not identical (see comparison of the nomenclature and structure in

the table below; Source: Pub Chem; ChemID; Chemical Book; Merck Index). Laetrile is a semi-synthetic compound that is synthesised from amygdalin by hydrolysis of one of the β-D-glucopyranosyl groups.

The toxicity of oral exposure to these cyanogenic glycosides is due to the release of cyanide after hydrolysis of the nitrile group in the gut by β-glucosidase.

International non-proprietary name (INN):	**Amygdalin***	**Laetrile**	**Hydrogen cyanide (AAN)**
Synonyms:	(R)-Amygdalin; (R)-Laenitrile; Amygdaloside; Vitamin B17; D-mandelonitrile-β-D-glucoside-6-β-glucoside; Mandelonitrile-β-gentiobioside; (R)-α-((6-o-β-D-Glucopyranosyl-β-D-glucopyranosyl)oxy)benzeneacetonitrile	(R)-Laetrile; Vitamin B(sub17); D-mandelonitrile-β-glucuronide; l-Mandelonitrile-β-glucuronoside; β-D-Glucopyrano siduronic acid, α-cyanobenzyl	Hydrocyanic acid*; Prussic acid
IUPAC Name	(2*R*)-2-phenyl-2-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-[[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]oxymethyl]oxan-2-yl] oxyacetonitrile	(2*S*,3*S*,4*S*,5*R*,6*R*)-6-[(*R*)-cyano(phenyl)methoxy] -3,4,5-trihydroxyoxane-2-carboxylic acid	Formonitrile
CAS Number:	29883-15-6	1332-94-1	74-90-8
Structural formula (Pub Chem)			H—C≡N
Molecular formula	$C_{20}H_{27}NO_{11}$	$C_{14}H_{15}NO_7$	HCN
Molecular weight	457.4 g/mol	309.27 g/mol	27.03 g/mol

* TGA Herbal Component Name.

Amygdalin is available for use as an Equivalent Ingredient in: Export Only, Listed Medicines.

Hydrocyanic acid is not available as an Active Ingredient in any application; Not available as an Excipient Ingredient in any application; Available for use as an Equivalent Ingredient in: Export Only, Listed Medicines.

Hydrogen cyanide is Available for use as an Active Ingredient in: Biologicals, Export Only, Listed Medicines, Over the Counter, Prescription Medicines; Available for use in Listed Medicines as a Homoeopathic Ingredient only; Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines; Not available as an Equivalent Ingredient in any application.

None of these substances is the subject of a pharmacopoeial monograph.

Monographs for Bitter Apricot Seed and Apricot Kernel are included in Pharmacopeia of the People's Republic of China and the Japanese Pharmacopoeia, respectively.

Pharmacology

PHARMACODYNAMIC PROPERTIES

Mechanism of action

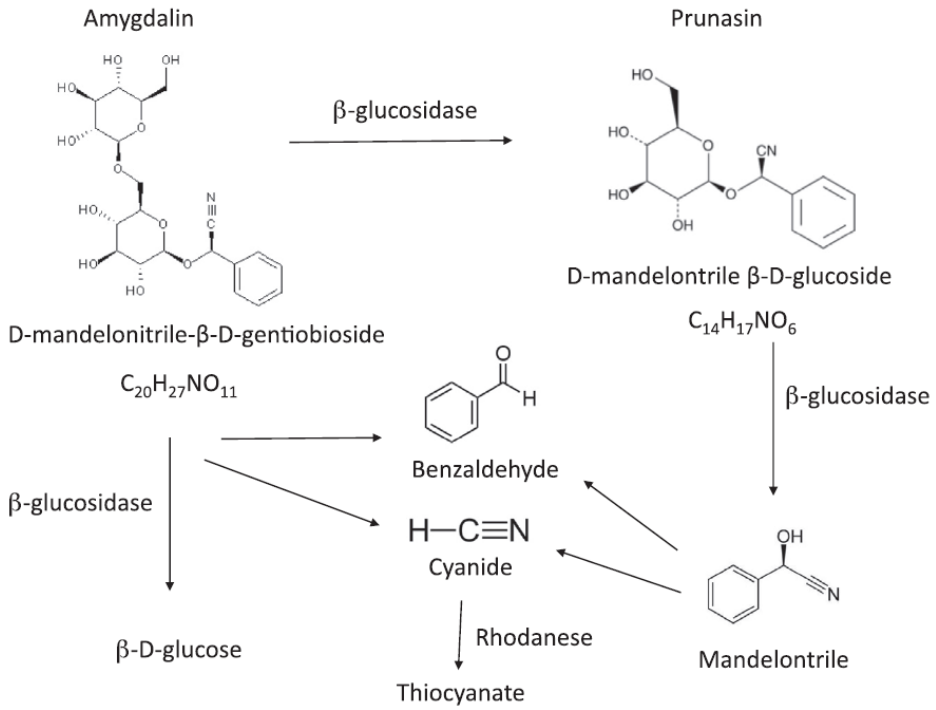
Amygdalin (D-mandelonitrile-β-D-glucoside-6-β-glucoside; mandelonitrile-β-gentiobioside) is a cyanogenic glycoside. It is metabolised in mammalian gut by β-glucosidase in the gut wall and gut flora to hydrogen cyanide. Thus, the acute toxic effects of amygdalin are those of cyanide, which halts cellular respiration by acting as a non-competitive inhibitor for the mitochondrial enzyme, cytochrome c oxidase.

Pharmacokinetics

The pharmacokinetics of orally administered amygdalin have been well studied, although the location, source and role of some of the enzymes involved in the metabolic processes are still unclear.

Metabolism

The metabolic pathway of amygdalin (Blaheta 2016) is shown below:



The main pathway of amygdalin metabolism involves the cleaving of the terminal glucose by β(1-6)-glucosidase activity in the gut wall of the small intestine, producing prunasin (D-mandelonitrile β-D-glucoside). Prunasin is in turn metabolised to mandelonitrile by β-glucosidase in gut bacteria in the large intestine or colon. Mandelonitrile subsequently dissociates to cyanide and benzaldehyde.

The proportion of amygdalin metabolised to cyanide varies depending on a range of factors, including co-ingestion of sources of β-glucosidase (such as in plant seeds and apricot kernels), which will increase production, and reductions in the gut flora responsible for conversion of prunasin to mandelonitrile, which may reduce production of cyanide (Toxicity review: amygdalin and hydrogen cyanide).

Absorption

Following ingestion of different foods containing 6.8 mg total cyanide, peak blood cyanide levels ranged from 1.44 to 16.95 µM with t_{max} ranging from ~25 to 150 min (Abraham 2016). The peak blood cyanide level after ingestion of about 2.1 g bitter apricot kernels was 15.46± 5.12 µM (t_{max} ~ 25 min). The differences in the rate of absorption of cyanide between the different foods was attributed to the different amounts of β-glucosidase in the foods and their rates of reaction. Despite blood cyanide levels reaching ≥20 µM (approximately 0.5 mg/L, the level at which flushing or tachycardia have been reported (ATSDR 2006) in several subjects after consumption of bitter almond kernels or cassava, no clinical symptoms of cyanide toxicity were observed.

The severity of cyanide toxicity from ingestion of bitter almonds or apricot kernels is influenced by a number of factors, including the amygdalin content of the kernels, whether the kernels are chewed or processed prior to ingestion, and the

combination with other ingredients. Chewing and some processing releases β-glucosidase in the kernels, thereby increasing toxicity, whereas other forms of processing or combination with herbs such as Mahuang (ephedra) that reduce levels of prunasin may reduce toxicity.

Distribution

Once cyanide is absorbed, it is rapidly distributed by the blood throughout the body.

Excretion

In humans, cyanide is detoxified primarily via trans-sulfuration to form thiocyanate but can also be detoxified by reaction with hydroxycobalamin (Vitamin B12) to form cyanocobalamin.

Thiocyanate undergoes renal clearance with an elimination half-life of approximately 2.7 days in normal renal function.

PRECLINICAL SAFETY DATA

A review of the non-clinical toxicity literature relating to amygdalina and hydrogen cyanide was carried out by the applicant (see Toxicity Review). A search of the Embase, Medline, Dart (for hydrogen cyanide) and ToxNet databases identified animal studies relating to acute, sub-acute and sub-chronic toxicity, carcinogenicity, mutagenicity/genotoxicity, reproductive and developmental toxicity, and toxicity in combination with herbal or other ingredients.

Acute toxicity

Acute oral toxicity studies in animals have reported LD_{50} values for amygdalin of between 522 mg/kg and 880 mg/kg in rats (Newton 1981; Song 2014; WHO 2012; Adewusi 1985; Carter 1979) and an LD_{10} value of 450 mg/kg bs in mice (Hill 1980). In dogs, cyanide poisoning resulting in death occurred at doses ≥1.00 g laetrile when administered with ≥20 sweet almonds, which contain the enzymes required to hydrolyse amygdalin, but not amygdalin itself. Single oral and IV doses of 50 mg amygdalin to Wistar rats and 500 mg to Beagle dogs found no evidence of cyanide toxicity (Rauws 1982).

The ATSDR (2006) reported oral LD_{50} values for cyanide of 3 to22 mg /kg in rats and approximately 2.5 mg/kg in rabbits.

Sub-acute and sub-chronic toxicity

In rats, amygdalin doses of 100, 250, 500 and 750 mg/kg bw/d for 5 days resulted in mortality of 4.7%, 30.8%, 44.1% and 56.6% respectively, with the majority of the deaths occurring in the first 3 days of treatment (Khandekar 1979). In guinea-pigs, pretreatment with ascorbate was found to enhance the toxicity of a single dose of potassium cyanide at 8 mg/kg bw but administration with cysteine reduced the toxic effects (Basu 1983). When oral amygdalin was administered to 32 rats (4 per group), at a dose of 20 mg/kg bw daily for 14 days, with or without hydroxycobalamin (25 mg/kg bw or 50 mg/kg bw), one of the rats who received

amygdalin without the antidote died of cyanide poisoning before the end of the experimental period while no mortality was recorded in rats who received the antidote (Oyewole 2009). In rabbits, IM amygdalin at a dose of 0.6 or 3.0 mg/kg bw (equivalent to 0.035 and 0.18 mg/kg bw cyanide) daily for 14 days, or 60 or 300 mg/kg bw crushed apricot seeds (equivalent to 3.12 mg/kg bw amygdalin or 0.18 mg/kg bw cyanide and 15.6 mg/kg bw amygdalin or 0.92 mg/kg bw cyanide, respectively) in food daily for 14 days had little effect on the health of the rabbits, with no deaths and no clinically significant changes in biochemical or haematological parameters (Kovacikova 2019).

A pivotal toxicity study conducted by the USA National Toxicology Program in 1993 found no treatment-related deaths, biologically relevant biochemical changes, clinical signs or histopathological effects in the central nervous system when rats and mice were administered sodium cyanide in drinking water at concentrations of 0, 3, 10, 30, 100 and 300 ppm for 13 weeks (equivalent to up to 12.5 mg/kg bw/d in rats and 26 mg/kg bw/d in mice). However, male rats exhibited effects on testicular sperm count, epididymal sperm motility and testicular and epididymal weights at the highest dose (12.5 mg/kg bw/d) and this was considered the Lowest observable adverse event level (LOAEL), with 4.5 mg/kg bw/d as the No observable adverse events level (NOAEL) for regulatory purposes.

Carcinogenicity

No long term or carcinogenicity studies of amygdalin have been identified but a one-year study found no carcinogenic effects in rats fed a diet of normal rat chow, 50% fresh cassava and 50% normal rat chow, or 75% fresh cassava and 25% normal rat chow (WHO report 2012). The average cyanide concentration in the cassava was 10 mg/kg, resulting in average exposures of 0, 0.075 or 0.102 mg cyanide per animal per day. Decreased body weights from 3 months until the end of the study were reported in animals fed both the cassava diets. Motor coordination was significantly decreased in both cassava diet groups from 5 months. Histopathology conducted at the 12 month time point showed signs of toxic hepatitis with hyperplasia and microvascular changes in hepatocytes, and mild atrophy of pancreatic acini with minimal focal dilatation of ducts, in both cassava diet groups also.

A 2-year, long-term study in which rats were administered up to 10.8 mg/kg cyanide in the diet, found no treatment-related effects on survival, growth, signs of toxicity or histopathological changes in organs (Simeonova 2004). Cyanide exposure has not been correlated with carcinogenicity in humans or animals (ATSDR 2006).

Genotoxicity

The mutagenicity of amygdalin as well as mandelonitrile glucuronide was tested in *Salmonella typhimurium* strains TA98 and TA100. Amygdalin was found to be mutagenic in mouse host-mediated assays after a single oral dose of 250 mg/kg bw amygdalin. Urine collected from mice dosed with either 125 mg/kg bw or 250 mg/kg bw amygdalin was also mutagenic, with mutagenicity increased in the presence of β-glucuronidase and arylsulfatase (Fenselau 1977). However, a study

found no mutagenic activity from amygdalin at concentrations up to 100 µg/mL in a test measuring spontaneous convertants and revertants in a diploid strain of *Saccharomyces cerevisiae* (Todorova 2017).

In a review of the use of the hepatocyte primary culture DNA repair test (HPC/DNA repair test), amygdalin is stated to be negative in the HPC/DNA repair test and its carcinogenic status is stated as "uncertain" (Williams 1984).

Cyanide salts (KCN, NaCN) have been found negative in a majority of bacterial mutagenicity tests in *Salmonella typhimurium* and *Escherichia coli*, and negative for chromosomal aberration and DNA repair. Cyanide induced DNA damage in some studies, but only at cytotoxic doses (Simeonova et al 2004, ATSDR 2006).

Fertility and Reproduction

A reproductive and developmental study with amygdalin in pregnant hamsters treated with a single oral dose of amygdalin (200 to 275 g/kg) on gestational day 8 (Willhite 1982; WHO 2012) found evidence of maternal toxicity at doses of 250 mg/kg and above, and dose-related foetal abnormalities at doses of 200 mg/kg and above. The whole blood cyanide concentration was 4.0 ± 1.1 nmol/mL 2.5 hours after the oral administration of 275 mg/kg amygdalin. A single IV dose of 275 mg/kg amygdalin on gestational day 8 did not produce maternal or foetal effects, and resulted in a whole blood cyanide concentration of 0.06 ± 0.03 nmol/mL. A single oral dose of 275 g/kg amygdalin resulted in no foetal abnormalities when administered with an initial i.p. injection of 300 mg/kg sodium thiosulfate followed by additional sodium thiosulfate i.p. injections administered every 120 minutes for 10 hours after the amygdalin dose. It is unclear whether the foetal effects seen in the oral dose study were due to maternal toxicity.

The effect of ground apricot kernels (10% in the diet) on reproduction in Sprague Dawley rats was examined in two studies (Miller 1981). Rats fed ground kernels containing low (<50 mg/100 g), medium (100 to 200 mg/100 g) or high (>200 mg/100g) levels of cyanide for 5 weeks showed no significant changes in blood chemistry between groups. In female but not male rats liver rhodanese activity and thiocyanate levels increased with increasing apricot kernel levels in the food. Urinary excretion of thiocyanate was higher in the two high dose groups than the control or low dose groups. Rats fed kernels containing either the low or high cyanide levels for 15 weeks and then bred with rats of the opposite sex on the same diet had a similar parturition index but 3 day survival index, lactation index and weaning weight were significantly lower in the high dose group than the low dose group, although the control group had a lower parturition index, 3 day survival index and weaning weight than the low dose group. Birth weights were not different between groups.

In a fertility study (Olusi 1979), female rats treated for 2 weeks with 5 or 10 g potassium cyanide/100 g diet (equivalent to approximately 1000 or 2000 mg cyanide /kg bw/d) failed to conceive and exhibited dose dependent decreases in body weight gain, blood haemoglobin (18% and 23%) and serum T4 concentration

(54% and 74%). Female rats fed raw cassava exhibited similar changes in body weight gain, blood haemoglobin and serum T4 concentrations as the high dose potassium cyanide-fed group, but 40% conceived compared to 90% in controls. Significant reductions in average litter size and individual birth weight and an increase in neonatal deaths and poor development and reduced brain weight in surviving pups.

However, a cassava based diet containing 0, 15, 30 or 45% cassava root meal had no effects in reproduction and growth in female rabbits or their offspring (Eshiett 1980).

These results suggest that high dose cyanide diets may have some effects on fertility and reproduction.

Toxicity in combination with herbal or other ingredients

A recent study (Song 2016) examined the toxicity of the individual and combined components of a Traditional Chinese herbal medicine composed of the dried ripe seeds of *Prunus armenica* (containing amygdalin, and known as *Xingren* in Chinese) and the dried herbaceous stems of *Ephedra sinica Stapf* (containing ephedrine and pseudoephedrine and known as *Mahuang* in Chinese). An acute oral toxicity study in Kunming mice, the LD_{50} of *Mahuang* (M), *Xingren* (X), and combinations of the two ingredients in the ratios MX(4:1), MX(2:1), MX(1:1), MX(1:2) and MX(1:4) were 93.2, 29.9, 87.9, 81.6, 81.4, 64.6, and 59.3 g/kg bw, respectively, demonstrating that *Xingren* alone is more toxic than *Mahuang* or the combinations but even a combination of MX(1:4) is markedly less toxic than *Xingren* alone. The concentration of amygdalin (L-amygdalin + D-amygdalin) was similar in all combinations to that of *Xingren* alone, but this was a consequence of a reduction in L-amygdalin and an increase in D-amygdalin in combination with *Mahuang*. It was suggested that the stereoselective metabolism of amygdalin facilitated by Mahuang acts to enhance and control the effects of Xingren in the MX combination.

A study in rats (Tang et al 2017) found that cinnamic acid (3.03 mg/kg), amygdalin (56.97 mg/kg), glycyrrhizic acid (12.42 mg/kg) and liquiritin (3.79 mg/kg), or a combination of all four compounds, significantly altered the pharmacokinetics of a combination of Ephedra alkaloids (20 mg each of ephedrine, pseudoephedrine and methylephedrine, administered orally). The addition of amygdalin significantly increased the Cmax and $AUC_{0\text{-}t}$ of ephedrine and pseudoephedrine, reduced the mean residence time of all three Ephedra alkaloids, and decreased the $AUC_{0\text{-}t}$ of methylephedrine. The Traditional Chinese herbal medicine Ephedra decoction contains the Ephedra alkaloids as well as the other 4 compounds and the study authors suggest that the pharmacokinetic changes in the Ephedra alkaloids by the other components of the decoction may be of relevance to the clinical use of ephedra in Traditional Chinese medicine.

Ihedioha (2002) examined the effect of traditional processing methods in the production of gari (toasted cassava granules), on the cyanogen content and toxicity of the gari. Traditionally gari is enriched with red palm oil (RPO, which consists

primarily of fatty acids) during production. The toxic component of cassava is prunasin, which is converted to hydrogen cyanide. Two samples of gari were produced, one with 15 mg/kg RPO mixed in prior to fermentation and one without. Otherwise the preparation of the two samples was identical. Total cyanogen, acetone cyanohydrin and free cyanide contents were determined in both samples and there were no significant differences between the two samples in the content of any of these compounds or in crude protein content. The two different samples of gari were then fed to groups of Sprague Dawley rats for 10 weeks, while a control group received normal rat chow. Total cyanogen, acetone cyanohydrin, free cyanogen, and crude protein contents were not found to be significantly ($p > 0.05$) different between the two. The samples were fed exclusively to two different groups of Sprague-Dawley rats for a ten week experimental period during which clinical observations were recorded daily. At the end, vital body organs were examined grossly and microscopically. There was a significant ($p < 0.05$) reduction in severity and percentage of animals exhibiting clinical abnormalities and lesions of chronic cyanide poisoning in the group fed gari produced with RPO. This result implies an association between the enrichment of cassava mash with RPO during gari production and the reduction of severity and percentage of animals affected by chronic cyanide poisoning.

Go et al (2018) examined the amygdalin concentration and toxicity of two different forms of syrups made from Maesil (*Prunus mume*, also known as Korean green plums, Chinese green plums or Japanese ume), known to contain amygdalin. Maesil syrup from which the plums were removed early in maturation process had significantly higher content of amygdalin (166.82 ± 4.16 μg/mL vs 134.98 ± 5.96 μg/mL) and prunasin (31.57± 0.16 μg/mL vs 26.06± 0.15 μg/mL) but lower polyphenols and a longer half-life in the bloodstream than the syrup matured with plums. This suggests that the complex Maesil syrup components have a role in preventing amygdalin degradation.

Lui et al (2017) investigated the inhibitory effects of various Chinese herbal extracts on the activity of β-glucosidase derived from almonds, and then examined the toxicity of a Chinese herbal medicine containing amygdalin (*Persicae Semen* ethanol extract) in mice when combined with β-glucosidase inhibitory herb extracts. Of 30 herbs assessed for β- glucosidase inhibitory effects, water extracts of 5 herbs, and ethanol extracts of 7 herbs, were found to have inhibitory activity against β-glucosidase. Of all the inhibitory herbal extracts, the ethanol and water extracts of *Lycii Cortex* had the smallest IC_{50} results (1.35 mg/mL for water extract and 0.56 mg/mL for ethanol extract). Further study found that *Lycii Cortex* inhibition of β-glucosidase was non-competitive in nature. By comparing decomposition rates of amygdalin at different concentrations with the inhibitory rate of the *Lycii Cortex* ethanol extract at different concentrations, a ratio of 7.19 *Persicae semen* ethanol extract to 9.18 *Lycii Cortex* ethanol extract was determined to be theoretically optimal. The *in vivo* oral toxicity of the *Persicae semen* ethanol extract alone and in the theoretically determined optimal ratio with *Lycii Cortex* ethanol extract was investigated by examining the relative LD_{50} values in Kunming mice using the up-

down method. The LD_{50} of the *Persicae semen* extract alone was 1750 mg/kg bw, while the LD_{50} when combined with *Lycii Cortex* extract was 4100 mg/kg bw, demonstrating that the toxicity of *Persicae semen* extract is decreased 2.43 times when administered in combination with *Lycii Cortex* extract.

Jaswal (2018) reviewed the effect of different gut bacterial compositions on the metabolism of amygdaline and noted studies in which some probiotics and foods were able to alter the gut microbiome and hence the β-glucosidase activity of the gut. In theory this should alter the cyanide production from amygdalin, although this has not been demonstrated in *in vivo* studies.

Tanwar (2018) reported a HCN content in wild apricot kernels of 136.85 ± 2.67 mg/100 g raw kernels. It is reported in this study that the range of HCN in wild apricot kernels is between 148 and 480 mg/100 g, and the HCN content in bitter almonds ranges from 106 to 250 mg/100 g. Detoxification of wild apricot kernels is possible by appropriate processing. Tanwar found that 100% of the hydrogen cyanide content of ground apricot kernels was removed by immersing the flour in 25% sodium chloride solution for 12 hours and then rinsing under running water, repeating this process, and then drying the flour for 36 hours at 45°C.

These studies suggest that the toxicity of amygdalin in herbal substances can be influenced by combination with other ingredients or the method of processing.

CLINICAL TOXICITY

Symptoms

The initial symptoms of acute cyanide poisoning (also the symptoms of amygdalin poisoning) include nausea, vomiting, diarrhoea and epigastric pain. These may be followed by neurological symptoms including dizziness, headaches, disorientation, irritability, lethargy, weakness, and stupor, as well as coma and seizures. Initial tachypnoea and dyspnoea may be followed by respiratory depression, cyanosis and eventual respiratory arrest (Hazardous Substances Database (HSDB) 2017). Hypotension and shock may also occur.

Chronic cyanide poisoning after chronic consumption of cyanogenic plants results in neuropathy and myelopathy, including Konzo, a specific tropical myelopathy observed in populations with a high intake of cassava, which contains linamarin, a cyanogenic glycoside metabolised to prunasin and then to HCN (HSDB 2017, COT 2006). Goitre is also associated with chronic consumption of cyanogenic plants, since thiocyanate interferes with iodine uptake in the thyroid (Speijers 1993). However, these populations with high intake of cyanogenic glycoside-containing plants also exhibit a high incidence of malnutrition, and it is considered that nutritional deficiency, particularly of methionine and riboflavin, or iodine, in combination with chronic cyanide exposure, is involved in the aetiology of neuropathy, myelopathy and goitre (Speijers 1993).

No reports of hepatotoxicity associated with acute or chronic exposure to amygdalin or other cyanogenic glycosides have been identified. Hepatotoxicity has been

reported in some rabbit studies after oral exposure to sodium or potassium cyanide at doses of 15 to 20 mg/kg/d cyanide ion, but no consistent evidence of hepatotoxicity has been associated with cyanide exposure in other animals or humans (ATSDR 2006).

Case reports and clinical studies

A review of the clinical toxicity literature was carried out by the applicant (see Toxicity Review). A search of the Embase, Medline and ToxNet databases identified a number of cases reports and clinical studies relating to amygdalin or HCN exposure.

These case reports included:

- 6 reports of toxicity in adults with single oral amygdalin/laetrile at the following doses:
  - 6 tablets (0.6 or 3g[#]) (O'Brien 2005)
  - 18 tablets (1.2 or 9g[#]) (Beamer 1983)
  - 6 tablets (3g) (Bromley 2005)
  - 1 ampoule (3g) (Leor 1986)
  - 3 ampoules (9g) (Moss 1981)
  - 3.5 ampoules (10.5g) (Sadoff 1978)[*]
- 5 reports of toxicity in adults with daily oral amygdalin/laetrile at the following doses:
  - 3 tablets (equivalent to 25-75mg cyanide or 0.42 -1.27g amygdalin) (Kalyanaraman 1983),
  - 1 tablet/capsule (0.5g) (Lam 2012),
  - 1 tablet (0.5g) (Smith 1977),
  - 2 tablets (1.0g) (Liegner 1981), and
  - 3 tablets (1.5g) (Smith 1977).

[#] dose reported as number of tablets of unknown content; tablets appear to be available in100mg and 500mg strengths.

[*] The review of the literature carried out by the applicant (see Toxicity Review: Attachment 2: Summary of case reports) reported the dose of amygdalin in the Sadoff 1978 report (which had been incorrectly reported by Blaheta 2016) as '12 g amygdalin'. When the original Sadoff 1978 reference was sourced, it was apparent that this case report related to a 17 year old female who had ingested 3.5 ampoules, each containing 3g amygdalin, equivalent to a dose of 10.5g, instead of 12 g. It is noted that the Sadoff 1978 case report was correctly cited in a review by Speijers 1993; however, the summary table in the Expert Report, when referring to the Speijers 1993 review, incorrectly reported the amygdalin dose as '2.6 g oral amygdalin' when it should have been 10.5 g.

- Fatalities were reported with single oral doses of 3g (Leor 1986) and 10.5g (Sadoff 1978).
- Four cases of toxicity were reported in adults after ingestion of apricot or peach kernel at the following doses:
  - 0.5g (1/4 teaspoon ground apricot kernels with cyanide content >3000mg/kg, *equivalent to >1.5 mg cyanide or >25 mg amygdalin*) (Vlad 2015);
  - 15g (30 apricot kernels, *equivalent to 450 mg amygdalin*) (Suchard 1998);
  - 10-20g (20-40 kernels, *equivalent to 692-1384 mg amygdalin, based on cyanide content of 409mg/100 seeds*) (Rubino 1979);
  - a daily dose of 60g peach kernels (in mixed Chinese herbal prescription containing 30g/dose, *equivalent to 600 mg amygdalin/dose, based on an amygdalin content of NLT 2.0%*) (Chan 2006).
- One case was reported after a combination of 12 bitter almonds (~6g, *equivalent to 74.4 mg amygdalin, based on average amygdalin content of 6.2mg/almond*) plus one laetrile tablet (11.5 mg) (Shragg 1982).
- Toxicity was also reported in adults after ingestion of:
  - bitter almonds (~80g, *equivalent to 2.4-4g amygdalin*)(Grass 2016);
  - apple seeds (80-100, *equivalent to 60-300 mg amygdalin, based on an amygdalin content of 0.1-0.4%*) (Roberts 2011);
  - alcohol macerated chokecherries (~300g, with an estimated cyanide content of 10-20mg, *equivalent to 169-338 mg amygdalin*) (Pentore 1996).
- In children, four cases of severe poisoning were reported following administration of amygdalin at the following doses:
  - 12 tablets (6g)(Hall 1986);
  - a combination of apricot kernels (5-10 per day, equivalent to 75-150 mg amygdalin) plus oral amygdalin (2g per day) in a 4 year old (Sauer 2015);
  - a combination of oral amygdalin (0.5g per day), I.V. amygdalin (3.5g per day) plus amygdalin enema in a 2 year old (Ortega 1978); and
  - 1-5 amygdalin tablets (0.5-2.5g) in a 11 month old infant, which was fatal (Humbert 1977).
- Poisoning was also reported in 13 children (severe in 9 children) aged 3-9 years following ingestion of between 5 and 21 (median 8) apricot seeds (estimated amygdalin content of 75-315mg (median 120mg)) (Akyildiz 2010).

Clinical studies (Mortel 1981; Ames 1981) reported no adverse effects and no clinical or laboratory evidence of toxicity (blood cyanide levels of up to 2.05 microgram/mL) when treating 6 cancer patients with DL amygdalin (4.5 g/m^2/day IV for 21 days) then D amygdalin (0.5 g orally 3 times daily) and "metabolic therapy" (Vitamins A, C, E, B-complex and pancreatin) for 5 to 15 weeks. In a similar but larger study in 165 patients (Moertel 1982), 5- 30% experienced adverse reactions

such as nausea, vomiting, headache, dizziness and mental obtundation, and one of the 14 patients on a high dose regimen (DL amygdalin 7 g/m^2/day IV for 21 days then D amygdalin 0.5 g orally 4 times daily) had bouts of tachycardia and dyspnoea; however, toxicity was sometimes but not always associated with high blood cyanide levels.

An open label pharmacokinetic, safety and tolerability study (Li 2016) reported no serious adverse events and no clinically significant changes in vital signs or serum biochemistry (except for 1 patient with raised serum alanine aminotransferase) with single or multiple IV doses of the traditional Chinese medicine Huoxue-Tongluo lyophilised powder for injection, formulated from Persicae semen and Paeoniae Radix Rubra.

Substance characteristics in relation to the Scheduling Factors[2]

This application proposes amendments to Schedules 10 and 4 of the Poisons Standard. The factors for these schedules and for 'unscheduled' are addressed below.

Factor	Applicant's response	Evaluation
Schedule 10		
The substance poses such a high public health risk, including potential risk, that its sale, supply and/or use require very strict control, with access generally being prohibited. The potential health risk does not include potential for abuse, diversion into illicit products or other factors which would warrant inclusion in Schedule 9.	In general, Schedule 10 is appropriate for amygdalin (including 'laetrile') as a stand-alone ingredient in medicines for therapeutic use.	The doses of amygdalin (including 'laetrile') used as a stand-alone ingredient in medicines for therapeutic use (100-500mg/dose) appear to be in the same range as those used in Chinese medicine (100-300 mg/dose). Due to the high degree of variability in the toxic effects of cyanide following consumption of herbal preparations containing amygdalin, these preparations may be associated with higher risk so that its sale, supply and/or use require very strict control, with access generally being prohibited. The potential health risk

[2]Scheduling Policy Framework https://www.tga.gov.au/publication/scheduling-handbook-guidance-amending-poisons-standard

		does not include potential for abuse, diversion into illicit products or other factors which would warrant inclusion in Schedule 9.
The substance has a public health risk that substantially outweighs the benefit to the extent that no other Schedule would provide appropriate public access to any proposed or known products. The serious public health risk may be restricted to particular uses.		The substance has a public health risk that substantially outweighs the benefit to the extent that no other Schedule would provide appropriate public access to any proposed or known products, with the exception of products containing a maximum daily dose of less than 5 mg amygdalin.
The Secretary may establish a cut-off from Schedule 10 where the substance no longer meets the factors for inclusion in this Schedule or in any other Schedule in the Poisons Standard.	This application proposes an exclusion from Schedule 10 for medicines that are included in Schedule 4 (see below).	Exclusion from Schedule 10 for medicines containing a maximum daily dose of less than 5 mg amygdalin may be appropriate.
Schedule 4		
The ailments or symptoms that the substance is used for require medical, veterinary or dental intervention Diagnosis, management or monitoring of the medical condition is such that it requires medical, veterinary or dental intervention before the substance is used.	The proposed inclusion in Schedule 4 relates solely to amygdalin when included as a natural component in traditional Chinese medicines for oral use in adults. Other medicines that include amygdalin (or 'laetrile') will remain in Schedule 10. The proposed entry will allow appropriate management of the public health risk associated with amygdalin while enabling its inclusion as a natural component of traditional Chinese medicines in 'prescription only medicines' (e.g. as a	Diagnosis, management or monitoring of the medical condition is such that it requires medical intervention before the substance is used.

	registered complementary medicine or via TGA's Special Access Scheme) with a cut-off at very low doses for sale as 'unscheduled medicines'. The selected cut-off of 5 mg per maximum daily dose is based on animal studies and assessment by a wide range of regulatory and expert committees that an oral intake of 5 to 20 µg/kg/d cyanide (equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult) is considered to present no appreciable risk. It is substantially less than the legal limit in many foods for human consumption in Australia and New Zealand.	
The use of the substance requires adjunctive therapy or evaluation or specialised handling for administration. Adjunctive therapy could include other medicines, non-pharmacological measures, or specialised medicine delivery devices. Evaluation could include laboratory tests or additional clinical assessments. For human medicines, a requirement for administration by injection will usually mean medical or dental supervision is required because of the additional risks and complexity of this route of administration.	No response from applicant	The use of the substance may require specialised handling for administration (e.g. preparation of decoction) but, under the terms proposed by the applicant, it is not expected that this would involve administration by injection.
The use of the substance at established therapeutic	The applicant is not aware of any reports of overdose,	Although the applicant is not aware of any reports of

dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use. Control of access and duration of therapy by a medical, veterinary or dental practitioner is required.	misuse or abuse of traditional Chinese medicines containing 'low doses' of amygdalin as a component of ingredients in traditional Chinese medicines. Single ingredient products containing amygdalin at high dose (as 'laetrile') have had a history of misuse for cancer treatment.	overdose, misuse or abuse of traditional Chinese medicines containing 'low doses' of amygdalin as a component of ingredients in traditional Chinese medicines, it is not clear if this also applies to Chinese medicines containing higher doses of amygdalin. There have been reports of poisoning from intentional ingestion of a large number of raw apricot kernels used as an alternative or complementary medicine, for cancer prevention or treatment, as a health tonic, or for suicide/deliberate self -poisoning. There have also been reports of toxicity from intentional ingestion of amygdalin in ampoules intended for parenteral administration and tablets.
The seriousness, severity and frequency of adverse effects are such that monitoring or intervention by a medical, veterinary or dental practitioner is required to minimise the risk of using the substance. **The margin of safety between the therapeutic and toxic dose of the substance is such that it requires medical, veterinary or dental intervention to minimise the risk of using the substance.**	No response from applicant	The adverse effects of amygdalin relate to cyanide toxicity, which is dose dependent and potentially lethal. The severity of cyanide toxicity following oral administration of amygdalin-containing substances exhibits wide variability, as it is affected by a range of factors which influence the metabolism and detoxification of amygdalin to cyanide (e.g. amygdalin and β-glucosidase content of the herbal ingredient, route of administration, processing, co-administration with other substances, and inter-individual variability with

		respect to gut microbial flora and nutritional status . This variability in the severity of cyanide toxicity following consumption of amygdalin-containing herbal ingredients means that it is difficult to predict a safe dose, even if the amygdalin content of herbal ingredients were standardised.
The seriousness or severity and frequency of the interactions of the substance (medicine-medicine, medicine-food, or medicine-disease) are such that monitoring or intervention is required by a medical, veterinary or dental practitioner.	No response from applicant	Co-administration of amygdalin with other substances or nutrients (e.g. Vitamins C and B12) has been found to affect the severity of toxicity and is potentially life-threatening.
The use of the substance has contributed to, or is likely to contribute to, communal harm. For example, the development of resistant strains of microorganisms. Appropriate use, and/or the decision to continue treatment, requires evaluation by a medical, veterinary or dental practitioner.	No response from applicant	The use of amygdalin has not been reported to contribute to communal harm. As it is not known to have any antimicrobial activity, it is not likely to result in the development of resistant strains of microorganisms.
The experience of the use of the substance under normal clinical conditions is limited. Unexpected effects of the substance may only become evident after widespread use. Close monitoring of the patient is required by a medical, veterinary or dental practitioner to	No response from applicant	The applicant asserts that the practice of TCM has developed from knowledge accumulated through clinical observation and treatment over several millennia. However, since no information has been provided to support this assertion, it is concluded that the experience of the

monitor for unanticipated effects.		use of the substance under normal clinical conditions is limited.
Unscheduled		
In accordance with the cascading principle, exemption of a particular medicinal preparation to allow supply from general sales outlets (such as supermarkets) means that it does not meet the factors for Schedules 2, 3, 4 or 8. Medicinal preparations exempted from scheduling must be determined to be able to be supplied, with reasonable safety, without any access to health professional advice.	Amygdalin as a natural component and in the low doses proposed for exclusion from Schedule 4 in traditional Chinese medicines for oral use in adults has no appreciable safety risk. It does not meet the factors for Schedules 2, 3, 4 or 8 and can be used with reasonable safety, without any access to health professional advice.	Amygdalin in the low doses proposed for exclusion from Scheduling (maximum daily dose not exceeding 5 mg) in traditional Chinese medicines for oral use in adults has no appreciable safety risk. It does not meet the factors for Schedules 2, 3, 4 or 8 and can be used with reasonable safety, without any access to health professional advice.
The term 'with reasonable safety' means: • The consumer is able to identify and self-manage the condition for which the medicine is intended without health professional input.	The classification of these medicines as 'unscheduled' will make them eligible for 'listing' on the Australian Register of Therapeutic Goods (ARTG) subject to TGA agreement to changes to the Therapeutic Goods (Permissible Ingredients) Determination. Controls within the listing system will ensure that only indications that do not require health professional input are available for use with these medicines. If the medicine cannot be listed it must be 'registered' and will be subject to full evaluation by TGA. Again, this will ensure that only indications that do not require health professional input are approved for use with these medicines	No information has been provided regarding the proposed conditions of use of these 'unscheduled' medicines. However, the evaluation of 'unscheduled' under the listing or registration system should ensure that only indications that do not require health professional input are approved for use with these medicines. Therefore, the consumer should be able to identify and self-manage the condition for which the medicine is intended without health professional input.

	(unless they have a specific exemption from TGA).	
• The risk of the consumer confusing their condition with more serious diseases or conditions is very small.	Controls within the listing / registration system will ensure that indications for more serious disease or for conditions that could be confused with more serious disease are not available / approved for use with these medicines.	Controls within the listing / registration system should ensure that indications for more serious disease or for conditions that could be confused with more serious disease are not available / approved for use with these medicines.
• The risks to health from the medicine are small and can be managed with packaging and labelling. Risks to be assessed include, but are not limited to, risks from adverse reactions, drug/food interactions and contraindications.	Controls within the listing / registration system will ensure that any risks from herbal ingredients that include amygdalin at very low dose are appropriately managed by packaging and labelling (e.g. by mandatory label warnings).	Controls within the listing / registration system should ensure that any risks from herbal ingredients that include amygdalin at a maximum daily dose not exceeding 5 mg are appropriately managed by packaging and labelling (e.g. by mandatory label warnings).
• The risk of inappropriate use and misuse is negligible.	The applicant is not aware of any reports of inappropriate use or misuse of traditional Chinese medicines.	The risk of inappropriate use and misuse of medicines containing a maximum daily dose of amygdalin not exceeding 5 mg is negligible.
• There is little need to take any special precautions in handling.	The applicant is not aware of any need to take special precautions in handling traditional Chinese medicines.	Since the risks relate to ingestion, there is little need to take any special precautions in handling.
• There is net public health benefit from wider availability for the consumer	The applicant submits that there is a substantial public health benefit from wider availability of a full range of traditional Chinese medicines for the consumer, including those that contain very low doses of amygdalin as a natural component of herbal substances used in those medicines.	Although exclusion from scheduling would allow wider availability for the consumer, it has not been established that wider availability would benefit the health of consumers.

The proposed Schedule 4 entries for amygdalin and hydrocyanic acid – AMYGDALIN when included as a natural component in traditional Chinese medicines for oral use in adults **except** when the maximum recommended daily dose is equivalent to no greater than 5 mg of amygdalin and HYDROCYANIC ACID for therapeutic use except when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults – are unusual in that they specify amygdalin when included as a 'natural component in traditional Chinese medicines'. Presumably, this was intended to exclude amygdalin extracted from herbal ingredients. However, there are no other schedule entries that apply specifically to Chinese medicines and based on the toxicity data, there does not appear to be any reason why this should not apply to all amygdalin preparations.

It is noted that the wording of some current entries in the Poisons Standard refers to 'preparations when labelled with a recommended daily dose not exceeding a specified quantity of the specified poison', and may also specify the maximum concentration and/or maximum dose (for undivided preparations) or maximum quantity per dosage unit (for divided preparations).

Subject to the provision of sufficient efficacy and safety data to support the inclusion of amygdalin in Schedule 4, suggested wording for a Schedule 4 entry for amygdalin could be – AMYGDALIN when included in preparations when labelled with a recommended daily dose not exceeding a specified quantity of the specified poison. Although the safety data support an exemption from scheduling for amygdalin in preparations labelled with a maximum recommended dose not exceeding 5 mg, there is insufficient evidence to support a Schedule 4 entry for amygdalin. Therefore, exclusion from Schedule 10 for preparations containing a maximum daily dose not exceeding 5 mg amygdalin may be appropriate, e.g. Schedule 10: AMYGDALIN for therapeutic use except when included preparations containing a maximum daily dose not exceeding 5 mg.

The proposed exclusion of hydrocyanic acid for therapeutic use from Schedule 4 when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults has not been justified. If amygdalin is excluded from scheduling at a maximum recommended daily dose not exceeding 5mg, a corresponding limit should be applied to the exclusion of hydrocyanic acid, e.g. at a dose not exceeding 0.3 mg hydrocyanic acid. Therefore, the Schedule 4 entry for could be worded as "HYDROCYANIC ACID for therapeutic use except when included in preparations labelled with a maximum recommended daily dose not exceeding 0.3 mg".

The NDPSC has previously expressed concern over the apparent contradiction that certain substances which had been included in Appendix C (now Schedule 10) on the grounds that they present such danger to health as to warrant prohibition should be made available for therapeutic use under special circumstances.

As an alternative to exclusion from scheduling, a lower schedule, e.g. S2, could be considered for preparations with a maximum daily dose of ≤ 5mg. This was not proposed by the applicant, possibly because one of the factors for pharmacy

medicines (Schedule 2) is that access to advice from a pharmacist should be available to maximise the safe use of the medicine.

It is noted that CMEC have made recommendations on maximum daily doses of active ingredients in Listed medicines.

4. EVALUATION

Considerations under section 52E of the Therapeutics Goods Act 1989

(a) the risks and benefits of the use of a substance

Risks

The primary risk associated with the use of amygdalin is the potential for severe acute cyanide poisoning, the symptoms of which are nausea, vomiting, diarrhoea, dizziness, and tachypnoea, progressing to cyanosis, seizures, coma, and eventually respiratory arrest and death. An additional risk would be the potential for adverse effects associated with chronic exposure of cyanogenic glycosides, such as neuropathy, myelopathy, and/or goitre.

These risks are exacerbated by the variability in the severity of cyanide toxicity resulting from the administration of amygdalin, which is influenced by a number of factors, which are discussed in detail in the section (c) the toxicity and safety of a substance. This variability in the severity of cyanide toxicity following consumption of amygdalin-containing herbal ingredients means that it is difficult to predict a safe dose, even if the amygdalin content of herbal ingredients were standardised.

Amygdalin for therapeutic use is currently included in Schedule 10 on the grounds that it presents such danger to health as to warrant prohibition of sale, supply and use.

This application proposes excluding amygdalin from Schedule 10 when included as a natural component in traditional Chinese medicines for oral use in adults and including it in Schedule 4 with a cut-off to unscheduled at a maximum daily adult dose of 5 mg or less.

The evidence provided in this application supports the view that an oral intake of 5 to 20 µg/kg bw/d cyanide (equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult), presents no appreciable risk to consumers, although it is noted that no evidence for efficacy of these doses was provided. Based on the absence of risk to consumers, it is considered that the proposed exclusion from scheduling of preparations containing a maximum daily dose of less than 5 mg amygdalin would be acceptable.

The evidence provided in this application is considered insufficient to support the efficacy and safety of amygdalin in doses above 5 mg per day. Therefore, it is

considered that the proposed scheduling of amygdalin (excluding it from Schedule 10 when included as a natural component in traditional Chinese medicines for oral use in adults and including it in Schedule 4 at a maximum daily adult dose of more than 5 mg) presents an appreciable risk to consumers due to the potential for cyanide toxicity.

Benefits

The applicant submits that there is substantial public health benefit, and very little risk, from removing the scheduling barrier from access to a full range of traditional Chinese medicines by medically qualified TCM practitioners and from access to TCM products at very low doses of amygdalin to Australian / Chinese consumers, as this would allow wider availability for the consumer.

The application provided little information about the efficacy of amygdalin in Chinese medicines at either very low or high doses. However, it is acknowledged that Traditional Chinese medicine (TCM) is a medical system based on theory, pathology, diagnosis, treatment and herbal pharmacology principles that differ from those of orthodox medicine or Western naturopathy and that the practice of TCM has developed from knowledge accumulated through clinical observation and treatment. TCM has an established history in Australia and has expanded rapidly in recent years, with Chinese medicines accounting for 3.2% of the total use of complementary medicines in Australia in 2003.

However, it cannot be concluded that wider availability would benefit the health of consumers.

(b) the purposes for which a substance is to be used and the extent of use of a substance

Amygdalin is a cyanogenic glycoside found naturally in many plants including cassava, sorghum, lima beans, linseed, apple seeds, bitter apricot seed (*Armeniacae Semen Amarum*), peach seed (*Persicae Semen*) and the seeds of other plants in the *Prunus* genus, including bitter almond (*Prunus amygdalus* var. *amara*), plum (*Prunus domestica*), and chokecherry (*Prunus virginiana*),.

Many traditional Chinese medicines are formulated to include one or more of these plant ingredients, mainly apricot kernels, usually in combination with other traditional Chinese herbs.

The submission states that amygdalin is only present in traditional Chinese medicines as a natural component of herbal substances (as opposed to single ingredient products containing amygdalin at a high dose). Examples of these substance include bitter apricot seed (*Armeniacae Semen Amarum*; Kuxingren CP), which is indicated in the Chinese Pharmacopoeia (CP) for *"cough and wheezing, chest fullness, profuse sputum, and constipation caused by intestinal dryness"*; and peach seed (*Persicae Semen*; Taoren CP), which is indicated for *"amenorrhea,*

dysmenorrhea, masses, stuffiness, lung abscess, intestinal abscess, traumatic injuries, constipation caused by intestinal dryness, cough and wheezing".

The submission did not include any other information about other herbal substances used in Chinese medicines that have amygdalin as a natural component.

The Pharmacopeia of the People's Republic of China (2015) includes the following information in the monographs for Bitter Apricot Seed and Peach Seed.

	Bitter Apricot Seed	Peach Seed
Names	Armeniacae Semen Amarum Kuxingren	Persicae Semen Taoren
Source	Dried ripe seed of *Prunus armeniaca* L. var. *ansu* Maxim. , *Prunus sibirica* L., *Prunus mandshurica* (Maxim.) Koehne or *Prunus armeniaca* L. (Fam. Rosaceae). The fruit is collected in summer and the seed is removed from the pulp and the shell, and dried in the sun.	Dried ripe seed of *Prunus persica* (L.) Batsch or *Prunus davidiana* (Carr.) Franch. (Fam. Rosaceae). The fruit is collected when ripe. The seed is removed from sarcocarp and shell (endocarp), and dried in the sun.
Description	Flattened-cordate, 1-1. 9 cm long, 0. 8-1. 5 cm wide, 0. 5-0. 8 cm thick. Externally yellowish-brown to deep brown, acute at one end, obtusely rounded plump and unsymmetrical at the other end. A short-line hilum situated at the acute end and a chalaza at the rounded end with numerous upwards deep-brown veins. Tests thin; cotyledons 2, milky-white, oily. Odour, slight; taste, bitter.	Seed of Prunus persica Prolate-ovate, 1. 2-1. 8 cm long, 0. 8-1. 2 cm wide, O. 2-0. 4 cm thick. Externally yellowish-brown to reddish-brown, with numerous granular protrudings. One end acute, expanded in the middle, the other end obtuse-rounded and slightly oblique, with relatively thin edge. A short linear hilum occurring by the acute end and a relatively distinct and slightly dark chalaza at the round end, with many longitudinal vascular bundles radiated from the chalaza. Tests thin, cotyledons 2, almost white and oily. Odour, slight; taste, slightly bitter.
Assay	It contains not less than 3.0 percent of amygdalin (C_{20} H_{27} NO_{11}) calculated with reference to the dried drug. (NLT 2.1% in dried slices)	It contains not less than 2.0 percent of amygdalin (C_{20} H_{27} NO_{11}) calculated with reference to the dried drug. (NLT 1.60% in dried slices)
Actions	To direct qi downward, suppress cough, relieve	To activate the blood to eliminate stasis, moisten the intestines, open

	wheezing, moisten the intestines and open the bowels.	the bowels, suppress cough, and relieve wheezing.
Indications	Cough and wheezing, chest fullness, profuse sputum, and constipation caused by intestinal dryness.	Amenorrhea, dysmenorrhea, masses, stuffiness, Lung abscess, intestinal abscess, traumatic injuries, constipation caused by intestinal dryness, cough, and wheezing.
Administration and dosage	5-10 g, unprocessed for decoction, added when the decoction is nearly done.	5-10 g.
Precautions and Warnings	Be care of overdosage for oral administration to avoid poisoning.	Used with caution during pregnancy.

The Pharmacopeia of the People's Republic of China does not include recommended maximum daily dosages of Bitter Apricot Seed or Peach Seed.

In Traditional Chinese Medicine, Bitter Apricot Kernel (xing ren) *Semen Armeniacae Amarum* can be used in combination with other ingredients such as Herba Ephedrae and Radix Glycyrrhizae (for treatment of cough due to exopathogenic wind-cold); Fructus Arctti, Folium Mori, Bulbus Fritillariae, Radix Platycodi, and Radix Glycyrrhizae (for treatment of cough due to exopathogenic wind-heat); Folium Mori, Bulbus Fritillariae, and Radix Adenophorae (for treatment of warm-dryness injury of lung, unproductive cough); Gypsum Fibrosum, Herba Ephedrae, and Radix Glycyrrhizae (for treatment of accumulation of pathogenic heat in the lung, pyrexia with acute asthma) and Radix Angelicae Sinensis, Radix Paeoniae Alba and Fructus Canabis (for treatment of constipation due to bowel dryness). (http://www.tcmtreatment.com/herbs/00-xingren.htm)

(c) the toxicity and safety of a substance

Amygdalin is a cyanogenic glycoside found naturally in many plants including cassava, sorghum, lima beans, bitter almonds, apricot kernels and seeds of other plants in the *Prunus* genus. Cyanogenic glycosides can convert to a type of cyanide when eaten. The mechanism of toxicity of hydrogen cyanide is by inhibition of mitochondrial cytochrome oxidase, which results in inhibition of oxygen consumption. Acute toxicity results in dyspnoea, weakness, dizziness, sweating, vomiting, disorientation, convulsions, paralysis, cyanosis, coma, and cardiovascular collapse.

The severity of cyanide toxicity is dependent upon a range of factors which influence the metabolism and detoxification of amygdalin to cyanide, including:

- The amygdalin content of the herbal ingredient, which may vary depending on varietal differences, seasonal effects on growth, freshness, and processing.
- The β-glucosidase content of the herbal ingredient, which aids the conversion of amygdalin to cyanide.
- The route of administration, e.g. oral administration results in higher cyanide levels compared to IV administration, which bypasses the gut β-glucosidase enzymes.
- Chewing or processing (e.g. grinding) of the herbal ingredient, which can release the β-glucosidase in the herbal ingredient, increasing the conversion to cyanide, and increasing the toxicity.
- Co-administration with other substances (e.g. other herbal ingredients) that may influence either the metabolism of amygdalin to cyanide or the detoxification of cyanide. An example of this is the reduced toxicity of Xingren when combined with Mahuang in Chinese medicine (Song 2016).
- Inter-individual variability with respect to gut microbial flora and nutritional status, which may affect the β-glucosidase dependent conversion of amygdalin to cyanide in the gut as well as the amino acid dependent detoxication processes.

Food Safety Australia New Zealand (FSANZ) has conducted a risk assessment on a number of foods containing cyanogenic glycosides and found only raw apricot kernels (both with and without skin) pose an acute public health and safety risk. Changes to the *Australia New Zealand Food Standards Code* to prohibit the sale of raw apricot kernels were made in 2015. FSANZ considers raw apricot kernels to be a food and does not address the issue of these foods being consumed for a therapeutic purpose or presented as a therapeutic good. FSANZ has set a limit of 10 mg HCN/kg in ready-to-eat cassava chips (FSANZ 2008, 2016). Limits of HCN in other foods and drinks (FSANZ 2015) include: 25 mg/kg in confectionery; 5 mg/kg in stone fruit juices; 50 mg/kg in marzipan; and 1 mg/kg per 1% alcohol in alcoholic beverages (e.g. apricot kernel derived products). ANZFSC Standard 4.5.1 has set a HCN limit of NMT 0.1 mg/L in wine, sparkling wine and fortified wine (ANZFSC Standard 4.5.1 – Wine production requirements (Australia only)).

By way of comparison, 100 g of confectionary could legally contain up to 2.5 mg of HCN. Assuming 100% conversion of amygdalin to cyanide (16.92 mg amygdalin is equivalent to 1 mg cyanide), this is equivalent to 42.5 mg of amygdalin, more than 8 times the proposed maximum adult daily dose of amygdalin in unscheduled traditional Chinese medicines. Similarly, one standard drink (~50 mL) of Amaretto Liqueur (28% alcohol) could legally contain up to1.4 mg cyanide, equivalent to 23.7 mg amygdalin, and one standard drink (100 mL) of wine could legally contain up to 1 mg HCN, equivalent to 16.9 mg of amygdalin, which are 3-4 times more than the proposed daily limit for unscheduled traditional Chinese medicines.

Surveys of currently available data by the FSANZ indicate there is considerable variability in levels of cyanogenic glycoside concentrations in apricot kernels. A

survey during the 2011 Queensland poisoning incident found levels of HCN in raw apricot kernels with skin (3 blended samples) ranged from 1,7000-2,3000 mg/kg. The ISFR* survey found levels of HCN in raw apricot kernels with skin (18 blended samples) ranged from 1,240-2,820 mg/kg; whereas those without skin (10 blended samples) ranged from 49 to 440 mg/kg. However, surveys with less samples reported higher levels in raw apricot kernels with skin (>3,000 mg/kg in 1 blended sample from 2014 WA incident and 4,090 mg/kg in a case study from poisoning incident). It is unlikely these surveys have identified the true range of cyanogenic glycosides in apricot kernels that are currently available for sale given the restricted number of studies and samples.

Based on a maximum HCN content in raw apricot kernels with skin of 2,820 mg/kg, a dosage of 3-10 g would contain 8.46-28.2 mg HCN. Assuming 100% conversion of amygdalin to HCN, this is equivalent to 143.8 to 479.4 mg amygdalin per dose (maximum amygdalin content of 47,705 mg/kg). This is consistent with the amygdalin content of 90-300mg per dose calculated based on an amygdalin content of NLT 3.0% (as specified in the Chinese Pharmacopoeia).

Solomonson (1981; quoted in Speijer 1993) reported that the lethal oral dose of amygdalin in adults is 0.02-0.13 mmol/kg bw (9 to 60 mg/kg). An average fatal dose of cyanide of 1.52 mg/kg (range 0.5 to 3.5 mg/kg) in adults has been estimated by the USA EPA from case reports of intentional or accidental poisonings (ATSDR, COT, 2006). Assuming 59.1 mg cyanide is released from 1000 mg amygdalin, this would equate to a fatal dose of amygdalin of 25.7 mg/kg (range 8.5 to 59.2 mg/kg). This could be considered a worst case situation, as it assumes the release in the gut of the total theoretical amount of cyanide from amygdalin, and it is unclear what proportion of the total possible cyanide would be released from amygdalin. The estimated range of 8.5 to 59.2 mg/kg is consistent with the lethal oral dose range of 9 to 60 mg/kg quoted in Speijers (1993).

Cyanide toxicity has been reported in humans at concentrations of 0.1 to 1.45 mg/L in blood, 1-5 mg/L in RBC, 0.2 mg/L in serum, and 0.03-0.035 mg/L in plasma. Lethal cyanide concentrations have been reported as 2.9-5 mg/L in blood, 3 mg/L in serum and 0.243 mg/L in plasma. This compares to cyanide levels of 8.7-58 microgram/L in blood, <29 microgram/L in RBC and 4-6 microgram/L in plasma that are typically found in healthy adults.

A review of the literature carried out by the applicant (see Toxicity Review) identified a number of cases reports and clinical studies relating to amygdalin or HCN exposure.

These case reports suggest that toxicity in adults can occur with oral amygdalin/laetrile in single doses ranging from 3 g to 10.5 g (but this could be as low as 0.6g) and daily doses from 0.42g to 1.5 g, with fatality at doses of 3g and 10.5g. Toxicity in adults was reported after ingestion of single doses of apricot or

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peach kernels containing the equivalent of 25 mg to 1384 mg amygdalin or after ingestion of other seed containing preparations (bitter almonds plus laetrile tablets, apple seeds, or chokecherries) with a total estimated amygdalin content ranging from 60 mg to 4 g. However, little evidence of toxicity has been observed in clinical studies using a combination of IV amygdalin treatment plus oral amygdalin in doses of 1.5 g or 2g daily. This suggests that there is significant variability in the toxic response to amygdalin ingestion.

The submission included little information about the doses of amygdalin used in Chinese herbal medicine. The Pharmacopeia of the People's Republic of China includes monographs for 'Bitter Apricot Seed' and 'Peach seed', which indicate that the standard dose of bitter apricot seed or peach seed is 5-10 g, which is equivalent to 150-300 mg amygdalin for bitter apricot seed and 100-200 mg for peach seed (based on the amygdalin content of NLT 3.0% in bitter almond seed and NLT 2.0% in peach seed, calculated with reference to the dried drug – Chinese Pharmacopoeia). However, it is possible that higher doses would be used, since the submission included one case report of toxicity with a daily dose of 60g peach kernels in a mixed Chinese herbal prescription containing 30g/dose, which would be equivalent to 600 mg amygdalin. The applicant could be requested to provide further information about the proposed use of amygdalin-containing herbal ingredients in Chinese herbal medicine, including the maximum single and daily doses of amygdalin likely to be prescribed.

On the basis of animal studies, and as assessed by a wide range of regulatory and expert committees, oral HCN intake of 5 to 20 microgram per kg body weight per day is considered to present no appreciable risk. This is equivalent to 300 to 1200 microgram/d of cyanide for a 60 kg adult and 100 to 400 microgram/d for a 20 kg child. Assuming 100% hydrolysis of amygdalin to hydrogen cyanide, on a molecular basis this is equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult and 1.7 to 6.8 mg/d for a 20 kg child.

A maximum adult daily dose of 5 mg amygdalin is at the low end of the range that is considered to present no appreciable risk (5.1 to 20.3 mg/d). This would provide some buffer to account for any variability in cyanide toxicity following ingestion of amygdalin-containing ingredients. A dose of 5 mg is also lower than the permitted quantity in some foods (e.g. 42.5 mg in 100 g of confectionary; 23.7 mg in one standard drink (~50 mL) of Amaretto Liqueur (28% alcohol); and 23.7 mg in one standard drink (100 mL) of wine.

However, there is less evidence for the safety of higher doses of amygdalin, especially considering the wide variability in cyanide toxicity observed following oral administration of amygdalin-containing substances. Further clarification of the maximum single and daily doses of amygdalin likely to be prescribed in Chinese medicine is required.

(d) the dosage, formulation, labelling, packaging and presentation of a substance

The submission did not include any information about the dosage, formulation, labelling, packaging or presentation of traditional Chinese medicines that include amygdalin as a natural component of herbal substances. However, it is noted that these aspects would be controlled under the registration or listing process. Labelling of such Chinese medicines is likely to include mandatory warning statements, although it is uncertain as to whether declaration of the amygdalin or HCN content would be required.

(e) the potential for abuse of a substance

Single ingredient products containing amygdalin at high dose (as 'laetrile') have had a history of misuse for cancer treatment. These products will remain in Schedule 10.

The applicant is not aware of any reports of overdose, misuse or abuse of traditional Chinese medicines containing 'low doses' of amygdalin as a component of ingredients in traditional Chinese medicines; however, it is not clear if this also applies to Chinese medicines containing high doses of amygdalin. Since this use is currently prohibited in Australia, reports would be from overseas.

There have been reports of poisoning in Australia and New Zealand from intentional ingestion of a large number of raw apricot kernels used as an alternative or complementary medicine, for cancer prevention or treatment, as a health tonic, or for suicide/deliberate self -poisoning (FSANZ).

Information from Poisons Information Centres in Australia has not been obtained. This could be requested.

A search of the Australian DAEN did not reveal any notifications of adverse events with Chinese herbal medicine, Kuxingren, amygdalin, laetrile, apricot kernels, which is expected, given the current restrictions on the use of these substances. A search of global databases (e.g. VigiBase, the WHO global database of individual case safety reports (ICSRs)) has not been undertaken.

Poisoning incidents following either accidental (children and adults) or intentional ingestion (by adults only) of raw apricot kernels in Australia and New Zealand have been reported to poison information centres (FSANZ). This includes the intentional ingestion of a large number of apricot kernels used as an alternative or complementary medicine, cancer treatment, health benefits/tonic or other reasons, suicide/deliberate self-poisoning.

There does not appear to be any potential for abuse resulting from addiction.

(f) any other matters considered necessary to protect public health

5. CONCLUSIONS

On the basis of animal studies, and as assessed by a wide range of regulatory and expert committees, oral intake of 5 to 20 μg/kg/d cyanide (equivalent to 5.1 to 20.3

mg/d amygdalin for a 60 Kg adult) is considered to present no appreciable risk to consumers.

This application proposes excluding amygdalin from Schedule 10 when included as a natural component in traditional Chinese medicines for oral use in adults and including it in Schedule 4 with a cut-off to unscheduled at a maximum daily adult dose of 5 mg or less. By way of comparison 100 g of confectionary could legally contain more than 8 times this proposed maximum daily dose. An associated change to exclude hydrocyanic acid from Schedule 4 when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults is also proposed.

The effect of these changes would be:

- To make TCM products containing very low doses of amygdalin available without prescription; and
- To allow medically qualified TCM practitioners to prescribe traditional Chinese medicines containing higher doses of amygdalin as Schedule 4 medicines (e.g. in registered complementary medicines or via the TGA's Special Access Scheme).

The applicant's submission that there is substantial public health benefit, and very little risk from access to TCM products at very low doses of amygdalin to Australian / Chinese consumers is accepted.

However, the applicant's submission that there is substantial public health benefit, and very little risk, from removing the scheduling barrier from access to a full range of traditional Chinese medicines by medically qualified TCM practitioners is not accepted, as there is less evidence for the safety of higher doses of amygdalin, especially considering the wide variability on cyanide toxicity observed following oral administration of amygdalin-containing substances.

It is suggested that access to TCM products at very low doses of amygdalin may be achieved through exclusion from Schedule 10 of preparations containing a maximum daily dose not exceeding 5 mg amygdalin and the exclusion from Schedule 4 of preparations containing a maximum daily dose not exceeding 0.3 mg hydrocyanic acid.

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