

Herbal preparations with phytoestrogens- overview of the adverse drug reactions

Introduction

For women suffering from menopausal symptoms, treatment is available if the symptoms are particularly troublesome. The main treatment for menopausal symptoms is hormone replacement therapy (HRT), although other treatments are also available for some of the symptoms (1). In recent years, the percentage of women taking hormone replacement therapy has dropped (2, 3). Many women with menopausal symptoms choose to use dietary supplements on a plant-based basis, probably because they consider these preparations to be "safe" (4). In addition to product for relief of menopausal symptoms, there are also preparations on the market that claim to firm and grow the breasts by stimulating the glandular tissue in the breasts (5). All these products contain substances with an estrogenic activity, also called phytoestrogens. These substances are found in a variety of plants (4). In addition, also various multivitamin preparations are on the market that, beside the vitamins and minerals, also contain isoflavonoids. Because those are mostly not specified and present in small quantities and no estrogenic effect is to be expected, they are not included in this overview. In 2015 and 2017 the Netherlands Pharmacovigilance Centre Lareb informed the Netherlands Food and Consumer Product Safety Authority (NVWA) about the received reports of Post-Menopausal Vaginal Hemorrhage Related to the Use of a Hop-Containing Phytotherapeutic Products MenoCool® and Menohop® (6, 7).

Reports

From September 1999 until November 2019 the Netherlands Pharmacovigilance Centre Lareb received 51 reports of the use of phytoestrogen containing preparations (see Appendix 1). The reports concern products with various herbs to which an estrogenic effect is attributed. In 26 reports the suspect supplement contains black cohosh (*Cimicifuga racemosa*), 13 reports concern hop (*Humulus lupulus*) based preparations, 4 reports concern soy bean (*Glycine max*), 3 reports chasteberry or monk's pepper (*Vitex agnus cactus*) and red clover (*Trifolium pratense*) and 1 report dong quai (*Angelica sinensis*) and kudzu root (*Pueraria lobata*) respectively. All reports concern women, aged 24 to 65 years. The reporter was a specialist doctor in 12 cases, a general practitioner in 6 cases, a pharmacist in 6 cases and patients in 27 cases.

Most commonly reported ADRs were complaints that may be related to uterine proliferation. Postmenopausal vaginal bleeding was reported in 10 cases, in 2 cases in combination with endometrial hyperplasia and 2 times only endometrial hyperplasia was reported. The latency times of these reports varied from 1 day to 2 years. One patient was treated with a curettage, some other patients with medroxyprogesteronacetate.

Liver function disorders (increased liver enzymes, hepatitis and liver failure) have been reported 7 times; 6 times with a preparation with black cohosh and 1 time with red clover.

Among the reports on preparations with red clover, there was a report (NL-LRB-188531) in which, in addition to the extremely long and severe vaginal bleeding, the occurrence of bruising was also reported. A sample of the tablets was analyzed by The National Institute for Public Health and Environment (RIVM) for possible presence of coumarins. The analysis result revealed only presence of the in scientific literature described components of red clover, ononin, formononetin, sissotrin and biochanin A. No other pharmacologically active substances were detected.

In 2 reports (NL-LRB-80863 and NL-LRB-181785) a possible interaction between levothyroxine and the phyto-estrogens containing product is reported (breastGRO® and Ymea silhuet®).

Table 1 shows the main phytoestrogen component of the reported products. It should be noted that the ingredients were recorded at the reporting time and some of the preparations may have a different composition today.

Table1. Product name and the main phytoestrogenic ingredient

Product name	(main) Phytoestrogen component
MenoCool®	Humulus lupulus + grains
Ymea silhuët® 2015	Humulus lupulus + yam
BreastGRO®	Humulus lupulus
Menohop®	Glycyne max + Humulus lupulus
Phyto soya®	Glycyne max
Soja isoflavonen	Glycyne max
Ymea®	Cimicifuga racemosa
Ymea totaal extra sterk® (not current)	Cimicifuga racemosa 80mg
Ymea silhouët®	Cimicifuga racemosa 20mg
Ymea dag& nacht®	Cimicifuga racemosa 10mg
Ymea overgang ®	Cimicifuga racemosa 80mg
Ymea Totaal & Vitaliteit®	Cimicifuga racemosa 100mg + Vitex agnus cactus
Valdispert overgang totaal®	Cimicifuga racemosa
Valdispert overgang vrouw ®	Cimicifuga racemosa
Davitamon FemFit® overgang	Cimicifuga racemosa
New Care overgang speciaal ®	Cimicifuga racemosa + Vitex agnus cactus
Famosan overgang balance®	Cimicifuga racemosa
Promesil®	Trifolium pratense
Rode klaver NOW®	Trifolium pratense
Davitamon FemFit®	Vitex Agnus Castus
Fem compleet De Tuinen® 2016	Angelica sinensis
Care for women Menopause®	Pueraria lobata

Other sources of information

Mechanism

Phytoestrogens display estrogen-like activity since they are structurally similar to human estrogens and therefore they can bind to the estrogen receptor. In this way they are able to mimic or block the action of the human hormone estrogen, although they are much less potent (8). In vitro assays have found that, although most phytoestrogens bind both ER α and ER β and activate ER-dependent gene transcription through both subtypes (9). Phytoestrogens can also manipulate steroid biosynthesis and transport by, for example, stimulating hormone-binding globulin (SHBG) synthesis in liver cells (10), and that will competitively displace either 17 β -estradiol or testosterone from plasma sex hormone binding globulin (SHBG) (11).

The four major classes of phytoestrogens are flavonoids, lignans, coumestans and stilbens. The flavonoids are subdivided into: flavanones, isoflavones, flavonols, flavones, anthocyanides and flavanols (4).

Isoflavones with a phytoestrogenic effect include genistein, daidzein and glycitein (12).

These substances are found in particular in soy and red clover, bound to sugars as glycosides.

The prenylflavonoid substance 8 prenylnaringenin (hopeine) is the phytoestrogen in hops. Of all phytoestrogens, 8-prenylnaringenin has the strongest estrogen receptor activity (13).

Lignans are phenolic compounds. The main sources of lignans are seeds, especially flax seeds. They are present in plants as glycosides. In the intestines, due to the action of intestinal bacteria, lignans are released. Of more than 1000 different lignans, only metaresinol and secoisolariciresinol show the estrogenic activity. They are weak estrogens that can attach themselves to estrogen-binding molecules (14-17). They can act as either weak oestrogens or they can oppose the actions of oestrogen, depending on the presence of stronger oestrogens like estradiol (4).

The most important coumestans with an estrogenic activity are coumestrol and trifoliol and occur in red clover, young sprouts or sprouts such as in alfalfa, soy and mungo beans. Coumestans have a coumarin structure. The amount of coumestrol is increased under the influence of the fungi. The correct processing of the herb red clover is very important: with a poor drying process with fermentation, dicumarol is produced, which has a strong anticoagulant effect (18).

Examples of stilbenes include resveratrol found in grape skin, red wine and peanuts. Resveratrol possesses estrogenic activity only in the *trans* form (17).

The molecular mode of and the active principles of the estrogenic action of black cohosh (*Cimicifuga racemosa*) are still not clear. The constituents of black cohosh include triterpenes glycosides and polyphenols. Black cohosh was initially believed to have estrogen-like activity and modulate tissue specific subtypes of the estrogen receptor; more recent investigations suggest that it may have serotonergic activity (19). Also the estrogenic activity of dong quai (*Angelica sinensis*) is controversial (Liu et al., 2001; Lau et al., 2005; Circosta et al., 2006) (20).

Literature

Many articles devoted to phytoestrogens can be found in the literature. Both positive and negative effects of phytoestrogens are described. Below the publications are listed that are related to the ADRs reported to Lareb.

ADRs related to uterine proliferation

The effect of intake of isoflavones from food supplements and histo(patho) logical changes in the endometrium of peri- and post-menopausal women has been investigated in several controlled trials. Significant changes in endometrium were reported in a randomized placebo controlled trial in which 376 subjects were randomized to receive either 150 mg isoflavones/day or placebo. After 5 years of treatment, six cases of hyperplasia (five cases of simple hyperplasia and one case of complex hyperplasia) were detected in the isoflavones group compared with none in the placebo group (21). Endometrial hyperplasia was also reported in a small randomized controlled trial in which 39 post-menopausal women were randomized to one of four treatment arms: low and high estradiol and low and high isoflavones. After 6 months, endometrial hyperplasia occurred in women from all groups (22). A relationship between vaginal haemorrhagia and phyto-estrogens from soy has been described by Chandrareddy et al. in case reports. Abnormal uterine bleeding with endometrial pathology was found in three women related to a high intake of soy products. All three women improved after withdrawal of soy from their diet (23). Some of the cases received by The Netherlands Pharmacovigilance Centre Lareb were described earlier in two case reports published in 2012 and 2015 (24, 25).

Hepatotoxicity

The most commonly reported ADR associated with black cohosh (*Cimicifuga racemosa*) is liver toxicity (26-32). The data on the nature of the active substances and the mechanism of action are still controversial (27). Lareb published a case in 2009 about hepatitis after using Ymea[®] preparation (33). Recently a case report has been published concerning the Lareb report with liver toxicity related to the use of black cohosh containing supplement Valdispert Overgang Totaal[®]. In this case hepatotoxicity resulted in a liver transplant (34). A similar case from the United States was described in 2004. A 57-year-old woman suffered from an autoimmune hepatitis 3 weeks after starting the use of "black cohosh" (35).

Coagulation disorders

One case report from the literature describes the occurrence of subarachnoid haemorrhage when using supplements with red clover, don quai and siberian ginseng (36). One of the components of red clover is coumestrol, a coumarin structure. In case of a poor drying process, fermentation processes can also take place that cause the formation of dicumarines (18).

Interaction with thyroid hormones

According to the literature, quercetin, found in onions, curly kale, leeks, broccoli, blueberries, and daidzein, found among others in soy beans and red clover, can act as effective inhibitors of sulphonyltransferases on the function of thyroid hormones, steroids and catecholamines (12). As isoflavones genistein and daidzein have a similar chemical structure to T3 and T4 and therefore interactions with the thyroid function can be expected. In vitro studies demonstrated that the genistein, daidzein and biochanin A inhibited thyroperoxidase (TPO), an enzyme involved in the synthesis of T4 (Divi et al, 1997) (37). Soy isoflavone genistein showed variable response in the pituitary and thyroid glands. In vivo genistein suppresses LH secretion and increases TSH release after single high dose administration. No effect on the LH levels was seen. In the longer term, it causes a lower level of free T3 (38, 39). On the other hand phytoestrogens could potentially interact with thyroxine medication since they could alter TBG concentrations and increase the binding capacity for thyroxine. If a fixed dose of thyroxine is used in treatment, ingestion of large amounts of phytoestrogens could lower the amount of thyroxine available in the free (active) form (37).

Discussion and conclusion

Various beneficial health effects have been ascribed to phytoestrogens, such as a lowered risk of menopausal symptoms like hot flushes and osteoporosis. In contrast to these beneficial health claims, the (anti)estrogenic properties of phytoestrogens have also raised concerns since they might act as endocrine disruptors, indicating a potential to cause adverse health effects (39). Lareb has received reports on ADRs like postmenopausal bleeding, endometrium hyperplasia, liver function disorders including one report where a liver transplant was required interactions with thyroid hormones and anticoagulants. The phyto-preparations from the overview are sold as food supplements and fall under the authority of the Dutch Food and Consumer Product Safety Authority (NVWA). The phytoestrogen supplements are available without a prescription and consumers often mistakenly think they cannot have side effects. Better information about the possible unwanted side effects would help women make a well-considered decision about the use of this type of supplements.

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This signal has been raised on December 10, 2019. It is possible that in the meantime other information became available.

Appendix 1

Reports of ADRs in association with phyto-estrogen supplements in the Lareb database

ID (NL-LRB) Patient Sex Age (years) Source	Suspect drug dose indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset Action with drug Outcome
Cimicifuga racemosa (black cohosh) contains polyphenols, lignans and triterpens Exact mechanism and compounds for phytoestrogenic action still unknown				
2579 F, 50-60 Specialist doctor	Ymea 1 dosage form per 1.0 Days for Menopausal symptoms		1: Postmenopausal haemorrhage	1: 3 Months Drug withdrawn Unknown
26349 F, 50-60 General practitioner	Ymea 1 dosage form per 1.0 Days		1: Breast pain	1: 3.1 Weeks Drug withdrawn Outcome unknown
31296 F, 20-30 Pharmacist	Davitamon fem fit 1 per 1.0 Days for Unspecified vitamin A deficiency		1: Hypersensitivity	1: Unknown Drug withdrawn Recovered/resolved
33183 F, 60-70 Pharmacist	Davitamon fem fit 1 per 1.0 Days for Malaise	etidroninezuur met calcium	1: Postmenopausal haemorrhage	1: 1 Month Drug withdrawn Recovered/resolved
55910 F, 50-60 Consumer	Ymea 2 dosage forms per 1.0 Days for Hot flushes		1: Abdominal pain 2: Diarrhoea 3: Nausea	1t/m3: 1 week Drug withdrawn Recovered/resolved
57316 F, 50-60, General practitioner	Ymea for Menopausal symptoms		1: Hepatic function abnormal	1: 4 Month Drug withdrawn Recovered/resolved
65126 F, 40-50 Specialist doctor	Ymea 1 dosage form for Menopausal symptoms		1: Autoimmune hepatitis	1: 1 Year Drug withdrawn Recovering/resolving
107316 F, 50-60 General practitioner	Ibandronic acid tablet 150mg for Osteoporosis macrogol/zouten pdr v drank (movic/molax/laxt/ge) 1 dosage form for Constipation Ymea 1 dosage form	meprazole Acetylsalicylic acid enalapril atorvastatin alprazolam mometasone formoterol fenoterol/ ipratropium salbutamol/ ipratropium theofylline montelukast acetylcysteine	1: Anaphylactic reaction	1: 1.5 Year Drug withdraw Outcome unknown 2: 11 Months Drug withdraw Outcome unknown 3: 9 MonthsAction unknown Outcome unknown

121182 F, 50-60 Consumer	Care for women 1 dosage form per 1.0 Days for Menopausal symptoms		1: Breast cancer	1: 2 Years Drug withdrawn Recovered/resolved with sequelae
128961 F, 50-60 Consumer	Ymea 1 dosage form per 1.0 Days for Menopausal symptoms		1: Postmenopausal haemorrhage	1: 1 Day Drug withdrawn Recovered/resolved
133307 F, 50-60 Consumer	Famosan overgang balans 1 dosage forms per 1.0 Days for Menopausal symptoms		1: Rash	1: 2 Weeks Drug withdrawn Recovered/resolved
133615 F, 50-60 Consumer	Ymea 2 dosage forms per 1.0 Days for Menopausal symptoms		1: Abdominal pain upper	1: 2 Weeks Drug withdrawn Recovered/resolved
137715 F, 40-50 Pharmacist	Ymea Cyress 10mg Mirtazapine 30mg 1DF per 1 days 10mg per 1 day 30mgper 1 day for Menopausal symptoms		Chest pain	3 Days Drug withdrawn Recovered
142625 F, 40-50 Consumer	Ymea totaal 2 dosage forms per 1.0 Days for Menopausal symptoms Ymea silhouet 2 dosage forms per 1.0 Days for Menopausal symptoms ymea dag en nacht 2 dosage forms per 1.0 Days for Menopausal symptoms	Inneov hairvolume	1: Hepatitis 2: Pruritus	1: 1216 Days Drug withdraw Outcome unknown 2: 1003 Days Drug withdrawn Recovered/resolved with sequelae
155650 F, 30-40 Consumer	Davitamon fem fit 2 dosage forms per 1.0 Days for Menstrual disorder		1: Headache 2: Vomiting	1: 2 Hours Drug withdrawn Recovering/resolving 2: 2 Hours Drug withdrawn Recovering/resolving
164307 F, 50-60 Specialist doctor	Valdispert overgang totaal 2 dosage forms per 1.0 Days for Menopausal symptoms	Oestrogen with dydrogesteron	1: Acute hepatic failure 2: Liver transplant	1: 10 Weeks Drug withdrawn Recovering/resolving 2: 70 Days Drug withdrawn Recovering/resolving
167399 F, 50-60 Consumer	Cimicifuga preparaat 2 dosage forms per 1.0 Days for Agitation		1: Hepatic function abnormal	1: 4 Months Drug withdrawn Recovered/resolved with sequelae
181785 F, 40-50 Consumer	Ymea silhouet 2 dosage forms per 1.0 Days for Menopausal symptoms levothyroxine tablet 25ug 24.50 dosage forms per 1.0 Weeks for Hashimoto's thyroiditis	Carbasalate calcium	1: Drug interaction 2: Goitre 3: Headache	Drug 1 1 t/m3: 5 Days Drug withdrawn Recovering/resolving Drug 2 5 Days Dose not changed Recovering/resolving,

183730 F, 50-60 Specialist doctor	Ymea 1 dosage form for Menopausal symptoms	emollientia/ protectiva calcipotriol acitretine clobetasole	1: Alanine aminotransferase increased 2: Gamma- glutamyltransferase increased 3: Hepatic enzyme increased	1 t/m3: 1 Month Drug withdrawn Recovering/resolving
189396 F, 40-50 Pharmacist	New care overgang speciaal (contains also Vitex agnus cactus) 1 dosage form per 1.0 Days for Menopausal symptoms fluoxetine 20mg 20mg per 1.0 Days for Depression	oxazepam	1: Depression 2: Drug interaction 3: Drug interaction	1 t/m3: 2 Weeks Dose reduced Recovering/resolving
199006 F, 20-30 Consumer	Biotisan hypericum dilutie 1 dosage form per 1.0 Days for Premenstrual syndrome Davitamon Fem Fit 1 dosage form per 1.0 Days for Premenstrual syndrome		1: Dizziness 2: Fatigue 3: Vision blurred 4: drug interaction	1: 3 Weeks Drug withdrawn Recovered/resolved
199557 F, 50-60, Consumer	Ymea 2 dosage forms per 1.0 Days for Menopausal symptoms	mirtazapine	1: Pruritus	1: 5 Days Drug withdrawn Recovered/resolved
206719 F, 40-50, General practitioner	Ymea totaal 1 dosage form per 1.0 Days for Hot flushes		1: Arrhythmia supraventricular 2: Sinus tachycardia	1,2: 9 Days Drug withdrawn Recovered/resolved,
225443 F, 40-50, Consumer	Orthica strata fem 1 dosage form per 1.0 Days for Feeling bad	Not specified oral contraceptive	1: Neuralgia 2: Oedema peripheral 3: Poor quality sleep	1 t/m3: Months Dose not changed Outcome unknown
226400 F, 20-30, Consumer	Fem compleet de Tuinen 1 dosage form per 1.0 Days		1: Hypoaesthesia 2: Neuralgia	1,2: 3 Weeks Drug withdrawn Not recovered/not resolved/ongoing
230871 F, 50-60 Consumer	Ymea silhouet 1 dosage form per 1.0 Days for Menopausal symptoms		1: Paraesthesia 2: Vitamin B6 increased	1,2: 3 Years Drug withdrawn Outcome unknown

<p>Flavonoids</p> <p>Humulus lupulus (Hop) contains a.o.8-prenylnaringenine</p>				
80863 F, 30-40 General practitioner	BreastGro 1 dosage form levothyroxine tablet 100ug (zuur) 100ug		1: Drug interaction 2: Hypothyroidism	1,2: 1 Month Action unknown Recovered/resolved
130733 F, 60-70 Specialist doctor	Menocool 1 dosage form per 1.0 Days for Menopausal symptoms		1: Endometrial hyperplasia	1: 0 Days Drug withdrawn Recovering/resolving

130735 F, 50-60 Specialist doctor	Menocool 1 dosage form per 1.0 Days for Menopausal symptoms		1: Postmenopausal haemorrhage	1: 212 Days Drug withdrawn Recovering/resolving
130736 F, 50-50 Specialist doctor	Menocool 1 dosage form per 1.0 Days for Menopausal symptoms		1: Endometrial hyperplasia	1: 390 Days Drug withdrawn Recovering/resolving
157909 F, 60-70 Specialist doctor	Menocool 1 dosage form per 1.0 Days for Flushing		1: Postmenopausal haemorrhage	1: 1 Year Drug withdrawn Outcome unknown
178148 F, 50-60, Specialist doctor	Menocool for Menopausal symptoms	progesteron	1: Postmenopausal haemorrhage	1: 2 Year Drug withdrawn Recovering/resolving
181715 F 50-60, Consumer	Menocool 2 dosage forms per 1.0 Days for Menopausal symptoms	mometaso fexofenadine	1: Abdominal pain 2: Endometrial hyperplasia 3: Vaginal haemorrhage	1: 2 Months Drug withdrawn Recovering/resolving 2: 2 Months Drug withdrawn Recovering/resolving 3: 2 Months Drug withdrawn Recovering/resolving
195247 F, 50-60 Consumer	Menocool 1DF per 1.0 Days for Hot flushes Menocool extra smelttablet	alendronate	1: Abdominal pain 2: Endometrial hyperplasia 3: Vaginal haemorrhage	1 t/m3: 5 Months Drug withdrawn Recovering/resolving
222608 F, 50-60 Specialist doctor	Breastgro 1 dosage form for Breast enlargement		1: Postmenopausal haemorrhage	1: 3 Months Drug withdrawn Recovered/resolved
228417 F, 50-60 Consumer	Menocool 1.50 dosage forms for Hot flushes Menocool extra smelttablet 1 dosage form for Hot flushes		1: Vaginal haemorrhage	1,2: 1 Year Drug withdrawn Recovered/resolved
236497 F, 60-70 Consumer	Menocool 1 dosage form for Hot flushes		1: Breast pain 2: Dry mouth 3: Endometrial hyperplasia 4: Muscle spasms 5: Vaginal discharge 6: Vaginal haemorrhage	1 t/m6: 10 Months Drug withdrawn Outcome unknown
240723 F, 50-60 Specialist doctor	Menocool 1 dosage form per 1.0 Days Menocool zuigtablet 1 dosage form per 1.0 Days for Menopausal symptoms	losartan	1: Postmenopausal haemorrhage	1: 3 Years Drug withdrawn Recovered/resolved
247078 F, 50-60 Consumer	Hop for her smelttablet 2 dosage forms per 1.0 Days for Menopausal symptoms		1: Postmenopausal haemorrhage	1,2: 4 Months Drug withdrawn Recovered/resolved

Flavonoids/ isoflavonen
Glycine max (soy bean) contains genistein and daidzein

135168 F, 50-60 Specialist doctor	Menohop (contains soy bean and hop) 1 dosage form for Menopausal symptoms		1: Postmenopausal haemorrhage	1: TTO unknown Action unknown Outcome unknown
160857, F, 50-60, Consumer	Phyto soya 1 dosage form per 1.0 Days for Menopausal symptoms	tramadol	1: Eczema	1: 2 Weeks Drug withdrawn Recovered/resolved with sequelae
229752 F, 50-60 Consumer	Soja isoflavonen 1 dosage form per 1.0 Days for Menopausal symptoms levothyroxine tablet 25ug 3 dosage forms per 1.0 Days for Hypothyroidism		1: Arrhythmia	1: 0 Days Drug withdrawn Recovered/resolved
204868 F, 40-50 General practitioner	Solgar isoflavones 1 dosage form per 1.0 Days for Menopausal symptoms		1: Vaginal haemorrhage	1: 22 Days Drug withdrawn Recovered/resolved

Flavonoids

Vitex Agnus cactus (chasteberry, monk's pepper) contains a.o. apigenine, vitexine

155650 F, 30-40 Consumer	Davitamon fem fit 2 dosage forms per 1.0 Days for Menstrual disorder		1: Headache, 2: Vomiting	1: 2 Hours Drug withdrawn Recovering/resolving 2: 2 Hours Drug withdrawn Recovering/resolving
31296 F, 20-30 Pharmacist	Davitamon fem fit 1 per 1.0 Days for Unspecified vitamin A deficiency		1: Hypersensitivity	1: TTO unknown Drug withdrawn Recovered/resolved
33183 F, 60-70 Pharmacist	Davitamon fem fit 1 per 1.0 Days for Malaise	etidronezuur met calcium, sequentiepreparaten	1: Postmenopausal haemorrhage	1: 1 Month Drug withdrawn Recovered/resolved

Coumestans

Trifolium pratense (red clover) contains coumestrol, trifoliol, (also genistein, daidzein)

57293 F, 40-50 Consumer	Promensil 1 dosage form per 1.0 Days for Menopausal symptoms	Calciumcarbonaat tibolon	1: Abdominal pain lower 2: Migraine	1,2: 6 Months Drug withdrawn Outcome unknown
188531 F, 40-50 Consumer	Rode klaver 1005mg per 1.0 Days for Supplementation therapy	Propranolol temazepam	1: Chromaturia 2: Dizziness 3: Haematoma 4: Menorrhagia 5: Petechiae 6: Swelling	1 t/m6: 3 Weeks Drug withdrawn Recovering/resolving

194372 F,50-60 Consumer	Promesil dosage form per 1.0 Days for Menopausal symptoms		1: Back pain 2: Liver function test increased 3: Myalgia	1 t/m3: 5 Months Drug withdrawn Recovering/resolving
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Prueraria lobata (kudzu root) contains a.o. puerarin, genistein

121182 F, 50-60 Consumer	Care for women1 dosage form per 1.0 Days for Menopausal symptoms		1: Breast cancer	1: 2 Years Drug withdrawn Recovered/resolved with sequelae
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Angelica sinensis (dong quai)

Exact mechanism and compounds for phytoestrogenic action still unknown

226400 F, 20-30, Consumer	Fem compleet Holland&Barrett 1 dosage form per 1.0 Days		1: Hypoaesthesia 2: Neuralgia	1,2: 3 Weeks Drug withdrawn Not recovered/not resolved/ongoing,
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