Classification of *Artemisia annua* as a prescription medicine

Submission to the Medicines Classification Committee

Medsafe
June 2019

Abbreviations and definitions

ACT	artemisinin-based combination therapy for malaria
Artemisia annua	includes *Artemisia annua* extract(s)
CARM	Centre for Adverse Reactions Monitoring
GCP	good clinical practice
GP	general practitioner
OA	osteoarthritis
PBRER	periodic benefit risk evaluation report
RMP	risk management plan
SmPC	summary of product characteristics
UK	United Kingdom
VigiBase	World Health Organization programme for international drug monitoring database
WHO	World Health Organization

Contents

Purpose

Artemisia annua is currently an unscheduled substance. Products containing *Artemisia annua* extract are sold as natural dietary supplements for maintaining and supporting joint health and mobility. They can be purchased from pharmacies and online.

Medsafe identified a potential risk of harm to the liver and a QT prolonging effect with the use of products containing *Artemisia annua* extract following reports to the Centre for Adverse Reactions Monitoring (CARM). It was noted from many of the CARM reports that consumers stated they were taking this product for arthritis which is a therapeutic purpose.

There is evidence the risks of products containing *Artemisia annua* outweigh the benefits making it unfavourable for these products to remain unregulated and available for patient self-selection. In addition, there is another artemisinin derivative, artemether, which is classified as a prescription medicine.

This paper presents background information and data to support the classification of *Artemisia annua* as a prescription medicine. Note that this paper relates to *Artemisia annua* and its extract(s).

Background

Artemisia annua and artemisinin derivatives

Artemisia annua (Sweet wormwood, Sweet Annie, Qing hao) has been used in traditional Chinese medicine for more than 2000 years to treat fever and malaria. It belongs to the Asteraceae (daisy) family and is an annual herb native to China, but now grows in many countries [1].

Chinese scientists took an interest in *Artemisia annua* during the late 1960s in their search for an effective treatment against malaria. The active ingredient *qinghaosu* (essence of *Qing hao*) was isolated in 1972 and later named artemisinin [2-4]. Artemisinin-based combination therapy (ACT) is now recommended by the World Health Organization (WHO) for the treatment of uncomplicated malaria caused by *Plasmodium falciparum [5]*. Semi-synthetic artemisinin derivatives currently used in ACTs include dihydroartemisinin, artesunate and artemether.

In addition to artemisinin, *Artemisia annua* extracts contain variable amounts of other chemicals that have mostly unknown biological/pharmacological activities. In a study of the toxicological and pharmacological profile of volatile constituents of a Serbian sample of *Artemisia annua,* 58 components were identified. Among them artemisia ketone (35.7%), a-pinene (16.5%) and 1,8-cineole (5.5%) were the most abundant. The chemical composition of *Artemisia annua* leaves has also been shown to vary depending on the method of extraction used. The concentration of artemisinin is highest in the leaves just prior to flowering.

Actions taken by Medsafe

In January 2018 Medsafe reviewed 14 cases of hepatotoxicity associated with the use of *Artemisia annua*. These were reported to the Centre for Adverse Reactions Monitoring (CARM). The available information suggested a strong possibility of an association between *Artemisia annua* and liver toxicity.

An alert was issued on 15 February 2018 under section 98 of the Medicines Act 1981 to advise consumers and healthcare professionals that the use of products containing *Artemisia annua* may result in harm to the liver. The alert advised consumers to stop taking these products immediately and to see their doctor if they develop any symptoms or signs of liver toxicity.

An additional 11 reports were reported to CARM following the alert. The Medicines Adverse Reactions Committee recommended at their September 2018 meeting to update the alert and republish it for visibility.

The alert was updated on 27 November 2018 providing the public with information on the total of 25 cases that were known at the time. All of the 25 reports identified Arthrem as the product suspected of causing the liver reaction. GO Arthri-Remedy 1-A-Day was co-suspected in two of these reports.

This paper is seeking the classification of *Artemisia annua* as a prescription medicine. For completeness, information on artemisinin-based products used in the treatment of malaria are included in some sections.

The antimalarial medicine artemether is classified as a prescription medicine in New Zealand. Riamet (artemether + lumefantrine) tablets and dispersible tablets were approved in New Zealand in 2006 and 2011, respectively. These products are not currently available and there is no data sheet published on the Medsafe website.

Part A: Administrative details

1. **International non-proprietary name (INN) of the medicine**

   Artemisia annua is not classified as a medicine currently. It is sold in products as a natural health supplement which are unregulated products.

2. **Proprietary name(s)**

   All products containing *Artemisia annua* and its extract(s), including, but not limited to Arthrem, Go Arthri, Doctor's Best Artemisinin, and Good Health Turmeric Extra Strength.

3. **Name of the company/organisation/individual requesting a classification**

   Medsafe.

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

   All dose forms, all strengths.

5. **Proposed pack size, storage conditions and any other qualifications**

   All pack sizes.

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

   All indications.

7. **Present classification of the medicine**

   Artemisia annua, its extract(s) and all associated names are sold as dietary supplements and have not been classified.

   Artemether, an artemisinin derivative, is classified as a prescription medicine with no conditions.

8. **Classification sought**

   Prescription medicine.

9. **Classification status in other countries**

   Australia: Products containing *Artemisia annua* are complementary medicines and can be listed on the Australian Register of Therapeutic Goods (ARTG).

   United Kingdom: *Artemisia annua* is not listed on the UK's list of herbal medicines that have bene granted a traditional herbal registration (www.gov.uk/government/publications/herbal-medicines-granted-a-traditional-herbal-registration-thr/herbal-medicines-granted-a-traditional-herbal-registration).

10. **Extent of use in New Zealand and elsewhere**

    Unknown but data suggests these products are widely used.

The marketer for Arthrem (Promisia) reported in their financial summary for the 6-month period ending 30 June 2017 that the sales revenue for Arthrem during this period was $1,318,000.

11. Local data or special considerations relating to New Zealand

Not known. *Artemisia annua* is currently an unscheduled substance.

12. Labelling or draft labelling

No products containing *Artemisia annua* extract have been given consent to market in New Zealand. All products containing *Artemisia annua* are currently unregulated. Medsafe does not have label samples.

13. Proposed warning statements

Not applicable as the classification sought is prescription medicine.

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

All products containing *Artemisia annua,* including, but not limited to, Arthrem, Go Arthri, Doctor's Best Artemisinin, and Good Health Turmeric Extra Strength.

It is not possible to generate a full list of products containing *Artemisia annua* as these products are unregulated and no such register exists for natural health products.

Part B: Evidence and benefit-risk analysis

The majority of the information presented in this part relates to one of the *Artemisia annua* containing products marketed by Promisia under the name of Arthrem and the risk of harm to the liver. This is because the majority of adverse reaction reports in New Zealand for *Artemisia annua* reported Arthrem as the brand name (see section 5 in Part B). Additional information has been added on other undesirable effects where possible, and also on other artemisinin derivatives.

1. Indications and dose

Products containing *Artemisia annua* are marketed as natural health supplements for maintaining and supporting joint health and mobility.

Arthrem is sold in bottles of 60 soft gel capsules containing 150 mg of *Artemisia annua* extract in grape seed oil. The recommended dose is one capsule twice a day (morning and evening). Note there may be additional products containing *Artemisia annua* extract currently available in New Zealand that have different strengths and different dose recommendations.

The classification sought for *Artemisia annua* is prescription medicine for any indication and at any dose.

Artemether, classified as a prescription medicine in New Zealand, can be used for the treatment of malaria.

2. Presentation

Products containing *Artemisia annua* are available in oral dose forms, including soft gel capsules, veggie caps, and vege caps.

The classification sought for *Artemisia annua* is prescription medicine for any dose form.

3. Consumer benefits

Currently marketed as natural health supplements for maintaining and supporting joint health and mobility.

Arthrem was investigated in a pilot clinical study and open label extension undertaken in New Zealand, conducted in the Rheumatology Research Unit, Department of Medicine, University of Otago, Dunedin, with funding by Promisia. The 12-week study and 6-month open label extension study are summarised below.

12-week pilot study [6]

ARTH01 was a Phase 2, randomised, placebo-controlled, double-blind 12-week study to investigate the efficacy and safety of Arthrem for pain, stiffness and functional limitations associated with hip and knee osteoarthritis (OA). The study received ethical approval from the Health and Disability Ethics Committee New Zealand, and was conducted in accordance with the principles of good clinical practice (GCP).

42 patients were randomised to one of three treatment groups (14 patients per group):

- Arthrem low dose 150 mg (one capsule twice daily)
- Arthrem high dose 300 mg (one capsule twice daily)

- Placebo (one capsule twice daily).

Study participants were seen at screening, baseline, week 6 and week 12. After the 12-week study there was an optional open-label follow-up study for an additional 6 months.

Participants were excluded if they had significant renal or hepatic impairment.

The primary efficacy endpoint was reduction in Western Ontario and McMaster Universities Arthritis Index (WOMAC®) 3.1 index overall score from baseline to week 12.

Safety outcomes included adverse events (classified using MedDRA), laboratory data and vital signs measurement.

38 patients completed the study and 4 patients withdrew.

Results are shown in Table 1. There was a significant improvement in WOMAC score in the Arthrem low dose treatment group but not in the Arthrem high dose treatment group compared to placebo.

Table 1: Changes in efficacy parameters from baseline to 12 weeks [6]

Parameter	ART low dose *N*=13	ART high dose *N*=11	Placebo *N*=14	All *N*=38
WOMAC total				
Baseline, mean (SD)	37.7 (16.75)	44.5 (10.99)	38.6 (19.52)	40.0 (16.32)
Change at 12 weeks (SD)	−12.2 (13.84)	−4.8 (17.88)	−7.8 (19.80)	−8.4 (17.19)
p value	0.0159*	0.3646	0.1029	
Confidence interval	−22.03, −2.44	−15.47, 5.83	−17.22, 1.65	
WOMAC pain				
Baseline, mean (SD)	7.9 (3.17)	9.0 (3.10)	8.6 (3.32)	8.5 (3.15)
Change at 12 weeks (SD)	−2.6 (3.84)	−0.7 (4.24)	−1.9 (4.48)	−1.8 (4.16)
p value	0.0313	0.5697	0.0948	
Confidence interval	−4.98, −0.25	−3.30, 1.85	−4.21, 0.35	
WOMAC stiffness				
Baseline, mean (SD)	3.9 (1.71)	3.9 (1.38)	3.7 (1.77)	3.8 (1.60)
Change at 12 weeks (SD)	−1.2 (1.42)	−0.4 (1.86)	−0.8 (1.53)	−0.8 (1.59)
p value	0.0087**	0.4550	0.0740	
Confidence interval	−2.13, −0.33	−1.34, 0.61	−1.65, 0.08	
WOMAC physical function				
Baseline, mean (SD)	25.8 (13.04)	31.6 (7.31)	26.3 (15.39)	27.7 (12.63)
Change at 12 weeks (SD)	−8.4 (9.49)	−5.2 (13.12)	−5.1 (14.42)	−6.2 (12.30)
p value	0.0213*	0.1794	0.1393	
Confidence interval	−15.45, −1.32	−12.86, 2.50	−11.88, 1.73	
VAS pain, mm				
Baseline, mean (SD)	56.2 (15.46)	59.8 (14.99)	53.8 (20.31)	56.3 (17.01)
Change at 12 weeks (SD)	−21.4 (23.48)	−11.5 (28.97)	−6.7 (29.66)	−13.1 (27.48)
p value	0.0082**	0.1757	0.3670	
Confidence interval	−36.86, −5.91	−28.28, 5.37	−21.63, 8.20	

*$p<0.025$; **$p<0.01$

ART Artemisia annua extract, *SD* standard deviation, *VAS* visual analog scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

Four patients withdrew from the study: one patient randomised to Arthrem low-dose and 3 patients randomised to Arthrem high-dose. One of the 3 patients who withdrew from the high-dose group developed hepatitis, which was reported to be serious and of moderate severity, and was considered by the study investigators possibly related to Arthrem. The time-to-onset of the hepatitis from starting Arthrem, the response to stopping Arthrem and the outcome are not reported for this case.

The published study report states: 'In general, clinical laboratory parameters were within normal limits with isolated results out of normal range. There were not laboratory changes that were

considered clinically significant.' The report does not indicate which laboratory parameters were measured at each visit.

A summary of the adverse events is shown in Table 2.

Table 2: Summary of adverse events from the 12-week pilot study [6]

Patients, *n* (%)	ART low dose *N*=14	ART high dose *N*=14	Placebo *N*=14	All *N*=42
Any AE	6 (42.9)	9 (64.3)	7 (50.0)	22 (52.4)
Serious AE	2 (14.3)	2 (14.3)	0	4 (9.5)
Discontinuation due to AE	1 (7.1)	2 (14.3)	0	3 (7.1)
Treatment-related AEs[a]	0	4 (28.6)	0	4 (9.5)
Gastrointestinal AEs	1 (7.1)	5 (35.7)	3 (21.4)	9 (21.4)
AEs reported in >1 patient[b]				
Gastroesophageal reflux	0	3 (21.4)	0	3 (7.1)
Abdominal pain	0	1 (7.1)	1 (7.1)	2 (4.8)
Vomiting	1 (7.1)	1 (7.1)	0	2 (4.8)
Back pain	0	1 (7.1)	1 (7.1)	2 (4.8)

[a] AEs considered probably or possibly related to treatment

[b] All other AEs were reported in only one patient

AE adverse event, *ART Artemisia annua* extract

Six-month extension study [7]

Patients who completed the 12-week pilot study were given the option to continue to take Arthrem for an additional six months in an open-label extension study. Of the 38 patients who completed the 12-week study, 34 patients entered the 6-month extension study: 12 from the Arthrem low-dose group, 9 from the Arthrem high-dose group and 13 from the placebo group. All patients received one 150 mg capsule twice-daily during the extension study.

There was no formal statistical analysis of this open-label extension study and results were presented descriptively.

A total of 28 patients completed the study. Efficacy results are shown in Table 3.

Table 3: Changes in mean (SD) efficacy parameters [7]

	Mean WOMAC® parameter score			
	Total	Pain	Stiffness	Physical function
Baseline double-blind study	41.1 (15.8)	8.6 (3.0)	3.9 (1.6)	28.6 (21.2)
Baseline extension study	33.0 (18.4)	7.0 (3.9)	3.1 (2.0)	23.0 (13.6)
Week 24	33.8 (20.8)	6.3 (4.2)	3.3 (2.0)	24.3 (15.3)
Week 36	31.1 (20.3)	5.9 (4.0)	3.3 (7.2)	21.9 (15.1)

N=34.
SD, standard deviation; WOMAC®, Western Ontario and McMaster Universities Osteoarthritis Index.

Six patients withdrew: five due to adverse effects and one due to patient choice. One of the withdrawals was due to elevated liver enzymes, which was considered by the investigators unlikely to be related to treatment. Further details of the case are not provided in the published study report. A summary of adverse effects is shown in Table 4.

Table 4: Summary of adverse events from the six-month extension study [7]

Patients, n (%)	N=34
Any AE	12 (35.3)
Serious AE	1 (2.9)[a]
Discontinuation due to AE	5 (14.7)[b]
Patients with treatment-related AEs[c]	3 (8.8)
Constipation and stomach pain	1 (2.9)
Flatulence	1 (2.9)
Diarrhea	1 (2.9)

[a]Serious AE was considered unrelated to treatment.
[b]Two AEs considered unlikely/unrelated to treatment; three possibly related to treatment.
[c]All considered possibly related to treatment.
AE, Adverse event.

Medsafe comments:

A significant primary efficacy result was only seen in the Arthrem low dose treatment group. No effect was seen in the Arthrem high dose treatment group. It could be considered unusual not to see a dose dependent effect. The efficacy results seen in the pilot study were reported as sustained over the 6-month open-label extension study.

Of the 14 patients who received Arthrem 300 mg twice daily (high-dose) during the 12-week pilot study, one patient developed hepatitis which was considered possibly related to the study medicine.

Of the 34 patients who entered the open-label extension study, one patient developed elevated liver enzymes which was considered unrelated to the study medicine.

Generally this would be considered a very high rate of liver problems.

The time-to-onset from treatment initiation is not stated in either case, but both clearly occurred during treatment. The outcome for each case is not reported. Laboratory parameters were said to be monitored during treatment, but it is not clear which parameters were measured or when.

4. Contraindications and precautions

Some of the cautions that could apply to *Artemisia annua* include hypersensitivity and those with risk factors for QT prolongation or those taking other QT prolongation medicines. More detailed contraindications and precautions are detailed below. There is currently an approved prescription medicine for an artemisinin derivative: artemether.

Riamet (20 mg artemether and 120 mg lumefantrine) was an approved product in New Zealand but its approval has lapsed and there is no published data sheet. The Riamet UK summary of product characteristics (SmPC) was used to gather some information.

Riamet UK SmPC

The following is included in section 4.3 contraindications:

Riamet is contraindicated in:

- patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- patients with severe malaria according to WHO definition.
- patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (eg, metoprolol, imipramine, amitriptyline, clomipramine).
- patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- patients taking drugs that are known to prolong the QTc interval (proarrhythmic). These include:
    - antiarrhythmics of classes IA and III
    - neuroleptics, antidepressive agents
    - certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents
    - certain non-sedating antihistamines (terfenadine, astemizole)
    - cisapride
    - flecainide
- patients with a history of symptomatic cardiac arrhythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- patients with disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesemia
- patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*).

There is a substantial amount of information listed under section 4.4 warnings and precautions.

> Medsafe comments:
>
> Riamet is a combination product. It is not known which of these contraindications apply to the artemether component or the lumefantrine component.

Micromedex

The following contraindications are listed for *Artemisia annua:*

- hypersensitivity to *Artemisia* or wormwood

- pregnancy
- breastfeeding
- stomach ulcers
- intestinal ulcers
- prolonged use of forms high in the essential oil.

Arthrem

The Arthrem website contains the following precautions (site accessed on 26 June 2019):

> Always read the label and take as directed. If symptoms persist, see your healthcare professional.
>
> It is recommended that Arthrem capsules should not be taken:
>
> - During pregnancy or breastfeeding, or in women intending to become pregnant
> - By people with elevated liver enzymes, liver disease or liver cancer
> - By children
> - By people taking antiretroviral drugs for HIV infection
> - By people who are taking drugs known to prolong the QT interval.
>
> Arthrem capsules appear to be well tolerated when taken with a number of concomitant medicines including proton pump inhibitors (eg, omeprazole), NSAIDs, aspirin and paracetamol.
>
> As with most supplements, patients are advised to discontinue use for 2 weeks before and after surgery.
>
> In very rare cases customers have experienced allergic-type reactions after taking Arthrem (fewer than 1 in 1000). If you do experience any of the following symptoms after taking Arthrem we advise you to stop taking the product immediately and seek medical attention as needed: rash (itching all over), extreme nausea (feeling sick), stomach pain, pale stools, dark urine, the whites of the eyes turning yellow or the skin turning yellow (jaundice), dizziness, shortness of breath, chest tightness.

5. Undesirable effects

New Zealand reports of adverse reactions (CARM data)

Reports to CARM of adverse reactions to *Artemisia annua* up to 30 September 2018 are summarised in Table 5. Based on these reports, the safety concerns of interest to Medsafe are liver reactions and QT prolongation.

Table 5: New Zealand reports of adverse reactions to Artemisia annua as reported to CARM up to 30 September 2018

CARM ID	Date	Age/Gender	Medicines	Reactions
110823	Mar 2014	64/F	Arthrem	Nausea Anorexia Diarrhoea
119615	Feb 2016	71/M	Arthrem Pantoprazole Atorvastatin	Hepatic enzymes increased

			Cilazapril/Hydrochlorothiazide Fluoxetine	
120267	Apr 2016	82/F	Arthrem Omeprazole Ibuprofen Atorvastatin Amiloride/Hydrochlorothiazide	Rash erythematous Pruritus
120445	Apr 2016	48/F	Arthrem Diltiazem Cilazapril Nortriptyline Paracetamol	Hepatic enzymes increased
121953	Aug 2016	54/M	Arthrem	Erythema
122052	Sep 2016	54/F	Arthrem	Hepatitis cholestatic
122230	Sep 2016	76/F	Arthrem	QT prolonged
123150	Jan 2017	76/F	Arthrem	Jaundice Pruritus Hepatitis
124405	May 2017	67/F	Arthrem	Hepatic function abnormal Jaundice Pruritus
124539	May 2017	72/F	Arthrem Cholecalciferol	Hepatic enzymes increased Jaundice
124873	Jun 2017	55/F	Arthrem Felodipine	Hepatitis cholestatic Jaundice Nausea Fever
125218	Jul 2017	82/M	Arthrem Doxazosin Insulin neutral iosphane Cilazapril Omeprazole	Fuzzy head Confusion
125378	Jul 2017	62/M	Arthrem Atorvastatin Omeprazole Candesartan	Hepatitis
125681	Aug 2017	71/F	Arthrem	Fever
125847	Sep 2017	66/F	Arthrem	Hepatic function abnormal Jaundice
125947	Sep 2017	64/F	Arthrem	Nausea Vomiting Hepatic enzymes increased
125969	Sep 2017	76/F	Arthrem	Jaundice Hepatic function abnormal
125970	Sep 2017	77/M	Arthrem	Jaundice Hepatic function abnormal

126933	Dec 2017	71/F	Arthrem	Jaundice Hepatic enzymes increased
126905	Dec 2017	55/M	Arthrem Metoprolol	Jaundice Hepatic enzymes increased
127117	Jan 2018	41/F	Arthrem Antihistamines Paracetamol Ibuprofen Tramadol	Diarrhoea Fever Vomiting Hypotension Nausea
127445	Feb 2018	65/M	Arthrem	Hepatic function abnormal Jaundice Pruritus Faeces pale Anorexia
127446	Feb 2018	57/F	Arthrem Magnesium	Urine discolouration Vision abnormal
127447	Feb 2018	60/M	Arthrem Paracetamol/codeine Diclofenac	Jaundice Vomiting Hepatic enzymes increased Anorexia Abdominal pain
127451	Feb 2018	57/F	Arthrem Go-Arthri	Hepatic enzymes increased
127458	Feb 2018	52/M	Arthrem	Urticaria
127475	Feb 2018	64/F	Arthrem	Jaundice Hepatic enzymes increased Pruritus Purpura Haematuria
127492	Feb 2018	69/F	Arthrem	Jaundice Pruritus Hepatic enzymes increased Tiredness
127498	Feb 2018	69/F	Arthrem Vitamin B complex Fish oil Magnesium Cranberry extract	Influenza-like symptoms Urticaria Vomiting Taste metallic Syncope
127545	Mar 2018	83/M	Arthrem Warfarin Metoprolol Allopurinol	Conjunctival congestion Pruritus
127583	Mar 2018	51/F	Arthrem Magnesium Ascorbic acid	Headache Pruritus Abdominal pain Chills
127632	Mar 2018	93/F	Arthrem Metoprolol Donepezil Pantoprazole	Hepatic enzymes increased

			Atorvastatin	
127666	Mar 2018	77/M	Arthrem	Dermatitis lichenoid Photosensitivity reaction
127841	Mar 2018	71/M	Arthrem	Hepatic function abnormal
128001	Apr 2018	69/M	Arthrem	Hepatic enzymes increased
128048	Apr 2018	81/M	Arthrem Cilazapril Metoprolol Allopurinol Thyroxine	Hepatic cirrhosis
128413	May 2018	83/F	Arthrem	Hepatic enzymes increased
128422	May 2018	86/F	Arthrem	Jaundice Hepatitis cholestatic Pruritus

In addition a case (133141) was received in May 2019 detailing a cardiac arrest due to QT prolongation in a 57 year old female also taking citalopram.

Below is a summary of the 25 reports of liver reactions up to 30 September 2018:

- 23 were either reported by a healthcare professional or had involvement from one.
- 13 met the seriousness criteria (8 hospitalised, 5 medically significant); no deaths.
- 22 cases where Arthrem was the sole suspect; 13 cases where Arthrem was the only reported product.
- 2 reports where the patient had changed from Arthrem to Go-Arthri 6 months and 10 days, respectively, prior to onset of the liver reaction.
- 62 adverse reaction terms coded: predominant reaction was jaundice (15 cases), hepatic enzymes increased (11 cases) and hepatic function abnormal (8 cases).
- 16 reports included information on the pattern of liver toxicity: hepatocellular (4 cases), cholestatic (7 cases), mixed (5 cases).
- 2 reports where patients underwent liver biopsy: consistent with toxicity in one case and indicative of hepatocellular damage in the second case.
- 6 cases where ultrasound scan results were reported one of which reported an enlarged liver and gall bladder.
- 7 cases where antecedent factors could potentially lead to liver enzyme disturbance.
- All cases reported stopping *Artemisia annua* (dechallenge) shortly after onset of symptoms: 22 indicated the patient had either recovered (11) or improved (11) after stopping, patients reported to be recovering in 2 cases and outcome unknown in the remaining case.
- Age range 48 to 93 years (median 69 years).
- Time-to-onset ranged overall from 1 to 52 weeks (median 5 weeks).

There are two reports of QT prolongation to CARM. One was received in 2016 and the other in May 2019. Arthrem was the only reported medicine in the 2016 case.

International reports of adverse reactions (VigiBase data)

A search of VigiBase was conducted on 26 June 2019 and returned 13 cases reporting *Artemisia annua* as a substance. The most commonly reported reaction term is vomiting (4 cases), with 1 case each reporting anaemia, cyanosis, drug eruption, dyspnoea, formication, haemoglobin decreased, hepatitis fulminant, hypotension, jaundice cholestatic, nausea, pneumothorax, renal pain, respiratory disorder, seizure, tubulointerstitial nephritis, urine analysis abnormal, weight decreased, and vertigo.

The search was widened to include the ATC level for artemisinin and derivatives both alone and in combination. A total of 6857 cases were retrieved. The most commonly reported reaction terms were dizziness (1914 cases), vomiting (1590 cases), headache (1363 cases), nausea (1301 cases) and asthenia (1232 cases). The MedDRA SOCs with the most reaction terms were gastrointestinal disorders (2921 cases), nervous system disorders (2883 cases) and general disorders and administration site conditions (1711 cases).

International reports of adverse reactions (United States)

A case of a patient who developed hepatitis after taking a short course of a supplement containing artemisinin has also been reported in the United States. CDC investigators concluded that the hepatitis might have been associated with ingestion of the herbal supplement containing artemisinin. Health-care providers should be aware of the possibility of hepatic toxicity in patients taking herbal supplements containing artemisinin (www.cdc.gov/mmwr/preview/mmwrhtml/mm5831a3.htm).

Medsafe comments:

There are reports of reactions involving the liver with *Artemisia annua*. Reports to artemisinin and derivatives should be interpreted with care as these are likely to be used as treatment for malaria and could reflect differences in the patient population, dose etc.

Micromedex

The following adverse effects are listed for *Artemisia annua*:

- abdominal pain and diarrhoea
- bradycardia
- flu-like symptoms and fever
- low reticulocyte count
- seizures
- skin rash
- nausea, vomiting, and loss of appetite.

Arthrem

The Arthrem website contains the following precautions (site accessed on 26 June 2019):

Some people have reported experiencing reflux (burping) although not all people find this unpleasant. If this is troublesome you can try keeping the capsules in the fridge or freezer and/or taking the capsules with food or a large glass of cold milk or water. As with any dietary supplement, we recommend customers stop taking the product if it makes them unwell.

There have been rare reports of allergic-type reactions after taking Arthrem (fewer than 1 in 1000). If you do experience any of the following symptoms after taking Arthrem we advise you to stop the product immediately and seek medical attention as needed: rash, vomiting, extreme nausea, dizziness, shortness of breath, chest tightness.

6. Overdose

The Riamet (20 mg artemether and 120 mg lumefantrine) UK SmPC states the following in section 4.9 overdose:

In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include ECG and blood potassium monitoring.

7. Medication errors and abuse/misuse potential

Medication errors are a possibility with any medicine. These can be monitored through Periodic Benefit Risk Evaluation Reports (PBRERs) and managed by having a Risk Management Plan (RMP).

Unlikely to have significant abuse/misuse potential.

8. Communal harm and/or benefit

Reports to CARM of liver reactions with the use of products containing *Artemisia annua* suggests there is communal harm with these products being freely available and unregulated. These are currently available for self-selection and can be purchased online with no advice or counselling from a healthcare professional. In addition, caution should be advised for patients with risk factors for QT prolongation or those taking other medicines that could prolong the QT interval.

The benefits of using *Artemisia annua* for joint health has been studied in a 12-week pilot study and a 6-month extension study. A total of 28 patients were exposed to *Artemisia annua* in these two studies. The efficacy results were modest and the number of patients exposed are considered very low for a short period of time.

9. Integrated benefit-risk statement

Artemisia annua is not classified as a medicine and therefore falls outside of any requirement for safety monitoring, and there is no approval pathway so the benefits and quality of products are unknown.

Approval of a medicine requires submission of data to support its efficacy, safety and quality. Pharmaceutical companies are responsible for monitoring medicines safety. Any potential risks are identified by the company, adequate risk management strategies are implemented and their effectiveness monitored. Medsafe is the medicines regulator and provides a framework in which companies can operate and meet their responsibilities. This ultimately ensures New Zealanders have access to high quality, effective and acceptably safe medicines.

Artemether is an artemisinin derivative used in the treatment of malaria. Artemether is classified as a prescription medicine. *Artemisia annua* contains artemisinin and it is possible that it has similar effects to artemether.

Products containing *Artemisia annua* are currently marketed as natural health products which are unregulated. There are no requirements to show these products are effective, of high quality and of acceptable safety. The effects of one of these products, Arthrem, was studied in a 12-week pilot study and a 6-month extension study. There was a statistically significant improvement in stiffness, physical function and mean VAS score. One patient developed hepatitis during the pilot study and another patient developed elevated liver enzymes in the open-label extension.

The effects of *Artemisia annua* on the liver were identified by Medsafe through spontaneous reports to CARM. Medsafe issued an alert on 15 February 2018 to warn the public of possible risk of harm to the liver and this alert was updated on 27 November 2018. Communication of potential safety concerns is an important component of risk management. It is possible these effects would have been identified earlier if these products were regulated as medicines. Monitoring of liver enzymes before treatment and regularly during treatment could be a potential risk management strategy which can only be effectively implemented if these products are prescription medicines.

The risk of harm to the liver with the use of products containing *Artemisia annua* outweighs the modest benefits in maintaining and supporting joint health and mobility.

10. Risk mitigating strategies

The classification of *Artemisia annua* as a prescription medicine would remove these products for self-selection and ensure adequate safety monitoring, including effects on the liver, can be implemented. The involvement of healthcare professionals is crucial for this to work and also to ensure patients receive adequate counselling.

Discussion

Artemisia annua (Sweet wormwood, Sweet Annie, Qing hao) has been used in traditional Chinese medicine for more than 2000 years to treat fever and malaria.

Products containing *Artemisia annua* extract are sold as natural dietary supplements for maintaining and supporting joint health and mobility.

Medsafe identified a potential risk of harm to the liver and a QT prolonging effect with the use of products containing *Artemisia annua* extract following reports to the Centre for Adverse Reactions Monitoring (CARM). *Artemisia annua* is currently an unscheduled substance. There is currently an approved prescription medicine for a purified and modified component of *Artemisia annua*: artemether.

In February 2018 and November 2018, Medsafe published alerts on its website regarding the potential risk of harm to the liver when taking products containing *Artemisia annua* extract.

Medsafe considers *Artemisia annua* should be classified as a prescription medicine in New Zealand due to both its indication and side effect profile. *Artemisia annua* products are used for malaria prophylaxis/treatment and arthritis. Medsafe does not consider it is appropriate for consumers to

self-diagnose themselves with arthritis. There are many different types of arthritis and related conditions which may need to be treated differently and it is important that consumers check with healthcare professionals when discussing diagnoses and potential treatments. In addition in order to avoid resistance it is important to have physician input into the prophylaxis and treatment of malaria. Noting the potential side effects (QT prolongation and hepatic injury) that have been seen in cases reported in New Zealand, Medsafe also considers it is important for healthcare professionals to be involved in treatment decisions regarding products containing *Artemisia annua*. A doctor can determine whether a specific treatment is appropriate for an individual by knowing what other medicines they are taking. For example it may not be appropriate for some people to be taking multiple QT prolonging medicines due to a possible increased risk of cardiac arrest or sudden death.

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