bijwerkingen centrumlareb

Overview of reports on St. John's wort (*Hypericum perforatum*)

Introduction

St. John's wort is one of the few herbal medicines that is officially registered in the Netherlands as a medicinal product (Laif 900®, A.Vogel Hyperiforce®) through the Dutch Medicine Evaluation Board (MEB). These registered preparations have been shown to be effective in the treatment of *mild to moderate depressive symptoms*. In addition to the products registered as medicines there are many preparations with St. John's Wort on the market not approved by the MEB, that vary in composition (sometimes multiple herbs or vitamins are also present), formulation (dry extract, tea, oil extract) and recommended daily dose. The effect of these products, as well as the potential for interactions with other medicines, is therefore unpredictable [1].

Well known side effects of St. John's wort are nervous system disorders (such as headache, dizziness and insomnia), gastrointestinal disorders (such as nausea, abdominal pain and diarrhea), skin diseases (e.g. redness and itching) and photosensitization. In addition, drug-drug interactions may occur. The interaction with oral contraceptive pills that may result in breakthrough bleeding is well-known [2]. Incidentally, this interaction applies both to the oral contraceptive as well as the morning-after pill with levonorgestrel. The effect of the latter drug can be reduced by concomitant use of St. John's Wort [3]. The drug-drug interaction with antipsychotics and antidepressants can be serious. These reports concern behavioral disorder, depression, agitation, anxiety disorder and even psychosis.

As herbal medicine registered product Laif 900® and as traditional herbal medicine registered A Vogel Hyperiforce® are sold as Over The Counter (OTC) product solely at the pharmacy which entails that relevant drug-related problems, such as interaction with prescription medicine, can be detected. The non-registered supplements are sold in the drugstores, supermarkets and via (web-) shops and no such safety check takes place.
This overview has been made in order to assess risks of St. John's wort containing products in daily practice, in particular those widely available in the drugstores, supermarkets and (web-) shops.

Reports

From June 1999 to September 2018 Pharmacovigilance Centre Lareb received 57 reports of possible adverse drug reactions (ADRs) and interactions concerning St. John's Wort (table 1 in Appendix). Besides the well-known mild side effects such as dizziness, diarrhea and skin reactions, other ADRs such as psychiatric symptoms were reported. Consumers reported 29 times, pharmacists 17 times, GP's nine times, specialist doctors five times, and one report concerns a case report received from the marketing authorization holder. The profession of one reporter is unknown, some reports have been reported by both the general practitioner and the pharmacist.
Four reports concerns a product which has been registered through the MEB; two were A Vogel Hyperiforce® and two Laif 900®, in one report on Laif® the strength was not reported. Laif 600® is not registered as a herbal medicine and is a supplement. The majority of the reports of the non-registered supplements concerns preparations of Arkopharma® (n=8), followed by Hyperiplant® (n=6) Perika® and Kira® (both n=4). The manufacturer of products used is unknown in some reports or not specified by the reporter. Three reports concerned St. John's wort tea.
The content of hypericum extract and hypericine of the registered products and of the supplements (if available) is shown in the table 2. The information in the leaflets or on the packaging is usually inadequate and it is not clearly stated whether the declaration relates to the amount of hypericum herb or the content of extract. The amount of hypericine is not always declared. Information found on different websites is not consistent.

Table 2: overview of the reported hypericum preparations

Product name	Hypericum (extract)	Hypericin
Registered as a medicine		
Laif 900® registered from 2010-02-22	900mg (3 -6:1)	*
A Vogel Hyperiforce ® registered from 2013-05-13	450mg (66mg etanol extraact 3,1-4,0=1) =425-1300mg fresh herb	0.36-0.84 mg
Not registered/ supplements		
Laif 600®	612mg (5-8:1)	*
Hyperiplant® registered from 2007-12-05 till 2017	300mg (3–7:1)	0,36–0,84 mg
Sintjanskruid Lamberts®	1700mg (340mg 5:1)	1000mcg
Springfield St. Janskruid®	500mg	0.3%
Zibrine sint janskruid®	425mg	0,40-1,3mg
Perika VSM®	300mg (3-5:1)	0,36-0,84mg
St. Janskruid Kneipp®	300mg	>= 180mcg
Kira forte Sintjanskruid® Registered from 2013-03-21 till 2017	300mg (3-6:1)	0.36-0.84mg
Sint-janskruid Etos®	300mg	0.9mg /2 caps
Bloem Kava fleur® caps	225mg	
Optimax Super Sintjanskruid®	233mg extract/tabl (4tabl/day)	
Sint-janskruid Arkopharma®	185mg extract	500mcg
Ruval Extra forte® **	120mg/3 caps	
Neuropas balance®	60mg extract /tabl (up to 6tabl/day)	
Hyperiforce forte A.Vogel®	198mg dry extract / 3tabl.	
Bonusan Hypericum perforatum®	Hypericum perf. herba 2:1 (70% v/v alc)	

Product information of the non-registered products through the manufacturers websites and drugstore websites:
https://www.vsm.nl/hyperiplan
https://www.adviesdrogisterij.nl/gezondheid/voedingssupplementen/lamberts-st-janskruid-1-tablet-per-dag-120-tabletten https://www.deonlinedrogist.nl/springfield-st-janskruid-500mg-p-7467
https://www.farmaline.be/apotheek/bestellen/zibrine-forte-60-capsules/
https://www.arcofarma.be/files/pdf/2378719_NL.PDF
https://www.gezondheidaanhuis.nl/nl/product/4962/Sint-Janskruid-Arkopharma-60-capsules
https://www.bloem.net/ruval-extra-forte
https://www.efarma.nl/neurapas-balance-tablet/15087352
https://www.avogel.nl/datafiles/datafeed/bijsluiters-pdf/Hyperiforce-forte-plus-sint-janskruid-80st.pdf
https://www.deonlinedrogist.nl/bonusan-hypericum-perforatum-p-9011.html

*The amount of hypericin not mentioned in the leaflet. The leaflet mentions that oral administration of 1 tablet Laif 900® (900 mg extract), a maximum plasma levels of hyperforin (122.45 ng / ml) was measured after 4.5 hours.
** Ruval extra forte contains beside St.John's (Hypericum perforatum) extract also grapevine-herb (Ruta graveolens), oat straw (Avena sativa), cleavers (Galium aparine), spiny spruce (Scrophularia nodosa) true valerian root (Valeriana officinalis), passiflora root and spice (Passiflora incarnata), hawthorn leaf and flowers (Crataegus oxyacantha), Horsetail herb (Equisetum arvense) Hop fruit cones (Humulus lupulus), dandelion root and herb (Taraxacum officinale), malayan herb (Veronica officinalis), lavender flowers (Lavandula officinalis). The leaflet mentions also that St. John's wort can also influence the effect of anti-depressant drugs of the SSRI type. Concomitant use is not recommended.

Ten reports (B, D, F, G, H, I, M, V, AD, AX) concern hormonal disorders whether or not reported as an interaction with the OAC. Report AX concerns an unplanned pregnancy due to the interaction between St. John's wort tea that the woman drank when using oral anticonception. The pregnancy was discovered 3 weeks before the birth of a healthy girl.

Ten reports (L, R, U, X, AB, AC, AF, AH, AM and BE) concern an ADR on the central nervous system with mainly psychiatric complaints such as depression, agitation, mania, hallucinations, (aggravation of), unrest, psychosis or panic.

Report BB concerns a possible interaction between an unregistered composite herbal preparation Ruval® containing, among others, 120mg St. John's wort per daily dosage of 3 capsules and food supplement Serozol® with 25mg 5- hydroxytryptophan (5-HTP). The reported symptoms match with the symptoms of serotonin syndrome.

Report BF concerns a special report received from the pharmaceutical industry and concerns a literature case report of a 41-50 years-old woman with disorganized schizophrenia experienced an exacerbation of her symptoms after she began taking hypericum (St John's wort; indication not stated) in addition to her established clozapine therapy. The woman became increasingly disorganized and tense 6 months after initiation of clozapine 500mg daily (route not stated). Her clozapine 12 h trough concentrations had previously been stable at 0.46–0.57 mg/L, but repeat laboratory tests revealed a plasma clozapine concentration of 0.19 mg/L, which further decreased to 0.16 mg/L three weeks later. It then became known that she had started taking St John's wort 3 tablets daily shortly before her symptoms worsened. Each tablet contained hypericum 300mg, hypericin 0.36–0.84mg and at least 9mg of hyperforin. St John's wort was discontinued, and the woman's plasma clozapine concentration had improved to 0.32 mg/L after 1 month, and to 0.41 mg/L after 2 months; her psychiatric condition also improved [4].

Table 3: overview of the reported adverse drug reactions (ADRs)*

System Organ Classes (SOC) of the reported ADR	**Non registered product**	**Registered product**
Psychiatric Effects	23	1
Neurologic Effects	14	-
Endocrine/reproductive Effects	9	1
Gastrointestinal Effects	7	2
Dermatologic/ photosensitivity Effects	5	1
Other	31	-
ADR reported as drug-drug interaction		
Drug-drug Interaction	6	-

* more than 1 ADR can be reported in a single report

Other sources of information

SmPC

Summary of the Product Characteristics of Laif 900® and A Vogel Hyperiforce® mention following possible side effects: gastrointestinal complaints, allergic skin reactions and sunlight hypersensitivity, fatigue or restlessness. Also interactions due to the induction of the liver enzymes CYP3A4, CYP2C9 and CYP2C19 and of the P-glycoprotein pump are mentioned with antidepressants such as nortriptyline and amitriptyline, benzodiazepines, triptans, inhibitors of the immune system, anticoagulants of the coumarin type, anti-epileptics, theophylline, digoxin, inhibitors of the HIV virus, simvastatin, oncolytics and antiandrogens. Due to the interaction with oral contraceptives there is a reduced protection against pregnancy. Concomitant use with SSRI's is not recommended, due to a possible occurrence of it serotonin syndrome with the symptoms nausea, vomiting, anxiety, restlessness, and confusion [8,9].

Prescription data

The number of consumer using St John's wort is not available because the registered products Laif 900® and A Vogel Hyperiforce® are sold as Over The Counter (OTC) product and the supplements are available in de Drugstores and via the web-shops. Therefore no central registration of the sales figures is possible for those products.

Mechanism

Hypericum perforatum (St John's Wort) is a non-specific inhibitor of the reuptake of various neurotransmitters in the brain (serotonin, norepinephrine, dopamine, GABA and glutamate). This results in a higher concentration of these neurotransmitters in the synapse gap and therefore an enhanced and longer lasting effect of the neurotransmitters. Most effects of hypericum can be explained by the major constituent hyperforin, although other constituents such as hypericin, may also play a direct or indirect role. St John's Wort may be considered a non-selective reuptake inhibitor [5]. At receptor level, chronic treatment with hypericum downregulates ß -adrenoceptors, upregulates post-synaptic 5-HT_{1A} receptors and upregulates 5-HT_2 receptors.
When St. John's Wort is used together with other neurotransmitter re-uptake inhibitors, an additive effect may occur, which can, for example, cause serotonergic syndrome. The risk of such interactions is estimated in an analysis by The National Institute for Public Health and the Environment (RIVM)

from moderate to very severe for the partial $5HT_{1A}$ agonist buspirone and among others SSRIs and MAO inhibitors [5].
In addition, St. John's Wort leads to the induction of different enzymes and strongly correlates with the amount of hyperforin in the product. Products that do not contain significant amounts of hyperforin (<1%) do not appear to produce clinically relevant enzyme induction in studies.[7] The National Institute for Public Health and the Environment (RIVM) indicates that St. John's wort appears to be an activator of the pregnane X receptor (PXR). PXR regulates the transcription of, among others, the following enzymes: CYP3A4, CYP3A5, CYP3A7, CYP1A2, CYP2C9 and CYP2C19. PXR is also involved in the induction of the transporters P-glycoprotein (P-gp or MDR1, multidrug resistance protein 1) and OATP2 (organic anion-transporting polypeptide 2). In vivo animal studies and human studies show that repeated intake of St. John's wort indeed results in an induction of CYP3A4, CYP2C19 and P-gp. This leads to a higher activity of the enzyme or transporter. This subsequently leads to a lower plasma level of drugs that are metabolized by these enzymes or transported by the transporters. However, St. John's wort does not appear to have an effect on CYP1A2, CYP2D6 and CYP2C9. in vivo [6,1]. The severity of the clinical effect of induction depends in particular on the indication for which the medicine is prescribed, as well as on the therapeutic breadth and the degree of toxicity of the interacting agent.

Discussion and Conclusion

Products containing St. John's wort are available beside as a registered (traditional) herbal medicine at the pharmacy also as a herbal supplement at the drugstore, health food store or web-shop. However, the quality and the quantity of the active ingredients of not registered herbal preparations available at the store is not checked in advance. Moreover the product information of these preparations is not consistent. The information about the used part of the plant (whole herb, root, leaves) to make the extract is not always provide in the leaflet. The content of the active ingredient hypericin and /or hyperforin is not always expressed in the same units or is even missing. This makes the comparison between the different products difficult. Reports in Lareb database show that freely available St. John’s wort containing supplements possess the same risks of side effects as the registered products. This is not surprising given that these products often contain the same amount of hypericum extract and the active substance hypericin (or possible even more) than the registered ones. Therefore, as could be expected, the nature of the reported adverse reactions caused by those products is similar to the side effects mentioned in the SmPC’s of the registered ones.

53 out of 57 reports received at the Netherlands Pharmacovigilance Centre concern an unregistered product, in 1 report on Laif® the strength is not reported. In the 57 reports in total 94 side effects have been reported, 89 occurred when using one of the non-registered supplements. From the five reported adverse reactions on registered products two of them concern product Hyperiforce® (A Vogel) obtained in the period before the registration as a traditional herbal medicine on 2013-05-13 (table1, table2). The majority of the reported adverse drug reactions concerns psychiatric complaints, followed by neurologic effects. In six reports the adverse drug reaction was labeled as an interaction between the St. John’s containing product and the co-medication, in all of those reports the interacting hypericum product was a not registered product. In one case the interaction between the hypericum tea with the contraceptive pill has led to the unintended pregnancy. One report concerns a possible interaction between two not registered products, namely St John’s wort containing Ruval® and 5-hydroxytryptophan supplement Serozol® where the symptoms of serotonin syndrome were reported. This case shows that the danger of the occurrence of an serious interaction is not only with the registered drugs, where a possible check by the pharmacist can take place, but also between the two freely available products.

Many consumers think that herbal products are safe because they are 'natural products'. But herbal products such as St. John's wort may also have side effects and interactions with other medicines or even food supplements.
The reports in our review indicate that the side effects and interactions occur in practice and can also be serious. It is important that consumers are well informed about the undesirable side effects and possible interactions. This warning should be included on all the packings of the St. John’s containing products.

References

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Appendix

Table 1: reports on St. John's wort

Case, ID (NL-LRB) Recievedate Sex, Age, Reporter	Suspect drug, Dose, Indication	Registered as medicine/ Seroius Yes/NO	Concomitant medication	Reaction MedDra term	Time to onset, Action with drug, Outcome
A 24953 23-06-1999 F, 31-40 years GP	Kira St. Janskruid® (300mg) 3 dosage forms / 1 day Depressive episode	No/Yes	amitriptyline	Oedema periipheral	Less than 1 day Drug withdrawn Outcome not reported
B 26391 9-11-1999 F, 21-30 years Pharmacist	Guttae Steigerwald psychotonin m® 3 dosage forms / 1 day Depressive episode	No	atenolol	Menstruation delayed	3 Months Dose not changed Outcome unknown
C 26977 13-01-2000 F, 21-30 years Pharmacist GP	Perika vsm® 3 dosage forms / 1 day	No		Nausea Rash	3 Days Drug withdrawn Outcome not reported 1 Day Drug withdrawn Outcome not reported
D 28169 28-04-2000 F, 31-40 years Pharmacist, Specialist doctor	Hypericum perforatum® 175 mg 3 dosage forms / 1 day Depressive episode	No	ethinylestradiol/ levonorgestrel	Menorrhagia	2 Months Drug withdrawn Outcome not reported

E 28453 23-05-2000 F, 41-50 years Pharmacist, GP	Sint-janskruid Arkopharma® caps.(185 mg extract flos Hypericum perforatum en max. 700 mcg hypericine). 3 dosage forms / 1 day Malaise	No		Photosensitivity reaction	Unknown Drug withdrawn Outcome not reported
F 29167 22-08-2000 F, 41-50 years Pharmacist	Perika VSM® 2 dosage forms / 1 day Depressive episode ethinylestradiol/desogestrel tablet 30/150ug 1 dosage forms	No/Yes		Metrorrhagia	Unknown Drug withdrawn Outcome not reported
G 29169 23-08-2000 F, 21-30 years Unknown function	Perika VSM® 1 dosage forms / 1 day Depressive episode ethinylestradiol/desogestrel tablet 20/150ug 1 dosage forms	No/Yes		Metrorrhagia	For suspect drug Perike VSM®: 3 days Action unknown Outcome not reported For suspect drug ethinylestradiol/deso-gestrel: Unknown Dose not changed Outcome not reported
H* 29170 23-08-2000 F, 31-40 years Pharmacist	Hyperiforce® 2 dosage forms / 1 day Depressive episode ethinylestradiol/gestodeen tablet 20/75ug 1 dosage forms	Yes/Yes	paracetamol/ coffein	Metrorrhagia	167 days Dose not changed Outcome not reported
I 29604 24-10-2000 F, 21-30 years Pharmacist GP	Sint-janskruid Arkopharma® caps 1 dosage forms / 1 day ethinylestradiol/levonorgestrel tablet 30/150ug	No/Yes		Metrorrhagia	Unknown Action Unknown Outcome not reported
J 29964 21-11-2000 F, 21-30 years Pharmacist, GP	Perika VSM® -300mg 1 dosage forms / 1 day Depressive episode ethinylestradiol/gestodeen tablet 30/75ug	No		Chloasma	4 Weeks Drug withdrawn Outcome unknown
K 31148 14-03-2001 F, 41-50 years Pharmacist	Sint-janskruid Arkopharma® 1 dosage forms / 1 day Depressive episode venlafaxine capsule mga 150mg	No		Fatigue	8 Months Action unknown Outcome unknown
L 31473 17-04-2001 F, 51-60 years Specialist doctor	Hyperiforce forte® 1 dosage forms / 1 day	No	oestrogens conjugated	Psychotic disorder	15 Days Drug withdrawn Recovered/resolved
M 35358 25-04-2002 F, 31-40 years Pharmacist, GP	Sint-janskruid Arkopharma® ethinylestradiol/levonorgestrel tablet 30/150ug	No		Metrorrhagia	Unknown Action not reported Outcome unknown
N 35608 21-05-2002 M, 41-50 years GP	Laif ®600mg 1 dosage forms Depressive episode	No	sumatriptan	Aggravation of cluster headache	12 Days Drug withdrawn Recovered/resolved

O 35802 05-06-2002 F, 41-50 years Pharmacist	Kneipp-Kruidendragee Sintjanskruid® 9 dosage forms / 1 day Depressive episode	No/Yes		Cerebrovascular accident	4 Months Drug withdrawn Not recovered/not resolved/ongoing
P 35928 24-06-2002 F, 41-50 years GP	Bloem Kava fleur® caps. Extra forte (225mg hypericum) 1 dosage forms / 1 day	No/Yes		Hepatic enzyme increased, Jaundice	Unknown Drug withdrawn Recovered/resolved
Q 36989 12-08-2002 F, 41-50 years Specialist doctor	Hyperiforce forte® 6 dosage forms / 1 day imipramine dragee 25mg 125mg / 1 day	No	valerianae radix olanzapine diazepam	Anticholinergic syndrome Dehydration	For suspect drug Hyperiforce forte®: 2 Days Drug withdrawn Recovered/resolved For suspect drug imipramine: 4 Months Dose not changed Recovered/resolved
R 50501 18-05-2005 F, Unknown age Pharmacist	Sint-janskruid Arkopharma® Depression	No		Depression Headache Paraesthesia	1 Week Drug withdrawn Outcome unknown
S 50866 06-06-2005 F, 51-60 years Pharmacist	Sint-janskruid Arkopharma® 2 dosage forms / 1 day enalapril tablet 20mg 2 dosage forms / 1 day hydrochlorothiazide tablet 25mg 1 dosage forms / 1 day	No		Drugs enalapril/hydrochlorothiazide ineffective	For suspect drug Sint-janskruid Arkopharma®: Unknown Drug withdrawn Recovered/resolved For suspect drug enalapril/hydrochlorothiazide Unknown Dose not changed Recovered/resolved
T 52830 11-10-2005 F, 51-60 years Pharmacist	Sint-janskruid Arkopharma® paracetamol	No	exemestane	Blood creatine phosphokinase increased Drug interaction Joint swelling Myalgia	4 Months Dose not changed Outcome unknown
U 53157 01-11-2005 F, 21-30 years Specialist doctor	Kira St. Janskruid® drage 300mg 600mg / 1 day Depression	No/Yes		Mania	8 Months Drug withdrawn Recovering/resolving
V 54461 17-01-2006 F, 41-50 years Consumer	Neurapas balance® tablets 4 dosage forms / 1 day	No		Breast enlargement Menorrhagia	15 Days Drug withdrawn Recovered/resolved
W 57741 23-05-2006 F, 51-60 years Pharmacist	Springfield St. Janskruid® extra sterk 500mg 500mg / 1 day Depressed state	No		Eye irritation Photophobia	2 Weeks Dose not changed Not recovered/not resolved/ongoing
X 60592 20-09-2006 M, 21-30 years Consumer	Zibrine® (sint janskruid) 425m; hypericine:0,40 - 1,3mg for Nervous tension, ginseng 100mg for Nervous tension	No/Yes		Agitation Mental disorder	For suspect drug Zibrine®: 2 Weeks Drug withdrawn Outcome Unknown For suspect drug ginseng: 4 Weeks Drug withdrawn Recovering/resolving

Y 62591 02-01-2007 F, 51-60 years Consumer	Laif Steigerwald ® 600mg	No		Visual acuity reduced	4 Weeks Drug withdrawn Outcome unknown
Z 82361 17-11-2008 F, 41-50 years Consumer	Kira St. Janskruid® drage 300mg 1 dosage forms	No		Feeling cold Periipheral coldness	10 Days Drug withdrawn Recovered/resolved
AA 83931 15-01-2009 F, 41-50 years Pharmacist	Laif Steigerwald® 1 dosage forms insuline detemir injvlst 100e/ml 1 dosage forms Diabetes mellitus	No	temazepam acetylsalicylic acid simvastatin	Blood glucose fluctuation Drug interaction	For suspect drug Laif Steigerwald®: Unknown Action unknown Outcome unknown For suspect drug insulin detemir: 459 Days Action unknown Outcome unknown
AB 87765 22-05-2009 F, 2-4 years, Specialist doctor	Hyperiplant® 300mg 900mg / 1 day Depressed mood	No		Abnormal dreams Hallucination	3 Months Drug withdrawn Not recovered/not resolved/ongoing 3 Months Drug withdrawn **Recovered/resolved** with sequelae
AC 87850 28-05-2009 M, 21-30 years Pharmacist	Hyperiplant® 300mg 3 dosage forms / 1 day Depressed mood	No	calcitriol	Abdominal discomfort Hallucination visual	For Abdominal discomfort : 2 Days Dose reduced Not recovered/not resolved/ongoing For visual hallucinations: 10 Days Dose reduced Recovered/resolved
AD 91249 18-09-2009 F,41-50 years Pharmacist	Hyperiplant ®	No		Amenorrhea	Weeks Dose not changed Not recovered
AE 106189 15-04-2009 M, 51-60 years GP	Hypericum Perforatum Bonusan® drops Weleda Hepatodoron® Depression Bio-MSN® for knee pain	No		Glossitis	Days Unknown Recovering
AF* 122521 30-05-2011 F, 21-30 years Consumer	Hyperiforce ® 3 dosage forms / 1 day Depressed mood	Yes	betahistine	Panic attack	13 Days Drug withdrawn Recovering/resolving
AG 137658 23-04-2012 F, 31-40 years Consumer	Hyperiplant ® 300mg 3 dosage forms / 1 day Depressed mood	No		Abdominal discomfort Diarrhoea Nausea	12 Hours Drug withdrawn Recovered/resolved
AH 154550 16-05-2013 F, 41-50 years Consumer	Laif ® 600mg / 1 day Depressed mood	No	quetiapine	Dizziness Dyspepsia Insomnia Panic attack	2 Weeks Drug withdrawn Not recovered/not resolved/ongoing

AI 159979 24-09-2013 F,41-50 years Consumer	Kira forte St. Janskruid ® 450mg Menopausal symptoms	No		Hypersensation skin	Days Drug withdrawn Recovered
AJ 174955 20-05-2014 M, 31-40 years Consumer	Zibrine® (sint janskruid) 425m; hypericine: 0,40 - 1,3 mg Depression	No		Dizziness Feeling abnormal Restlessness	1 Day Drug withdrawn Recovered/resolved
AK 199006 02-06-2015 F, 21-30 years Consumer	Hypericum plus (van Golden Naturalis® 0,3% hypericine?) Davitamon fem fit 1 dosage forms / 1 day Premenstrual syndrome	No		Dizziness Fatigue Vision blurred	3 Weeks Drug withdrawn Recovered/resolved
AL 200522 30-06-2015 F, 41-50 years Consumer	Sint janskruid 2 dosage forms / 1 day Anxiety disorder	No	pantoprazole	Toothache	Less than 1 day Action unknown Not recovered/not resolved/ongoing
AM 204685 19-09-2015 M, 31-40 years Consumer	Sint janskruid 2 dosage forms / 1 day Mood altered	No		Impulsive behaviour Irritability	2 Weeks Dose not changed Outcome unknown,
AN 209680 04-12-2015 F, 51-60 years Consumer	Hyperiplant® Depressed mood	No	oxazepam	Vitamin d deficiency	10 Years Drug withdrawn Recovered
AO 212708 25-01-2016 F, 51-60 years Consumer	Sint janskruid capsule Etos® 300 mg 300mg / 1 day Insomnia	No		Blood pressure increased	1 Day Drug withdrawn Recovered/resolved
AP 217294 14-04-2016 F, 31-40 years Consumer	Hyperiplant ® 300mg 300mg / 1 day Depression	No		Diarrhoea	1 Day Dose not changed Outcome Unknown
AQ 217495 18-04-2016 F, 21-30 years Consumer	Sintjanskruid Lamberts een per dag® (1332mg Sintjanskruid; 333mg 4:1 extract; 1000mcg hypericine) 4.50mg / 1 day Depressed mood	No		Dermatitis allergic	1 Day Drug withdrawn Outcome unknown
AR 218197 02-05-2016 F, 41-50 years Consumer	Hypericum kruidenthee 2 dosage forms / 12 Hours Unknown indication Fluoxetine Unknown indication	No		Anxiety Drug interaction Hallucination	11 Months Drug withdrawn Recovered/resolved Outcome unknown Recovering/resolving,
AS 218367 03-05-2016 F, 41-50 years Consumer	Sint janskruid thee AH® 5 dosage forms / 1 day Anxiety desloratadine tablet 5mg 5mg / 1 day Allergy	No		Chest discomfort Drug interaction Fatigue Musculoskeletal pain Somnolence	For suspect drug Sint janskruid AH®: 16 Hours Drug withdrawn Recovered/resolved For suspect drug desloratadine: 1 Hour Drug withdrawn Recovered/resolved

AT 231740 27-12-2016 F, 51-60 years Consumer	Sint -janskruid Arkopharma® 2 dosage forms / 1 day Depression	No	Iud with levonorgestrel	Dry mouth Pruritus	3 Hours Dose not changed Not recovered/not resolved/ongoing 3 Hours Dose not changed Recovered/resolved
AU 245460 23-08-2017 F, 21-30 years Consumer	Sint janskruid Lamberts® (hypericum) tablet 1 dosage forms / 1 day Depressed mood	No		Hyperaesthesia Paraesthesia	8 Months Drug withdrawn Recovered/resolved
AV 245645 25-08-2017 F, 41-50 years Consumer	Sint janskruid 900mg / 1 day Depression	No	cabergoline	Insomnia	8 Days Drug withdrawn Not recovered/not resolved/ongoing
AW 246287 04-09-2017 F, 21-30 years Consumer	Laif ® 900mg 900 mg / 1 day Depressed mood	Yes	oxazepam	Photosensitivity reaction	25 Days Dose not changed Not recovered/not resolved/ongoing
AX 264069 22-01-2018 F, 31-40 years Consumer	Hypericum kruidenthee Unknown indication Not specified oral contraception	No/Yes		Drug interaction Unintended pregnancy	Unknown Action Unknown
AY 264071 22-01-2018 F, 31-40 years Consumer	Hypericum tablet 1 dosage forms / 12 Hours Depressed mood	No		Depressed mood Panic attack	2 Weeks Drug withdrawn Recovered/resolved
AZ 264072 22-01-2018 F, 71 years and older Consumer	Sint-janskruid Lamberts® Depressed mood	No	enalapril/ lercanidipin doxazosine dabigatran metoprolol levothyroxine	Anxiety Dizziness	2,5 Hours Drug withdrawn Recovered/resolved
BB 264802 26-01-2018 F, 31-40 years Consumer	Ruval® (120mg Hypericum) 1 dosage forms / 12 Hours Withdrawal reaction Serozol® (25mg 5-HTP)	No	metoprolol	Anxiety Potentiating Drug interaction Restlessness	For suspect drug Ruval®: 415 days Not applicable Recovered/resolved For suspect drug Serozol®: Unknown Action not reported Recovered/resolved
BC 280190 14-04-2018 F, 31-40 years Consumer	Laif ®900mg Depressed mood	Yes		Stomach discomfort Diarrhoea	2 Hours Dose reduced Recovered
BD 285911 29-05-2018 F, 31-40 years Consumer	Optimax Super Sintjanskruid® Unrest	No		Palpitations	1 Week Withdrawn Recovered
BE 297041 29-08-2018 F, 51-60 years Consumer	Hypericum Etos® Listlessness	No		Myalgia Muscle tension General unrest	2 Hours Withdrawn Not recovered/resolved

BF NL-STADA-045407 26-03-2012 F, 41-50 years MAH	Hypericum 300mg 3dd300mg Clozapine	No	Psychosis aggravated Schizophrenia aggravated Drug interaction Antipsychotic drug level below therapeutic	Unknown Drug withdrawn Unknown Unknown

* before the registration date 2013-05-13

This signal has been raised on December 20, 2018. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl