Australian Government
Department of Health
Therapeutic Goods Administration

Safety review of *Andrographis paniculata* and anaphylactic / allergic reactions

Version 1.0, October 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Pharmacovigilance and Special Access Branch	01/10/2015

Contents

Executive summary

The TGA has detected a number of anaphylactic/ allergic-type adverse drug reactions (ADRs) reported for products in the Australian Register of Therapeutic Goods (ARTG) that contain the herbal ingredient *Andrographis paniculata* (*A.paniculata*). Previous investigation of this issue by the TGA, in 2008, found it to be related to certain products that were subsequently cancelled from the ARTG, followed by an apparent decline in the number of ADRs reported. However, continued monitoring noted that subsequent to the initial decline, ADRs of this type continued to be reported.

There are no restrictions or label warnings required for the use of *A.paniculata* in medicines in Australia, and the majority of the reviewed information suggests that the use of *A.paniculata* is safe at typically recommended doses. However multiple ADRs have been reported to the TGA and adverse effects, including anaphylactic/ allergic-type reactions, have been documented in the literature.

On review of literature based on traditional use of *A.paniculata,* no cautions or contraindications were identified that referred to the potential for this herb to cause allergic reactions. However, literature sources based on current use of *A.paniculata* recommend to avoid this herb in cases of known allergy or hypersensitivity to products that contain *A.paniculata* or its constituents [1], or to plants of the Acanthaceae family, with a warning against injecting crude extracts of the herb due to the potential for anaphylactic reactions. [2]

A presentation by the Thai FDA at the 34th annual meeting of the WHO Programme for International Drug Monitoring (2011 Dubrovnik, Croatia) concluded that *A.paniculata* containing products are likely to induce hypersensitivity reactions, with this potential risk documented in the Thai National List of Essential Medicines (NLEM), and recommended that amendments be made to the product information for these products. [3]

An article by Farah et al. [4] concluded that international pharmacovigilance data suggest that oral use of *A.paniculata* containing products can cause acute hypersensitivity reactions such as anaphylaxis, and although the frequency of such reactions is unknown and the causative ingredient is unidentified, the authors recommended that a warning be included in the product information of these products.

Sixteen anaphylactic/ allergic-type cases were located in the WHO Vigibase database between 2008 and 2013 for *A.paniculata*. Eight of these reports were from Australia, seven from Thailand and one from Canada.

Analysis of the TGA ADR database located 43 reports of anaphylaxis and 78 reports of allergic-type reactions associated with products that contain *A.paniculata* that were submitted between December 2002 and April 2014. A review of the ADR reports suggests that this ingredient may play a causative and/or contributing role in anaphylactic and allergic-type ADRs, including when present in multi-ingredient formulations.

Analysis of the ADR cases found that a higher number of ADR reports were for products manufactured using *A.paniculata* extracted with methanol compared with products manufactured using herb material extracted with an aqueous solvent or an aqueous-ethanol mixture, with a higher number of anaphylactic cases reported for the methanol extract products than for the aqueous/ethanol extract products.

Investigation of the reported ADRs also noted a higher number of anaphylactic/ allergic-type ADRs for products that contain *A.paniculata* extracts with a concentration ratio of greater than 10:1, with a higher quantity of equivalent *A.paniculata* per dosage unit.

It is difficult to establish a definitive correlation between methanol extracts or highly concentrated extracts and anaphylactic/ allergic-type reactions in the absence of usage data, as it may be the case that there are more medicines in use that contain these types of preparations

of *A.paniculata*, considering the majority of *A.paniculata* containing medicines in the ARTG contain highly concentrated methanol extracts of this ingredient.

To conclude, the reviewed information suggests an association between anaphylactic/ allergic-type reactions and the herbal ingredient *A.paniculata*, however a particular type of extract or solvent cannot be conclusively identified as causative, therefore a precautionary approach appears warranted to include all products that contain *A.paniculata* in any proposed action.

The number of anaphylactic/ allergic-type ADRs reported and the severity of the ADRs suggests that the ingredient *A.paniculata* presents a potential risk sufficient to warrant further action. The most appropriate regulatory action may be to require warning statements on the labels of medicines containing *A.paniculata*, with a review of ADRs reported for these products in future to assess the effectiveness of this risk mitigation strategy.

1. Issue under investigation

In 2008, a spike in anaphylactic/ allergic-type ADRs was observed for products in the ARTG that contained the ingredient *A.paniculata*. An investigation of this issue found it to be related to certain products that were subsequently cancelled from the ARTG, followed by an apparent decline in the number of ADRs reported (see Section 4.1 Regulatory history for more detail). However, further monitoring noted that, subsequent to the initial decline, ADRs of this type continued to be reported for medicines in the ARTG that contain the herbal ingredient *A.paniculata*.

2. Objectives / scope of review

To identify a possible association between reported anaphylactic/ allergic-type ADRs and products that contain the ingredient *A.paniculata,* and to determine if any regulatory action is warranted for these products*.*

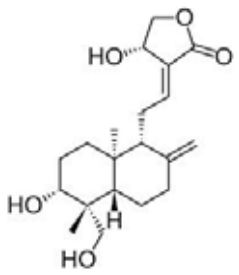
3. Product identification

3.1 Product, active ingredient or class of medicine under review

The active ingredient under review is the herb *A.paniculata* and various preparations of this herb that are used in therapeutic goods in Australia.

Andrographis paniculata (Burm.f.) Nees (*A.paniculata*) belongs to the Acanthaceae family and is indigenous to India, Ceylon, and Java, and also known as Kalmegh and green chiretta in Ayurvedic medicine. Parts used are the whole plant, leaves and roots. [5]

A comprehensive list of chemical constituents found in *A.paniculata* according to the literature is at Appendix 1. The major diterpenoid in *A.paniculata* is andrographolide, the chemical structure of which is illustrated below.



According to Chao and Lin [6], active compounds reported to have been extracted with ethanol or methanol from the whole plant, leaf and stem of *A.paniculata* include over 20 diterpenoids and over ten flavonoids. Andrographolide ($C_{20}H_{30}O_5$), being the major diterpenoid in *A.paniculata*, is reported to make up about 4%, 0.8~1.2% and 0.5~6% in dried whole plant, stem and leaf extracts respectively.

3.2 Formulation

As at October 2013, there were 63 medicines included in the ARTG listed to contain *A.paniculata*. Of these, 4 were export only listed medicines which were excluded from further analysis, while the remaining 59 products are included in the ARTG as listed (ie. low risk) medicines.

A review of these 59 products found:

- 26 products contained *A.paniculata* in the form of concentrated dry extracts with an extraction ratio of 14:1, while 11 products contained *A.paniculata* in the form of concentrated dry extracts with an extraction ratio of 19:1. The extraction ratio in the remaining products varies from 1:2 (ie. dilution) to 20:1. 'Standardised' extracts are commonly used in medicines on the ARTG containing *A.paniculata*[1].
- Most products with an extraction ratio of 14:1 were standardised to contain 30% to 40% of andrographolides in the extract (average: 35% andrographolides).
- Most products with the extraction ratio 19:1 were standardised to contain on average between 20% and 22% of andrographolides in the extract.
- Three products in the ARTG use traditional herbal extraction ratios, i.e. 1:2 and 1:1.
- The equivalent quantity of *A.paniculata* per dosage unit varies between 40 mg to 6000 mg.
- The leaf is the plant part most commonly used in medicines on the ARTG containing *A.paniculata*—evidence suggests that the highest concentration of andrographolides is found in the leaf. [7]
- The solvents used to extract *A.paniculata* were: ethanol, methanol or water, or a combination of these, with methanol being the most frequently used solvent.

3.2.1 Dose form(s)

The medicines included in the ARTG comprise the following dosage forms: film coated tablets (34), hard capsules (14), soft capsules (4), oral liquids (3), enteric coated capsules (2), sugar-coated tablets (1), and granules (1).

[1] In the context of herbal medicine, the use of the term 'standardised extract' is generally taken to mean an extract that is manufactured to contain a consistent level of one or more plant constituents present in the original starting material.

3.2.2 Active ingredient

The majority of medicines in the ARTG that contain *A.paniculata* are multi-ingredient formulations that mostly include other herbal ingredients and in some cases vitamin, mineral and other complementary medicine ingredients.

3.2.3 Dose strength(s) and regimen

Traditional preparations include dried plant material, infusions, decoctions and tinctures with extract ratios of between 1:1 and 1:6. [8] Typically used daily doses in traditional medicine systems are 1.5-6g of the dried aerial parts of the herb; 1.5-9g of the dried herb as an infusion or 3-6 mL of a 1:2 liquid extract [9-10]. Modern preparations often present the dried herb in capsule or tablet form, or contain a standardised extract containing 11.2mg of andrographolides per 200mg of extract, with a typical dose being 400mg thrice daily. [9]

Where a maximum daily dose (MDD) is included in ARTG entries of products that contain *A.paniculata*, it ranges from 200-18000mg (equivalent quantity of *A.paniculata*).

3.2.4 Route of administration

Oral

3.4 Therapeutic indications

Indications for listed medicines in the ARTG that contain *A.paniculata* vary widely. As listed medicines, the products have not been evaluated for efficacy prior to their inclusion in the ARTG (although sponsors are required to hold evidence to support indications).

Examples of indications included in the ARTG for medicines that contain *A.paniculata* are as follows:

- Andrographis is traditionally used as an antipyretic remedy for the relief of fever. Traditionally used to alleviate fever.
- Andrographis is traditionally used for the symptomatic relief of the common cold. Traditionally used for the relief of symptoms of colds.
- Andrographis is traditionally used to relieve sore throat and cough with thick sputum. Traditionally used to alleviate sore throats.
- Andrographis is traditionally used to alleviate gastro-intestinal upsets (dyspepsia, loss of appetite, flatulence) and acute diarrhoea.
- Andrographis is traditionally used as a tonic to aid convalescence after general debility caused by fevers and uncomplicated respiratory tract infections.
- Traditionally used to aid recovery from mild respiratory tract infections, including colds.
- Andrographis has been used traditionally for relief of influenza, cough and sore throat, to relieve fever, to help maintain appetite and digestion and as a liver tonic.
- Andrographis extracts standardised for andrographolides may relieve the symptoms of uncomplicated upper respiratory tract infection.
- May reduce the severity and duration of colds.
- Andrographis supports healthy immune function and is used traditionally to support healthy intestinal function.

According to a review article, traditional medicine systems recognise *A.paniculata* as having antibacterial, antifungal, antiviral, choleretic, hypoglycemic, hypocholesterolemic, and adaptogenic effects. [11]

3.5 Contraindications/Cautions

There is no requirement in Australia for medicines that contain *A.paniculata* to display label warnings or risk communication in relation to this ingredient, nor are there any other restrictions specific to the use of this ingredient in medicines in the ARTG.

Traditional Chinese literature states that *A.paniculata* (Chuanxinlian) has few toxic side effects, but that large oral doses may cause gastric discomfort and anorexia. Emesis may be caused by the bitter andrographolide. [7]

The lack of traditional contraindications does not support the safety of modern preparations of *A.paniculata*, as traditionally the plant was used as an infusion, decoction or powder, either alone or in combination with other medicinal plants. [11] Commercial preparations in current use tend to be highly concentrated and standardised extracts, which may significantly change the safety profile of this ingredient.

The World Health Organisation (WHO) monograph for 'Herba Andrographidis'(dried aerial parts of *A.paniculata*) contraindicates the use of Herba Andrographidis during pregnancy or lactation, or in cases of known allergy to plants of the Acanthaceae family. [2] The WHO monograph also warns against injecting crude extracts of Herba Andrographidis due to potential anaphylactic reactions.

The then Natural Standard (NS)[2] monograph for *A.paniculata* advises to avoid in cases of known allergy or hypersensitivity to products that contain *A.paniculata* or its constituents. [1] The monograph also includes several other cautions/contraindications for this herb.

4 Background

4.1 Regulatory history in Australia

A.paniculata was approved for use in listed medicines in 2002. At this time, andrographolide was also approved as a constituent of *A.paniculata*, however it is not mandatory to declare the presence or quantity of this constituent in the ARTG entry for listed medicines.

In September 2008 the TGA initiated an investigation following receipt of a large number of ADR reports associated with Nyal cold and flu products, several of which described anaphylactic and allergic reactions. The investigation identified that the ingredient *A.paniculata* was common to all of the Nyal products reported in these cases. Further review revealed that the TGA received twenty-two reports of anaphylactic/ allergic-type reactions in 2008 that were associated with several of the Nyal range of listed medicines and a small number of other listed medicines that contained *A.paniculata*, most of which contained other ingredients. The issue was considered by the then Complementary Medicines Evaluation Committee (CMEC) which advised the TGA to continue to monitor and investigate.

However, following extensive investigation of this issue, including raw herbal ingredient analysis, no single causative factor was identified in association with the large number of reactions to these products. Nevertheless, the sponsor of two Nyal products; Nyal Day and Night Cold and Flu Fighter Tablets (AUST L 146263) and Nyal Cold and Flu Fighter Tablets

[2] Natural Standard (NS) is now known as Natural Medicines.

(AUST L 146264), initiated a consumer level recall of these two medicines and subsequently cancelled them from the ARTG in June 2009[3].

A safety review conducted by the TGA in December 2008 concluded that there was insufficient information in the literature regarding the safety of *A.paniculata* to warrant further action.

Further review of this issue in September 2010 concluded that of the ADRs reported to the TGA since 2008 associated with products that contained *A.paniculata*, only one could be positively attributed to this ingredient, as all other cases had confounding factors. The review also considered adverse events reported during the previous six years and concluded that only three to four events could be positively attributed to the ingredient *A.paniculata*, and that this number of adverse events was considered consistent with other herbs that are known to cause allergic reactions, such as *Echinacea purpurea*. The review reiterated that investigations to date had provided insufficient data on which to base regulatory action. As a result the TGA resolved to continue to monitor adverse events associated with *A.paniculata*.

4.2 Place in clinical practice

4.2.1 Target population

The target population for complementary medicines including *A.paniculata* is mainly consumers who self-treat with products purchased from health food stores, pharmacies or the Internet; patients of Traditional Chinese Medicine or Ayurvedic health practitioners; and those who consult with a western herbalist or naturopath. As all medicines in the ARTG that contain *A.paniculata* are listed (low risk) medicines, they are available over the counter without consultation.

4.2.2 Utilisation

A.paniculata is traditionally used in its whole plant form (dried, infused or decocted) as a tea or alcoholic extract, and dispensed by practitioners of Ayurvedic and Traditional Chinese Medicines. The wide range of potential therapeutic applications of *A.paniculata* and andrographolide has attracted high levels of interest among researchers. [12] Subsequently *A.paniculata* has more recently gained popularity as a plant of choice for prescribing by Western herbal and naturopathic practitioners for conditions such as immune support during upper respiratory tract infections and digestive disorders. *A.paniculata* preparations with high concentrations of plant to solvent ratio and/or standardised to contain a certain concentration of andrographolide (which go well beyond traditional use) are also now common in complementary medicines marketed to the general public, available from pharmacies, health food shops and supermarkets.

Based on information in the ARTG and the Adverse Drug Reaction System (ADRS) database, preparations containing *A.paniculata* are often self-prescribed for immune-stimulating effects. Further data on the use of medicines containing *A.paniculata* are not available as they are not included in the Pharmaceutical Benefits Scheme and are not required to be prescribed by a registered healthcare professional.

4.3 Guidelines

Australian regulatory guidelines specific to the ingredient *A.paniculata* include the United States Pharmacopeia (USP) dietary supplement monographs for 'Andrographis', 'Powdered Andrographis', and 'Powdered Andrographis Extract'. These monographs are standards

[3] These products have since been re-listed with new formulations that do not include *A.paniculata.*

applicable to these ingredients when used in therapeutic goods in Australia, in accordance with Section 3 of the *Therapeutic Goods Act 1989* (the Act).

4.4 Status in other countries

A search of international regulatory agencies' internet sites did not locate information about a potential association between *A.paniculata* and allergic/anaphylactic reactions. The European Medicines Agency (EMA) released a final assessment report on *A.paniculata* dated 27 August 2014 which concluded that products containing *A.paniculata* have been found safe during the clinical studies in adults and that no adverse events had been reported. [13]

Failure to locate relevant information prompted the TGA to request information from six overseas regulatory agencies about reported adverse events, safety reviews and the current regulatory status of *A.paniculata*. Responses were received from four agencies, which referred to one case of an allergic reaction to a product that contained *A.paniculata* as the sole active ingredient, and 6 reports (one case of anaphylaxis and 5 cases of allergic-type reactions) where insufficient information was included to establish a definitive causal association with the ingredient *A.paniculata.* One agency reported an additional 6 adverse event reports to products that contained *A.paniculata* in either multi-ingredient formulations, or in cases where more than one product had been taken. Details of the reactions in these 6 reports were not provided.

The TGA undertook a stimulated reporting project in 2011 (see section 6.2) which resulted in the submission of 50 previously unreported ADR cases. This project is a likely contributing factor to the greater number of reports in Australia.

World Health Organization (WHO)

The publication 'WHO monographs on selected medicinal plants' includes a monograph on 'Herba Andrographidis', which refers to the dried aerial parts of *A.paniculata*. [2] As previously stated in section 3.5 (Contraindications/Cautions), the monograph contraindicates the use of Herba Andrographidis in cases of known allergy to plants of the Acanthaceae family. The monograph also warns that crude extracts of Herba Andrographidis should not be injected due to the potential for anaphylactic reactions.

5 Overview of data

A total of 43 articles were selected for review from the search results produced by TGA's Information Resources and Research Services. Additional literature sourced by the authors of this paper was also reviewed[4] .

6 Safety issues

6.1 Extent of clinical exposure

The extent of clinical exposure is unknown, as usage data for products containing *A.paniculata* is not readily available.

[4] Details of the search strategies used and a full list of articles and literature reviewed are available on request to the TGA (Ph: 1800 020 653 Email: info@tga.gov.au).

6.2 Safety evaluation methodology

Because the efficacy of *A.paniculata* has not been evaluated, a comprehensive risk-benefit analysis cannot be conducted. Therefore, the methodology used for this safety evaluation comprises an analysis of ADR data held in the TGA database, as well as any available information on ADRs and safety issues in published literature and from international pharmacovigilance activities.

Reporting ADRs to the TGA is compulsory for sponsors only, and ADRs are generally under-reported by healthcare professionals and consumers, therefore the ADR data held by the TGA is likely to be below the actual figures. In 2011, the TGA conducted a stimulated reporting project, whereby ADR information was requested from sponsors of current medicines that contained *A.paniculata*. This resulted in the submission of 50 previously unreported ADR cases to the TGA, 2 of which described anaphylactic reactions, and 26 of which described allergic-type reactions.

The TGA ADRS database has limited capacity to search for ADRs associated with an ingredient in multi-ingredient formulations. A one-off interrogation was conducted in November 2011 of the ARTG and the ADRS database for ADRs to current and cancelled products that contained *A.paniculata*, which provided the majority of the data used for the review.

Subsequent to this, a more limited interrogation of the ADRS database was conducted up to April 2014 for *A.paniculata* containing products that were involved in previously reported reactions, and for *A.paniculata* containing products listed after November 2011. Consequently there may be recent reports for previously uninvolved medicines that have not been detected.

Another significant limitation to the analysis is the absence of usage data for products that contain *A.paniculata*. Nevertheless, there are sufficient reports to allow some conclusions to be drawn.

6.3 Continued ADR reporting

Following the conclusion of TGA's review in September 2010, ADRs involving products containing *A.paniculata* continued to be reported, prompting further investigation of this issue. The results of TGA's stimulated reporting project and the one-off interrogation of the TGA ADR database against the ARTG were combined and analysed. Between December 2002 and January 2012 the TGA received a total of 165 ADR cases reported for products containing *A.paniculata*. Of these, 38 cases were recorded as anaphylactic reactions. Cases were classified as anaphylactic in accordance with the Brighton anaphylaxis case definition, if any one of the three levels of diagnostic certainty was met (see appendix 2). Where insufficient information was provided to make an assessment against the Brighton anaphylaxis criteria, cases were classified according to the reaction term(s) provided, most of which were included in the analysis as allergic-type cases[5] In 36 of the anaphylaxis cases, the medicine containing *A.paniculata* was the sole suspected medicine, although most were multi-ingredient formulations. In two of the 38 anaphylaxis cases, two medicines were suspected, but in both cases, both medicines contained *A.paniculata* as a part of multi-ingredient formulations. In five of the anaphylaxis cases, the sole suspected product contained *A.paniculata* as the sole active ingredient, while in one of the anaphylaxis cases the name of the *A.paniculata* product was not specified, therefore the formula is unknown.

Of the remaining non-anaphylactic cases, 72 were considered cases of allergic-type reactions. These include one or several of the following reactions: hypersensitivity, dyspnoea, urticaria, pruritis, paraesthesia, rash, periorbital oedema, lip swelling, face oedema, angioedema, erythema, auricular swelling, throat tightness, wheezing, palpitations, hyperhidrosis, respiratory

[5] Cases submitted as 'Anaphylactic reaction' or 'Anaphylaxis' with no other information about the reaction were classified as allergic-type, as anaphylaxis could not be confirmed.

rate increased, hypoxia, erythematous rash, pruritic rash. In 65 of these cases the medicine containing *A.paniculata* was the sole suspected medicine, and in 11 of these cases the sole suspected product contained *A.paniculata* as the sole active ingredient. In one of the 72 allergic-type cases, two medicines were suspected, however both medicines contained *A.paniculata* as a part of multi-ingredient formulations. The highest number of ADR reports for any one product (23 reports) was in relation to the only product that contains the single active ingredient *A.paniculata*, including 11 allergic-type cases and 5 cases of anaphylaxis (up to January 2012). Two other ADR reports may have been allergic-type cases (ocular hyperaemia and periorbital oedema for one case, and dizziness, dyspnoea and laryngitis for the other), however insufficient information was provided to make a conclusive assessment[6].

In some cases additional information was provided regarding existing allergies, as displayed in Table 1.

Table 1. Information provided in ADR reports about known allergies (up to January 2012)

Type of reaction	Number of cases (%)				
	History of allergy/ anaphylaxis	No known history of allergy	History of asthma	Positive skin prick test post-reaction	No history provided
Anaphylaxis (38)	3 (7.9)	9* (23.7)	3* (7.9)	2 (5.3)	24 (63.2)
Allergic-type reactions (72)	14* (19.4)	4 (5.6)	2* (2.8)	0 (0)	53 (73.6)

*some cases reported more than one history category, e.g. asthma with no known allergies.

In the absence of allergy history for each report, a conclusion cannot be drawn about the potential increase in likelihood of allergic/anaphylactic reactions in individuals with a history of allergy/anaphylaxis/asthma.

By April 2014 the TGA had received at least 13 additional ADR reports for products containing *A.paniculata*[7]. Five of these were anaphylactic reactions, with the medicine containing *A.paniculata* the sole suspect in four of five cases, and in two of the five cases contained *A.paniculata* as the sole active ingredient. An additional case was reported as an anaphylactic reaction, however insufficient details were provided to assess this case against the Brighton criteria, therefore this was classified as an allergic-type reaction. In this case, the medicine containing *A.paniculata* was a multi-ingredient formulation, and was one of two suspected medicines. In six of the 13 more recent cases, reactions could be considered allergic-type reactions, and in all six cases the medicine containing *A.paniculata* was the sole suspect, while in one of these cases the (sole) suspected medicine contained *A.paniculata* as the sole active ingredient.

There have been no deaths reported from anaphylactic/allergic-type reactions associated with products containing *A.paniculata*.

[6] These cases were excluded from the analysis.

[7] A definite number cannot be produced due to the limited capacity of the TGA ADR database for searching for ADRs associated with an ingredient in multi-ingredient formulations. This most recent search was conducted on medicines containing *A.paniculata* for which previous ADRs have been reported, and for products containing *A.paniculata* listed in the ARTG after November 2011 (when the initial comprehensive ADR/ARTG search was conducted).

6.4 ADR analysis

In total, 178 ADR reports for 29 products containing *A.paniculata* were examined for this review (177 reports with an identified brand name and 1 with no brand name provided).

As shown in Table 2, analysis of the ADR data found that there have been significantly more ADR reports received for products (current and cancelled) that contain herb material extracted with methanol compared with products that contain herb material extracted with an aqueous solvent or an aqueous-ethanol mixture (143 vs. 34). There has also been a higher proportion of anaphylactic cases reported for the methanol extract products than for the aqueous/ethanol extract products (27.2% vs. 8.8%). This suggests that methanol extracts from the herb may contain substances (or higher levels of substances) that are more likely to cause serious allergic reactions (anaphylaxis) than those in aqueous/ethanol extracts.

Table 2. Adverse drug reaction reports for *A.paniculata* products

ADR Reports	Methanol Extracted	Aqueous/EtoH Extracted	Unknown extract
Anaphylaxis	39 (27.2%)	3 (8.8%)	1
Allergic-type (excluding anaphylaxis)	60 (42.0%)	18 (52.9%)	0
Non-allergic type	44 (30.8%)	13 (38.2%)	0
Total Reports	143	34	1

It is unknown if aqueous and/or ethanol extracts contain the same constituents as methanol extracts. Studies comparing constituents in aqueous extracts and methanol extracts of *A.paniculata* could not be located. Testing by TGA's Laboratories Branch (LB) in 2010 detected the presence of andrographolide in aqueous extracts of *A.paniculata*, with the extraction process done on the 'marc', ie. remaining *A.paniculata* plant material that had already been subject to extraction with methanol. While the LB commented that the methanol extract (extracted first) should contain virtually all of the andrographolide that was present in the sample, these results suggest that andrographolide may be present in both methanol and aqueous extracts of *A.paniculata*.

The higher number of ADRs reported for products that contain methanol extracts of *A.paniculata* may be due to the fact that the majority of *A.paniculata* containing products in the ARTG (and possibly in use) contain this type of extract. However it appears that regardless of this, there have been proportionally more ADRs reported to products with methanol extracts relative to the total number of products in the ARTG with this solvent (as at October 2013). Although this data is suggestive of a correlation between anaphylactic ADRs and methanol extracts of *A.paniculata*, it is difficult to establish a definitive correlation in the absence of usage data, as it may be the case that the majority of *A.paniculata* products in use contain methanol extracts.

Table 3 compares numbers of products on the ARTG that contain *A.paniculata* extracted with different solvents, and the number of ADRs reported for these products.

Table 3. Extract solvents listed in the ARTG for the ingredient *A.paniculata* and ADRs

Extract solvent	Number of medicines in ARTG (% of total containing *A.paniculata*)	Number to which ADRs have been reported (% total medicines with this solvent)*
Methanol, or Methanol/H_20	35/59 (59.3)	14/35 (40.0)
Ethanol, or Ethanol/H_20	9/59 (15.2)	1/9 (11.1)
H_20	15/59 (25.4)	3/15 (20.0)

*this figure only relates to medicines that were current in the ARTG at October 2013 (excluding export only products), and may not reflect total numbers of ADRs as many of the ADR reports are for medicines that are no longer current in the ARTG (eg. there have been 2 additional ADRs reported for products containing aqueous/ethanolic extracts, however these products have been cancelled from the ARTG).

Further difficulty arises when analysing ADR cases due to the large number of other ingredients often present in the suspected medicines. Table 4 on the following page provides a summary of ADR cases analysed, including anaphylaxis and allergic-type cases with *A.paniculata* as the sole suspected product.

For the majority of cases that involved medicines containing *A.paniculata* as the sole suspected product, a multi-ingredient formulation was implicated. Of the seven anaphylactic ADR cases that involved the product with the single active ingredient *A.paniculata* as the sole suspected medicine, six were assigned a causality rating of possible, while one was assigned a causality of probable. For the 12 allergic-type ADR cases reported for this product, nine were possible, two were probable and one was certain.

Additional ingredients in the multi-ingredient products associated with ADRs include herbs, minerals, vitamins and other ingredients such as amino acids.

Echinacea species are known to be a cause of allergic/anaphylactic reactions. 16 products involved in 68 ADR cases contained an Echinacea species in addition to *A.paniculata* (4.3 ADR cases per product on average), whereas there were 15 products containing *A.paniculata* and no Echinacea species involved in 113 ADR cases (7.5 ADR cases per product on average). No other common ingredients were identified that were likely to collectively contribute to the allergic-type and anaphylactic reactions. Considering this, and the fact that the product that contains the single active ingredient *A.paniculata* accounted for the highest number of ADRs (27), including 12 allergic-type cases and seven cases of anaphylaxis, with causality ratings ranging from possible to certain, it appears that *A.paniculata* may play a causative and/or contributing role in anaphylactic and allergic-type ADRs, including when present in multi-ingredient formulations.

A review of excipient ingredients in products for which ADRs were reported did not identify any ingredients that may have played a causative role, as the excipients reviewed are commonly included in other products, and most do not require label declarations or restrictions on quantity, and are not associated with adverse effects.

Table 4. Multi-ingredient compared to single active *A.paniculata*

Type of ADR	To January 2012	Additional to April 2014	Totals to April 2014
Total reports	165	13	178
Anaphylaxis	38	5	43
Sole suspected medicine – multi-ingredient including *A.paniculata*	30/38	2/5	32/43
Sole suspected medicine - single active *A.paniculata*	5/38	2/5	7/43
Sole suspected contains *A.paniculata* – unknown formula	1/38	0/5	1/43
More than one medicine suspected (both contained *A.paniculata*)	2/38	0/5	2/43
More than one medicine suspected (only one of which contained *A.paniculata*)	0/38	1/5	1/43
Allergic-type	72	6	78
Sole suspected medicine – multi-ingredient including *A.paniculata*	54/72	5/6	59/78
Sole suspected medicine - single active *A.paniculata*	11/72	1/6	12/78
More than one medicine suspected (only one of which contained *A.paniculata*)	6/72	0/6	6/78
More than one medicine suspected (both contained *A.paniculata*)	1/72	0/6	1/78

Investigation of the reported ADRs noted a higher number of ADRs to products that contain *A.paniculata* extracts with a concentration ratio of greater than 10:1, with a higher quantity of equivalent *A.paniculata* per dosage unit. The majority of products in the ARTG contain highly concentrated extracts of *A.paniculata*, which may be a contributing factor to the higher number of ADRs for these products. Further, the extreme bitterness of *A.paniculata* is a likely deterrent for its use in more traditional oral liquid preparations with a lower concentration, which may also be a contributing factor to the lack of ADRs reported for the three oral liquid products that contain *A.paniculata*. Very few ADR reports included information on dose and duration of use. Considering this, as well as the absence of general usage data, a correlation between ADRs and dose/concentration could not be conclusively established. Nevertheless further monitoring of highly concentrated herbal extracts may be warranted to determine if such medicines are more likely to cause adverse effects.

6.5 WHO Vigibase

A search was undertaken on 9 October 2013 of the WHO Vigibase database using the key search terms *Andrographis paniculata, Kalmegh, anaphylactic reaction, dermatitis, allergic and dyspnoea.*

Sixteen cases were reported between 2008 and 2013. Eight of these originated from Australia, while seven came from Thailand, and one came from Canada. In the latter case, seven different herbs including *A.paniculata* were 'suspected'.

The cause of the reaction(s) was documented as 'certain' for *A.paniculata* in one case; 'probable' in two cases; 'possible' in 12 cases and 'unknown' in one case.

The reports lacked detail in terms of dosage and duration, and in seven cases the patients were concomitantly using other medicines.

Data from the WHO Vigibase includes information from a variety of sources, and the likelihood that the suspected adverse reaction is related to the associated medicine is not the same in all cases. The information does not represent the opinion of the World Health Organization.

The discrepancy between the number of ADRs reported to the TGA discussed in this review and the number of Australian reports located in the WHO Vigibase database can be attributed to the fact that trade names of suspected medicines are reported to and recorded by the WHO, which rarely identify active ingredient(s) for complementary medicines (unless active ingredients are explicitly included in the report).

6.6 ADRs in the literature

An article by Farah et al. [4] described the potential for acute hypersensitivity reactions (including anaphylaxis) after oral administration of *A.paniculata*. This article referred to 19 cases of adverse reactions to six products containing ingredients derived from *A.paniculata* identified on the WHO global ICSR database (Vigibase), coming from three countries. In all reports the product containing *A.paniculata* was the sole suspected drug. 17 of the reports concerned acute hypersensitivity reactions, including seven reports of anaphylaxis. The article concluded that International pharmacovigilance data suggest that oral use of *A.paniculata* containing products can cause acute hypersensitivity reactions such as anaphylaxis, and although the frequency of such reactions is unknown and the causative ingredient is unidentified, the authors recommended that a warning be included in the product information of these products.

In a systematic review of the safety and efficacy of *A.paniculata* the authors noted that 'as of June 2003, no reports of suspected adverse events associated with *A.paniculata* had been received by the national drug safety bodies of the United Kingdom, Germany or Australia'. [14] The authors referred to three reports, one of anaphylactic shock and two of anaphylactic reactions, provided by the WHO Collaborating Centre for International Drug Monitoring, all of which occurred in Sweden in 1996. In relation to these reports, the authors noted that 'the World Health Organisation states that the information provided is not homogenous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction and that the information does not represent the opinion of the World Health Organisation'. [14] In relation to data from manufacturers, the authors reported that information was received from one of four manufacturers/distributors of *A.paniculata* products contacted; the Swedish Herbal Institute. As of 1981 they had received five reports of adverse events (allergic reactions). According to the authors, no further information was available. In relation to clinical trials and case series, the article noted that adverse events were reported in five of the thirteen clinical trials included in the review, with no adverse events reported in any of the case series. [14] A higher incidence of adverse events was observed in HIV patients during a Phase I trial that examined the effects of pure andrographolide, including one anaphylactic reaction. [15] However the dose in this trial

(5-10mg/kg/day) was in the region of six to twelve times higher than that used in the other studies (eg., 60mg/day). Reported adverse events in the remaining trials were mild, infrequent and reversible, with no cases of anaphylaxis other than in the study conducted on HIV patients.

A study examining safety monitoring of herbal medicines on the Thai National Essential Drug List (NEDL) examined the use and adverse effects of eight herbal medicines, including *A.paniculata.* [16] Of 54 adverse events documented, 17% were for *A.paniculata* and were listed as abdominal pain, anorexia, and inflammations. No further details were included in the report.

An abstract presented at the 25th International Conference on Pharmacoepidemiology and Therapeutic Risk Management held in Providence Rhode Island in the United States in 2009 provided a summary of an epidemiological and safety profile for Andrographolide in Thailand. [17] Thai Vigibase data from 1 January 1998 to 31 December 2008 were reviewed, yielding a total of 53 adverse reaction reports. Adverse reactions involving the skin system were the most commonly reported. 5.66% of all reports were serious adverse reactions including erythema multiforme and Stevens Johnson syndrome. [17] This correlates with a similar report that provided Thai Vigibase data from February 2000 to December 2008 involving adverse events reported in association with herbal products. [18] Of 593 reports, 60 (10%) were associated with *A.paniculata*. Within the 60 reports, 131 adverse reactions were reported. These are summarised in Table 5 on the following page.

The authors comment that these reports do not necessarily mean that the adverse events are caused by the herbal products, and that such events could be related to other contributing factors.

A presentation by the Thai Food and Drug Administration (FDA) at the 34th annual meeting of the WHO Programme for International Drug Monitoring (2011 Dubrovnik, Croatia) discussed ADR reports between 2001 and 2011 for *A.paniculata* containing products, several of which were allergic-type reactions, with three cases of anaphylactic shock and two cases of anaphylactic reactions. The presentation concluded that *A.paniculata* containing products are likely to induce hypersensitivity reactions, with this potential risk documented in the Thai National List of Essential Medicines (NLEM), and recommended amendments be made to the product information for these products. [3]

Another study reviewed 150 reports of patients suffering adverse reactions (anaphylaxis) to herbal injections in China. [19] Only cases involving patients who were diagnosed with a common cold or an upper respiratory tract infection (URTI) and treated with an herbal injection that resulted in severe non-lethal allergic shock (N = 129) or fatality (N = 21) were included in the analysis. The authors reported on nine different types of herbal injections, which included four cases of anaphylactic shock following intramuscular injection of 'Chuanxinlian herbal injection' (*A.paniculata* leaf and root extract). No deaths were reported.

A text book on the safety of herbal medicines reported that *A.paniculata* has generally been well tolerated in clinical trials. [10] The text summarised that one out of 90 patients reported intense headache and unpleasant sensation in the chest, and two out of 50 patients reported urticaria when Andrographis extract was administered for three to five days at a dose of 1020mg/day (containing 63mg andrographolide and deoxy-andrographolide). The text book also referred to the study conducted on HIV patients, and commented that the dosages used in this trial were much higher than normal therapeutic doses.

Table 5. Reactions associated with *A.paniculata* reported in Thailand, February 2000 to December 2008. [18]

Herb (no. of reactions)	System Organ Class	Total no. for class (%)[a]	Detail (n)
Andrographis paniculata (131)	Skin and appendages disorders	51 (38.9)	Pruritus (13), rash (8), rash maculopapular (7), urticaria (6), sweating increased (4), erythema multiforme (3), angioedema (2), rash erythematous (2), skin exfoliation (2), exfoliative dermatitis (1), dry lips (1), itching (1), Stevens-Johnson syndrome (1)
	Body as a whole – general disorders	18 (13.7)	Fatigue (6), oedema periorbital (3), eyelid oedema (2), fever (2), therapeutic response decreased (2), anaphylactic shock (1), flank pain (1), oedema of extremities (1)
	Gastrointestinal system disorders	18 (13.7)	Vomiting (6), nausea (5), abdominal pain (4), diarrhoea (2),throat dry (1)
	Psychiatric disorders	15 (11.5)	Anorexia (12), sleepiness (2), insomnia (1)
	Respiratory system disorders	12 (9.2)	Dyspnoea (5), coughing (4), bronchospasm (2), sputum increased (1)
	Central and peripheral nervous system disorders	9 (6.9)	Headache (6), burning sensation (1), dizziness (1), faintness (1)
	Urinary system disorders	3 (2.3)	Face oedema (2), urinary frequency (1)
	Application site disorders	2 (1.5)	Anaesthesia local (2)
	Vascular (extracardiac) disorders	2 (1.5)	Vasculitis (2)
	Musculoskeletal system disorders	1 (0.8)	Muscle weakness (1)

[a] Percentage of each herbal product.

In a double-blind placebo controlled study that examined the effects of an Andrographis extract (KalmCold™) in treating uncomplicated upper respiratory tract infection (URTI) in 223 patients, there was no significant difference in adverse effects observed between the placebo and active

groups.[8][20] In terms of allergic-type adverse effects, one case of urticaria was reported in the treatment group. However subjects who had any known allergy or were allergic to any medication were excluded from the trial, which may have resulted in fewer adverse reactions of this type.

6.7 Acute toxicity

Most acute toxicity studies on *A.paniculata* or andrographolide were conducted in animals and the majority found that the herb or extracts of the herb exhibited little toxicity, apart from an in vitro study that found that andrographolide reduced the viability of rat mast cells. [21] This study compared the cytotoxic effects of 14-Deoxy-11,12-didehydro-andrographolide (1) and andrographolide (2) and found that andrographolide (2) dose-dependently and time dependently reduced the viability of A549 and BEAS-2B human lung epithelial cells and RBL-2H3 mast cells. In contrast, (1) did not reduce cell viability of these cultured cells at all concentrations tested at both 24 and 48 hour time points. The cytotoxicity of andrographolide on RBL-2H3 mast cells observed in this study may present a possible mechanism of action for the potential allergy inducing effects of *A.paniculata*, however further studies in human mast cell lines would be required to confirm this postulation.

6.8 Summary of safety issues

Analysis of the TGA ADR database up to April 2014 located 43 reports of anaphylaxis and 78 reports of allergic-type reactions associated with products that contain *A.paniculata*. The majority of the ADRs reported were for multi-ingredient formulations, which confounds a definitive causal association. However considering the common ingredient *A.paniculata*, the multiple allergic-type and anaphylactic reactions, as well as the high number of these reactions reported for the product that contained *A.paniculata* as the sole active ingredient, it appears likely that this ingredient plays a causative and/or contributing role in anaphylactic and allergic-type ADRs, including when present in multi-ingredient formulations.

Examination of ADRs reported for products that contain *A.paniculata* shows that there have been significantly more ADR reports received for products manufactured using herb material extracted with methanol compared with products manufactured using herb material extracted with an aqueous solvent or an aqueous-ethanol mixture, with a significantly higher number of anaphylactic cases reported for the methanol extract products than for the aqueous extract products. This suggests that methanol extracts from the herb may contain substances (or higher levels of substances) that are more likely to cause serious allergic reactions (anaphylaxis) than those in aqueous extracts. Although the majority of products in the ARTG contain methanol extracts of *A.paniculata*, which may be a contributing factor to the higher number of ADRs for these products, it appears there have been proportionally more ADRs reported to products with methanol extracts relative to the total number of products in the ARTG with each type of solvent. Although this data is suggestive of a correlation between anaphylactic ADRs and methanol extracts of *A.paniculata*, it is difficult to establish a definitive correlation in the absence of usage data, as it may be the case that the majority of *A.paniculata* products in use contain methanol extracts.

The investigation noted a higher number of anaphylactic / allergic-type ADRs for products that contain *A.paniculata* extracts with a concentration ratio of greater than 10:1, with a higher quantity of equivalent *A.paniculata* per dosage unit. However further monitoring of highly

[8] The active treatment arm received a capsule of KalmCold, which contains an extract from the leaves of *A.paniculata* made via a 2 step extraction process using both methanol and water as solvents (which equates to a 10.7:1 concentration ratio).

concentrated herbal extracts and additional information on dose and usage are required to confirm this association.

Considering these complexities, a particular type of extract or solvent cannot be conclusively identified as causative. Therefore a more precautionary approach appears warranted to include all products that contain *A.paniculata* in any proposed action.

Several anaphylactic and allergic-type ADRs were reported in the literature for *A.paniculata* containing products, which supports the possibility that this ingredient plays a causative and/or contributing role in anaphylactic and allergic-type ADRs.

7 Current risk mitigation activities

There are no regulatory restrictions or risk mitigation strategies currently applied to the use of *A.paniculata* in listed medicines in Australia.

8 Commentary

This issue was discussed at the 23rd meeting of the Advisory Committee on the Safety of Medicines (ACSOM) on 11 July 2014 (Item 3.1)[9]. The committee advised that while further statistical analysis would be beneficial, taking account of the heterogeneity of the products and preparation methods, there is still sufficient information currently available to confirm an association between anaphylactic / allergic-type reactions and the herbal ingredient *A.paniculata* and that this is more likely in products with higher concentrations of active ingredient obtained using the methanol extraction method.

In view of the above advice and in noting that products containing *A.paniculata* are available over the counter (and therefore consumers are not likely or compelled to discuss usage with their health professional), the committee agreed there is a safety concern sufficient to warrant the adoption of risk mitigation strategies.

The committee advised that it would be appropriate for the TGA to give consideration to the following strategies:

- the addition of a warning statement to the labels of all products containing *A.paniculata*;
- development and implementation of an education or 'awareness raising' program for GPs and complementary medicine practitioners; and
- continue to monitor and review ADR case reports involving *A.paniculata.*

9 Conclusions and recommendations

To conclude, the reviewed information suggests an association between anaphylactic / allergic-type reactions and the herbal ingredient *A.paniculata*, however a particular type of extract or solvent cannot be conclusively identified as causative. Therefore, a precautionary approach appears warranted to include all products that contain *A.paniculata* in any proposed action.

The number of anaphylactic / allergic-type ADRs reported and the severity of the ADRs suggests that the ingredient *A.paniculata* presents a potential risk significant to warrant further action, particularly considering that *A.paniculata* containing products are available over the counter

[9] The ACSOM 23 Meeting statement can be found at http://www.tga.gov.au/committee-meeting-info/acsom-meeting-statement-meeting-23-11-july-2014

and are regulated as low risk (listed) medicines. The TGA is considering the most appropriate regulatory action, including the requirement for warning statements on the labels of medicines containing *A.paniculata*, and will continue to monitor and review ADRs reported for these products to assess the effectiveness of any introduced risk mitigation strategies.

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11 Appendices

Appendix 1 - List of chemical constituents found in *A.paniculata*

Appendix 2 - Case definition: Anaphylaxis

Appendix 1 – List of chemical constituents found in *A.paniculata*

14-deoxy-11,12 didehydroandrographolide
14-deoxy-11-dehydroandrographolide
14-deoxy-11-oxy-andrographolide
19-glycosyl-andrographolide
19-glycosyl-deoxyandrographolide
2',5-dihydroxy-7,8-dimethoxyflavone
5-Hydroxy-2',7,8-trimethoxyflavone
5-hydroxy-7,8,2',3'-tetramethoxy flavone
5-hydroxy-7,8-dimethoxyflavanone
A B C D 14-deoxy-11-oxoandrographolide
acidic polysaccharides PA, PB
andrograpanin
andrograpanin E & F
andrographan
andrographidine A B C D E and F
andrographin
andrographiside
andrographolides
andrographosterin
andropanoside
apigenin-4',7-dimethylether
apigenin-7-4'di-O-methyl ether (roots)
caffeic acid
carvacrol
chlorogenic acid
deoxyandrographolide
dicaffeoyl-quinic acids
eugenol
hentriacontone
homoandrographapholide
hydroxyflavones
myristic acid
neoandrographolide
ninandrographolide
oroxylin A
panicolin
paniculide
paniculide A B C
saponins.
tannins
tritriacontrone
wogonin

Appendix 2 – Case definition: Anaphylaxis

For all levels of diagnostic certainty

Anaphylaxis is a clinical syndrome characterized by

- sudden onset AND
- rapid progression of signs and symptoms AND
- involving multiple (≥ 2) organ systems, as follows

Level 1 of diagnostic certainty

- ≥ 1 major dermatological AND
- ≥ 1 major cardiovascular AND/OR ≥ 1 major respiratory criterion

Level 2 of diagnostic certainty

- ≥ 1 major cardiovascular AND ≥ 1 major respiratory criterion OR
- ≥ 1 major cardiovascular OR respiratory criterion AND
- ≥ 1 minor criterion involving ≥ 1 different system (*other than* cardiovascular or respiratory systems) OR
- (≥ 1 major dermatologic) AND (≥ 1 minor cardiovascular AND/OR minor respiratory criterion)

Level 3 of diagnostic certainty

- ≥ 1 minor cardiovascular OR respiratory criterion AND
- ≥ 1 minor criterion from each of ≥ 2 different systems/categories

The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

Major and minor criteria used in the case definition of anaphylaxis

Major criteria	
Dermatologic or mucosal	Generalized urticaria (hives) or generalized erythema Angioedema*, localized or generalized Generalized pruritus with skin rash
Cardiovascular	Measured hypotension Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: · Tachycardia · Capillary refill time >3 s · Reduced central pulse volume Decreased level of consciousness or loss of consciousness
Respiratory	Bilateral wheeze (bronchospasm) Stridor Upper airway swelling (lip, tongue, throat, uvula, or larynx) Respiratory distress—2 or more of the following: · Tachypnoea · Increased use of accessory respiratory muscles (eg. sternocleidomastoid, intercostals) · Recession · Cyanosis Grunting

*Not hereditary angioedema

Minor criteria	
Dermatologic or mucosal	Generalized pruritus without skin rash Generalized prickle sensation Localized injection site urticaria Red and itchy eyes
Cardiovascular	Reduced peripheral circulation as indicated by the combination of at least 2 of · Tachycardia · A capillary refill time of >3 s without hypotension A decreased level of consciousness

Minor criteria	
Respiratory	Persistent dry cough Hoarse voice Difficulty breathing without wheeze or stridor Sensation of throat closure Sneezing, rhinorrhea
Gastrointestinal	Diarrhoea Abdominal pain Nausea Vomiting
Laboratory	Mast cell tryptase elevation > upper normal limit

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