

Red yeast rice – an update overview of the reported ADRs

Introduction

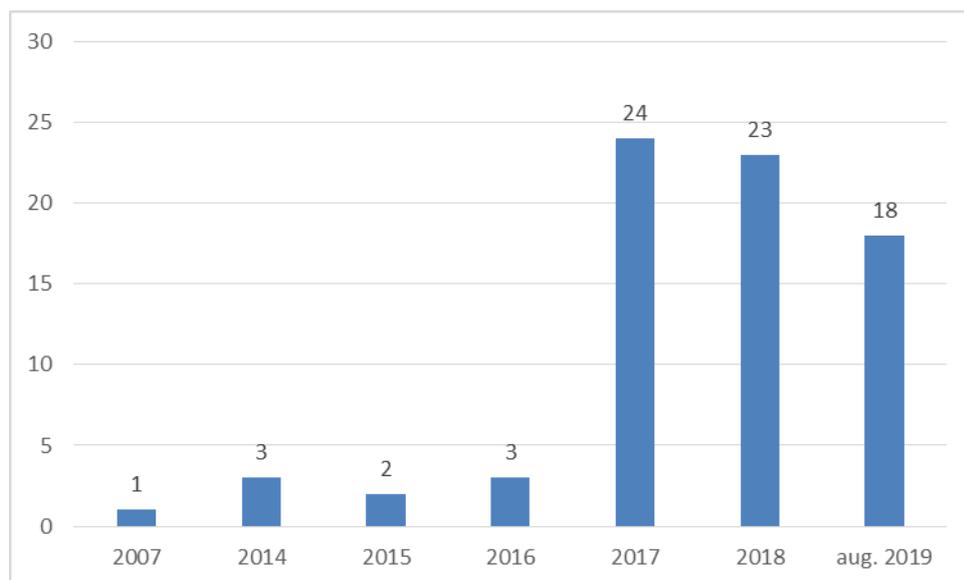
Statins are effective agents for improving lipid spectrum in order to reduce the risk of atherosclerotic disease. However, not all patients use statins to lower their cholesterol level. Some patients use alternative products to influence their lipid levels. Also, consumers without dyslipidemia or increased cardiovascular risk use alternative products to lower their cholesterol. One of these alternative products is red yeast rice extract (RYR) [1]. Red yeast rice is a Chinese herbal supplement produced by fermenting white rice with the yeast *Monascus purpureus*. RYR contains a variety of monacolins, which inhibit hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis. The consumption of RYR has increased recently, especially among patients who might be intolerant to standardized therapy due to statin-associated myalgia [2]

In July 2017 the Netherlands Pharmacovigilance Centre Lareb informed the Netherlands Food and Consumer Product Safety Authority (NVWA) about the received reports on red yeast rice supplements [3]. Because Lareb sees an increase in the number of reports on RYR (Figure1), among which some serious reactions, this up-date overview has been written to give insight in the reported reactions for RYR.

Reports

In the period from December 2007 till August 2019, the Netherlands Pharmacovigilance Centre Lareb received **74 reports** of adverse drug reactions (ADRs) in association with the use of the RYR containing supplements. See appendix.

Figure1: number of reports on Red Yeast Rice



The pharmacological active ingredient in red yeast rice is monacolin K which is structurally identical to lovastatin. Lovastatin is available as approved medicine Mevacor® in a large number of countries, but not in the Netherlands. RYR can also contain citrinin, mycotoxin produced during the fermentation process. Due to the similarity between Monacolin K and lovastatin also similar adverse reactions can be expected. Most of the ADRs reported to Lareb concern myalgia and related musculoskeletal complaints (32 reports) followed by neurological symptoms, such as headache, dizziness, paresthesia, confusion and memory impairment. Also a few gastrointestinal complaints and palpitations were reported. Two reports concern a decreased INR in patients using acenocoumarol. A possible mechanism for this effect is unknown. Decreasing of the INR is contradictory to the information found in the literature for the effect of lovastatin on the coumarins: bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin based anticoagulants concomitantly with lovastatin [4].

Some of the reports contain serious adverse reactions as pancreatitis, rhabdomyolysis and acute hepatic failure. Those reports are described more in detail below.

Pancreatitis

Reports nr.5, 12 and 42 concern patients who developed pancreatitis. Consumer from the report nr.5 used also codeine for which pancreatitis is labelled in the SmPC [5].

The patient in report 12 concerned a 61-70 year old female who was hospitalized due to developing pancreatitis after she had used a red yeast rice product for 4 years. A differential diagnosis excluded other causes for the condition. The RYR supplement was withdrawn. She was treated with pantoprazole and pain killers. She had a history of pancreatitis with an unknown/not reported etiology. The patient in report nr.42 developed acute pancreatitis after 2.5 years of use.

Rhabdomyolysis/ polymyalgia rheumatica

The patient in report nr.13 was intolerant to statins and therefore she switched to a red yeast rice supplement brand Kruidvat®, containing 10mg monacoline K. She reported symptoms fitting rhabdomyolysis; flank pain, muscle pain, cramps and darkly orange colored urine. She consulted a rheumatologist. She was admitted to the hospital and was treated with morphine and muscle relaxants. The diagnosis polymyalgia rheumatica was postulated. Polymyalgia rheumatica is mentioned in the product information of simvastatin as a possible hypersensitivity syndrome related to statins [6] but it is not a known adverse drug reaction of RYR.

The patient in report nr.14 had been using a red yeast rice supplement already for a few months. Four days after she accidentally fell, she was admitted to the hospital due to the malaise, red brown discoloration of urine and nausea. The diagnosis rhabdomyolysis was confirmed, based on the lab tests: CK was 2550U/l and her eGRF was 14ml/min. She was treated with a saline i.v. and paracetamol. The RYR supplement and also her other medication consisting of hydrochlorothiazide, diclofenac, telmisartan and omeprazole, were withdrawn. She recovered after 4 days, her CK normalized to 372 u/l and the eGRF raised above 60ml/min.

Acute liver failure with liver transplant

The patient in report nr.60 concerns a female aged 61-70 years suffering from Graves' disease. She used a fermented red rice supplement for 2 years for hypercholesterolaemia. An methyl prednisone i.v. was given during 6 weeks 500mg, followed by 250mg weekly. During the methyl prednisone treatment the supplement was withdrawn. But 7 days after restart with of the red yeast rice the patient experienced flu-like symptoms accompanied with vomiting and developing icterus. She was hospitalized and acute hepatic failure was diagnosed. The patient's condition deteriorated and the liver transplant was necessary.

Concomitant medication was: calcium carbonate, carbomer eye gel, cholecalciferol tablet 800ie, levothyroxine tablet 100ug, eye ointment Duratears, magnesium citrate, alendronate 70mg.

In the past the patient experienced during use of fermented red rice abdominal pain, nausea, myalgia and muscle cramps. The last 1, 5 years the patient also experienced fatigue. The week before the hospitalization the urine was dark colored. Liver biopsy showed disturbed architecture with considerable inflammation. Connective tissue staining (VVG) revealed no cirrhosis or fibrosis. A sample of the pills was collected and was sent to the RIVM for analysis. Unexpectedly a very low amount of lovastatin was found and also no remnant of citrinin could be detected.

Analysis of samples

The samples of the RYR products used by the consumers from the report nr.3, nr.6 and nr.60 were analyzed by The National Institute for Public Health and Environment (RIVM).

In the sample from the patient 3, beside monacoline K at least two other monacolines with a similar pharmacologic effect were found. The recommended daily intake of 4 capsules provided 8mg lovastatin or total 16mg on total monacolines.

In the sample from the patient 6 also two other monacolines beside monacoline K were found (hydrolovastatin and lovastatin hydroxyl acid). The content of lovastatin in two analyzed capsules differed from each other for a factor 2. The recommended intake of 2 capsules daily provided a dosage between 6-14mg lovastatin.

In the sample from the patient 60 a very low amount of Monacoline K was found (less than 0.2mg lovastatin in one capsule and even less in a second one). By the applied analysis method no mycotoxin citrinin was detected. Because the focus of the analysis was the identification of monacolines and citrinin and not to other potentially hepatotoxic ingredients, adulteration or

contaminants, the causality between the reported acute hepatitis and the suspect RYR product remains therefore unclear.

Other sources of information

Literature

The Panel of the European Food Safety Authority (EFSA) concluded that a cause and effect relationship has been established between the daily consumption of about 10mg of monacolin K from red yeast rice and maintenance of normal blood LDL- cholesterol concentrations. The target population is assumed to be adults in the general population [7].

Red yeast rice contains a fungus (*Monascus purpureus*), which was utilized in the original production of lovastatin (Mevacor®), the first marketed pharmaceutical statin, and is chemically identical to this product. Their identical properties account for the similarity in therapeutic and side effects of red yeast rice and lovastatin. The red yeast rice ingredient that blocks cholesterol production is monacolin K. Since red yeast rice preparations have large variability in monacolin K content, predicting or understanding dose-related efficacy and side-effect risks of red yeast rice is practically impossible. The lipid-regulating potency of red yeast rice in commercial preparations was found extensively different according to the number and/or concentration of monacolin K they possess. Furthermore, more than one type of monacolins were found in different preparations (or batches) of red yeast rice. Other ingredients found in red yeast rice are also known to be potentially toxic [8]. Red yeast rice can contain the mycotoxin citrinin and several other substances that are not yet toxicologically evaluated [9]. Citrinin is a mycotoxin that produces the *Monascus* fungus as antibiotic for defense against bacteria. Citrinin is a nephro- and hepatotoxic component that should be avoided at all times in finished dietary supplements. However, a study (Gordon et al., 2010) found that citrinin levels were observed in four of the twelve analyzed products. This is probably because production without citrine production is not possible [10]. The consumption of such yeast preparations in the amount required to obtain the claimed effect would result in an exposure significantly higher than the concentration with no reason for concern regarding the nephrotoxicity of citrinin. A maximum content of 2 mg / kg for citrinin in red yeast rice preparations has been established to ensure that the potential exposure to citrinin from red yeast rice preparations remains considerably lower than the nephrotoxicity level of 0.2 µg / kg body weight for an adult. Therefore, a maximum content of citrinin in red yeast rice preparations should be established [11].

One literature study on 36 publications on 20 studies involving 6663 subjects in which RYR with a known content of Monacoline K was tested against placebo or an active control group for at least 4 weeks revealed no difference in the risk for myalgia, risk of liver abnormalities or kidney injury between RYR and control groups. Rhabdomyolysis or myopathy with increased CK > 10 times upper limit of normal was not observed in any of the studies. Patients mainly complained of gastro-intestinal and musculoskeletal symptoms [1].

A recent study on the safety profile of RYR conducted within the Italian Surveillance System of Natural Health Products on possible unwanted side effects due to consumption, observed cases of myalgia and/or an increase in creatine phosphokinase, liver injury and gastrointestinal reactions and in some cases patients were hospitalized [12].

Mechanism

Red yeast rice contains several structurally related substances called monacolins. The most abundant is monacolin K, which is pharmaceutically known as lovastatin [13]. Their identical properties account for the similarity in therapeutic and side effects of red yeast rice and lovastatin [7]. Lovastatin causes dose independent myopathy which sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria. In the Expanded Clinical Evaluation of Lovastatin (EXCEL) study also pancreatitis, hepatitis, cirrhosis and fatal and non-fatal hepatic failure were observed [6]. Potent inhibitors of CYP3A4 and grapefruit juice increase the risk of adverse drug reactions by reducing the elimination of lovastatin [13].

As with synthetic statins, RYR products can expect drug interactions with CYP3A4 inhibitors, especially if the daily dose is equivalent to contain 10 mg or more monacolone K. Even with the simultaneous use of certain foods or herbs such as grapefruit and St. John's wort, hazardous interactions may occur [14].

In the Italian study of the spontaneous reporting of adverse effects of RYR, myopathy occurred much more frequently in women than in men [15]. This male-female difference is not specific to RYR and has also been shown for lovastatin and other statins. The fact that side effects during statin use are reported more frequently for women than men can be explained by the 15-20% higher plasma concentration achieved with statins in women and due to the increased risk of adverse drug-drug interactions via CYP3A4 [16].

There is evidence that lovastatin inhibits the membrane transport protein P-glycoprotein, which plays an important role in the detoxification of drugs. The inhibitory effect of monacolin K (lovastatin) on this transporter can also significantly influence the bioavailability and the distribution of other drugs [17].

Discussion

In July 2017 Lareb published an overview about the reports of ADRs related to RYR supplements, based on 16 cases. Since then, the number of reports has quickly risen to a total of 74 in the Lareb database. The reported adverse reactions correspond to those described in the product information of lovastatin. Given the structural similarity between the two substances, this is not surprising. The presented cases in this overview showed that RYR may cause typical statin-related adverse drug reactions.

The FDA issued warnings to consumers in 2007 and in 2013 against taking red yeast rice products due to the lack of assurance regarding its efficacy, safety, and lack of standardized preparation methods [8]. Lovastatin has been considered by the FDA as a means absolutely contraindicated in pregnancy [17]. The same warning should therefore apply to RYR. However, the enclosed texts of some RYR products in the Netherlands are not unambiguous at this point. The patient information leaflets also do not provide or provide insufficient information about interactions [14].

Based on the lovastatin content alone, the investigated product could be considered an unregistered medicine. Also additive pharmacological effects may be expected for other monacolins present [13]. RYR contains pharmacologically and toxicologically relevant constituents including monacolin K (lovastatin) and at least 14 other monacolins [19] as well as possibly citrinin and further constituents with largely unknown biological effects. In the one Lareb case that was tested on citrinin, this was not detected. Monacolins are potent cholesterol lowering drugs to be administered under medical supervision. However, its use as food supplement may be questioned by the proven pharmacological effect of the individual RYR constituents. Moreover, the variability in contents and types of constituents, many of them are inadequately characterized or tested for safety, precludes an adequate safety evaluation [20]. It may be useful to specify a total monacolin content in the form of "monacolin equivalents" [17].

On the other hand due to the lack of the quality control and standardization, also the presence of the toxic metabolite citrinin could not be excluded. For marketed RYR products there exist neither data on identity and content of constituents nor product specifications and purity criteria. Basic toxicological data are not available for a scientifically based safety evaluation of RYR [20]. Users of RYR should be alerted to the potential drug interactions and serious risks associated with its use [2].

The analyses of the samples executed by the RIVM discussed in this overview show that a big variation in the amount of monacolin K exist, not only between the different products, but also between the single dosages of the specific product. Besides the declared content of monacolin K also a substantial amount of other monacolins with similar pharmacological activity can be present. The contribution of those to the total effectivity of the RYR supplements is unknown and possibly underestimated.

Conclusion

Red yeast rice (red fermented rice, RYR) is advertised as a cholesterol-lowering substance as an alternative treatment option for statin intolerant patients [2]. It should be noted that consumers often assume dietary supplements to be less dangerous than the regular medicines. In the case of red yeast rice this can be deceptive and even harmful [17].

References

1. Gerards MC, Terlouw RJ, Yu H, Koks CH, Gerdes VE. Traditional Chinese lipid-lowering agent red yeast rice results in significant LDL reduction but safety is uncertain - a systematic review and meta-analysis. *Atherosclerosis*. 2015; 240(2):415-23.
2. Burke FM. Red yeast rice for the treatment of dyslipidemia. *Curr Atheroscler Rep* 2015;17(4):495.
3. Red yeast rice-an overview of the reported ADRs (access date 27-06-2019) https://www.lareb.nl/media/3078/signals_2017_rode-gistrijstoverviewadr.pdf
4. FDA Professional Drug information, Lovastatin. (access date:27-06-2017) <https://www.drugs.com/pro/lovastatin.html>.
5. Dutch SmPC Codeine. (version date:11-11-2012, access date:27-06-2017) <https://db.cbq-meb.nl/IB-teksten/h53361.pdf>.
6. Dutch SmPC Simvastatin. (version date:25-03-2003, access date: 27-06-2017) <https://db.cbq-meb.nl/IB-teksten/h29285.pdf>.
7. EFSA Panel on Dietetic Products, N.a.A.N. Scientific Opinion on the substantiation of health claims related to monacolin K from red yeast rice and maintenance of normal blood LDL-cholesterol concentrations (ID 1648, 1700) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. 2011; *EFSA Journal* 2011;9(7):2304.
8. Dujovne CA. Red yeast rice preparations: are they suitable substitutions for statins? *Am J Med* 2017-06-07.
9. Steffen C. Red yeast rice: An unsafe food supplement? *Bundesgesundheitsblatt.Gesundheitsforschung.Gesundheitsschutz*. 2017;60(3):292-6.
10. Rode gist rijst ter behandeling van hypercholesterolemie. *Antwerps Farmaceutisch Tijdschrift*. 2013.
11. VERORDENING (EU Nr. /.. VAN DE COMMISSIE van XXX tot wijziging van Verordening (EG nr. 1881/2006 wat betreft de maximumgehalten aan de verontreiniging citrinine in voedingssupplementen op basis van met Rode gist *Monascus purpureus* gefermenteerde rijst, 2013.
12. Mazzanti G, Moro PA, Raschi E, Da Cas R, Menniti-Ippolito F. Adverse reactions to dietary supplements containing red yeast rice: assessment of cases from the Italian surveillance system. *Br J Clin Pharmacol* 2017; 83: 894–908].
13. Venhuis BJ, van HF, van de Koppel S, Keizers PH, Jeurissen SM, De KD. Pharmacologically effective red yeast rice preparations marketed as dietary supplements illustrated by a case report. *Drug Test.Anal* 2016;8(3-4):315-8.
14. Brouwers JR, Roeters van Lennep JE, Maas AH. Red yeast rice' as a cholesterol-lowering substance? Caution is warranted. *Ned Tijdschr Geneesk* 2016;160(0):D99
15. Menniti-Ippolito F, Da Cas R, Moro PA, Mazzanti G. Safety of red rice yeast food supplements [abstract nr. O42; 15th ISoP Annual Meeting "Cubism in Pharmacovigilance, Praag, 2015]. *Drug Safety* 2015;(38):954
16. Rosano GM, Lewis B, Agewall S, Wassmann S, Vitale C, Schmidt H, Drexel H, Patak A, Torp-Pedersen C, Kjeldsen KP, et al. Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC. *Eur Heart J* 2015;36(40):2677-80.
17. Farkouh A, Baumgärtel C; Mini-review: medication safety of red yeast rice Products, *International Journal of General Medicine* 2019;12 167–171
18. Pickering TG. The Food and Drug Administration and over-the-counter statins: an opportunity lost? *J Clin Hypertens.(Greenwich.)* 2008;10(3):245-8.
19. Li YG, Zhang F, Wang ZT, Hu ZB. Identification and chemical profiling of monacolins in red yeast rice using high-performance liquid chromatography with photodiode array detector and mass spectrometry.. *J Pharm Biomed Anal*, 2004. 35(5):p.1101-12.].
20. Toxicological evaluation of red mould rice: An update; DFG Permanent Senate Commission on Food Safety, English Version: November 13th/14 2013.

This signal has been raised on September 4, 2019. It is possible that in the meantime other information became available.

Appendix

Table 1: Reports of reactions in association with red yeast rice supplement

Number, ID NL-LRB- Sex, Age, Reporter	Suspect drug	Concomitant medication	Reaction MedDra term	Time to onset Action with drug Outcome
1-73756 F, 51-60, Consumer	Red Yeast Rice	zinc gluconate wild yam Re-Cal-B Manga-Vita	1: Decreased appetite 2: Eye swelling 3: Hyperhidrosis 4: Lip swelling 5: Myalgia 6: Nausea 7: Palpitations 8: Rash 9: Weight decreased	1 t/m 9: 4 Weeks Dose not changed Recovering/resolving
2-169611 M, 61-70, Consumer	Red Yeast Rice (Monascus purpureus) Arkosterol Arkopharma®		1: Abdominal discomfort	1: 1 Day Drug withdrawn Recovered/resolved with sequelae
3-182222 F, 51-60, Consumer	Rode gist rijst capsules		1: Abdominal pain upper 2: Decreased appetite 3: Fatigue 4: Myalgia 5: Regurgitation	1 t/m 5: 4 Months Drug withdrawn Recovered/resolved
4-183981 F, 61-70, Consumer	Rode gist rijst Botox Osta k2& d3 algae Macrogol		1: Urinary incontinence	1: 2 Weeks Not applicable Not recovered/not resolved/ongoing 2: 2 Weeks Dose increased Not recovered/not resolved/ongoing 3: 2 Weeks Not applicable Not recovered/not resolved/ongoing 4: 2 Weeks Not applicable Not recovered/not resolved/ongoing
5-189210 F, 61-70, Pharmacist & General Practitioner	Rode gist rijst Codeine	omeprazole calcium with vitamin d acetylsalicylic acid dipyridamole perindopril with diuretics atorvastatin levothyroxine amitriptyline	1: Cholecystitis 2: Pancreatitis acute	1 t/m 2 (Rode gist rijst) : 1 Day Drug withdrawn Recovering/resolving 1 t/m 2 (codeine) : 1 Day Drug withdrawn Recovering/resolving
6-189654 M, 71 years and older, Consumer	Rode gist rijst Arkosterol	sabalıs serrulatae fructus	1: Diarrhoea 2: Vomiting	1 t/m 2: 50 Minutes Drug withdrawn Recovering/resolving
7-215976 F, 61-70, Pharmacist	Rode gist rijst Arkosterol	acetylsalicylic acid ffecainide hydrochlorothiazide metoprolol valsartan	1: Blood pressure increased	1: 17 Days Drug withdrawn Recovered/resolved

8-221937 M, 41-50, Consumer	Rode gist rijst Arkosterol		1: Fatigue 2: Malaise 3: Myalgia	1 t/m 3: 3 Days Drug withdrawn Recovered/resolved
9-224019 M, 61-70, Pharmacist	Arcocaps	acenocoumarole	1: International Normalised Ratio decreased	1: 1 Month Dose not changed Recovering/resolving
10-233126, M, 61-70, Consumer	Rode gist rijst		1: Chest pain	1: 2 Days Drug withdrawn Recovered/resolved
11-233127 M, 61-70, Consumer	Rode gist rijst Kruidvat	pantoprazole clopidogrel hydrochlorothiazide olanzapine oxazepam zolpidem	1: Arthralgia	1: 2 Days Drug withdrawn Recovered/resolved
12-233873 F, 61-70, Specialist doctor	Rode gist rijst	pantoprazole metoclopramide cholecalciferol nadroparine carbasalate calcium metoprolol morphine paracetamol oxazepam amitriptyline	1: Pancreatitis	1: 4 Years Drug withdrawn Recovered/resolved
13-237752 F, 61-70, Consumer	Rode gist rijst Kruidvat	acetylsalicylic acid Isosorbide mononitrate	1: Chromaturia 2: Flank pain 3: Muscle spasms 4: Myalgia 5: Urine odour abnormal	1: 0 Days Drug withdrawn Recovered/resolved 2: -18 Days Drug withdrawn Outcome unknown 3: -18 Days Drug withdrawn Outcome unknown 4: 0 Days Drug withdrawn Recovered/resolved 5: -18 Days Drug withdrawn Outcome unknown
14-239411, M, 71 years and older, Specialist doctor	Bio active Rode gist extract 315mg	omeprazole hydrochlorothiazide telmisartan diclofenac	1: Abdominal pain 2: Chromaturia 3: Malaise 4: Nausea 5: Rhabdomyolysis	1 t/m 5: 385 Days Drug withdrawn Recovered/resolved
15-239870 M, 71 years and older, Consumer	Rode gist rijst		1: Inhibitory drug interaction 2: International Normalised Ratio decreased	1 t/m 2: 3 Months Dose not changed Recovered/resolved
16-242505 M, 51-60, Consumer	Rode gist rijst		1: Insomnia	1: 0 Days Not applicable Recovered/resolved
17-242899 F, 61-70, Consumer	Rode gist rijst		1: Memory impairment	1: 2 Weeks Drug withdrawn Recovered/resolved

18-24290 F, 61-70, Consumer	Rode gist rijst		1: Muscle spasms	1: 1 Week Drug withdrawn Recovered/resolved
19-242984 F, 51-60, Consumer	Bio Active Rode Gist rijst	vitamin b complex	1: Dyspnoea 2: Palpitations	1,2: 8 Weeks Drug withdrawn Outcome unknown
20-243390 M, 61-70, Consumer	Rode gist rijst Its Pure	cholecalciferol	1: Abdominal distension 2: Infrequent bowel movements 3: Intraocular pressure increased	1 t/m 3: 20 Days Drug withdrawn Recovering/resolving
21-243482 M, 51-60, Consumer	Red rice 1,5% Monacoline K Its-Pure		1: Osteoarthritis	1: 14 Days Drug withdrawn Recovered/resolved
22-244062 M, 61-70, Consumer	Rode gist rijst Puro	prednisone	1: Erectile dysfunction 2: Libido decreased	1,2: 1 Year Drug withdrawn Not recovered/not resolved/ongoing
23-244224 F, 61-70, Pharmacist	Rode gist rijst met Q10		1: Arrhythmia	1: 2 Years Drug withdrawn Recovered/resolved
24-244467 M, 51-60, Consumer	Rode gist rijst	metformin gliclazide metoprolol amlodipine	1: Musculoskeletal pain	1: 2 Months Action unknown Not recovered/not resolved/ongoing
25-244534 F, 41-50, Pharmacist	Rode gist rijst bio active	clopidogrel	1: Myalgia	1: 14 Days Drug withdrawn Recovered/resolved
26-246268 F, 41-50, Consumer	Rode gist rijst		1: Fluid retention 2: Muscular weakness	1,2: 2 Weeks Dose reduced Recovering/resolving
27-246276 F, 61-70, General Practitioner	Rode gist rijst	omeprazole psyllium seeds furosemide valsartan with amlodipine ureum betamethasone paracetamol	1: Somnolence	1: 41 Days Drug withdrawn Recovering/resolving
28-247664 F, 71 years and older, Consumer	Rode gist rijst -Lucovital	pantoprazole psyllium seeds clopidogrel	1: Confusional state 2: Decreased appetite 3: Gastrointestinal disorder 4: Listless 5: Myalgia 6: Poor quality sleep	1 t/m 3 and 5: 7 Months Drug withdrawn Not recovered/not resolved/ongoing 4 and 6: Unknown Drug withdrawn Not recovered/not resolved/ongoing

29-248798 F, 61-70, Consumer	Rode gist rijst	valsartan clomipramine	1: Infrequent bowel movements	1: 2 Days Dose not changed Not recovered/not resolved/ongoing
30-250372 F, 51-60, Consumer	Rode gist rijst -Lucovital		1: Feeling abnormal 2: Palpitations	1,2: 1.5 Weeks Drug withdrawn Recovered/resolved
31- 00251816 M, 51-60, Consumer	Rode gist rijst met ubiquinon -Bonusan	magnesium citrate vitamin C	1: Myalgia	1: 1,5 Year Drug withdrawn Not recovered/not resolved/ongoing
32- 00256296 F, 61-70, Pharmacist	Rode gist rijst Vitals	omeprazole dipyridamole carbasalate calcium oxcarbazepine lamotrigine levetiracetam	1: Paraesthesia	1: 1 Day Drug withdrawn Recovering/resolving
33- 00257814 M, 71 years and older, Consumer	Rode gist rijst		1: Tendonitis	1: 18 Days Drug withdrawn Recovering/resolving
34- 00259434 F, 71 years and older, Consumer	Rode gist rijst Holland&Barrett en It's Pure	pantoprazole cholecalciferol ascorbic acid clopidogrel Isosorbide mononitrate metoprolol amlodipine perindopril	1: Myalgia	1: 3 Weeks Drug withdrawn Recovered/resolved with sequelae
35- 00259708 M, 51-60, Consumer	Rode gist rijst Holland& Barrett		1: Muscle atrophy	1: 3 Weeks Drug withdrawn Recovered/resolved
36- 00260280 F, 61-70, Consumer	Rode gist rijst		1: Myalgia	1: 3 Days Drug withdrawn Recovering/resolving
37- 00265685 F, 61-70, Consumer	Rode gist rijst Lucovital		1: Depressed mood 2: Disturbance in attention 3: Fatigue 4: Limb discomfort 5: Listless 6: Myalgia	1 t/m 6: 13 Days Drug withdrawn Recovered/resolved
38- 00266956 F, 71 years and older, Pharmacist	Rode gist rijst	rosuvastatin betahistine	1: Myalgia	1: 3 Months Drug withdrawn Not recovered/not resolved/ongoing
39- 00270612 F, 61-70, General Practitioner	Rode gist rijst Holland&Barrett 600mg	bisoprolol/HCT	1: Myalgia 2: Pain in hip 3: Back pain 4: Fatigue	1 t/m 4 : 6 Months Withdrawn Recovered/resolved

40- 00276330 F, 61-70, Consumer	Rode gist rijst Luconvital		1: Frequent bowel movements	1: 3 Years Not applicable Recovered/resolved
41- 00286523 F, 61-70, Consumer	Rode gist rijst	pantoprazole carbasalate calcium darifenacin	1: Myalgia	1: 6 Weeks Drug withdrawn Not recovered/not resolved/ongoing
42- 00289080 M, 31-40 Medical Student	Rode gist rijst	telmisartan with diuretics	1: Pancreatitis acute	1: 2.5 Years Drug withdrawn Recovering/resolving
43- 00291103 F, 71 years and older, Consumer	Rode gist rijst	omeprazole vitamin b complex alendronate	1: Arthralgia 2: Myalgia 3: Urticaria	1t/m 3: 35 Days Dose not changed Recovering/resolving
44- 00293771 F, 61-70, Consumer	Rode gist rijst	cholecalciferol diclofenac naproxen	1: Headache 2: Malaise 3: Myalgia 4: Poor quality sleep	1t/m 4: 1216 Days Dose not changed Not recovered/not resolved/ongoing
45- 00294896 F, 71 years and older, Consumer	Rode gist rijst	indapamide	1: Diarrhoea	1: 7 Months Not applicable Not recovered/not resolved/ongoing
46- 00295664 F, 71 years and older, Consumer	Rode gist rijst	omeprazole cholecalciferol flecainide hydrochlorothiazide atenolol losartan paracetamol	1: Arthralgia 2: Muscular weakness 3: Myalgia	1 t/m 3: 1 Week Dose not changed Not recovered/not resolved/ongoing
47- 00299357 F, 61-70, Consumer	Rode gist rijst		1: Musculoskeletal pain	1: 2 Months Drug withdrawn Outcome unknown
48- 00299722 M, 61-70, Consumer	Rode gist rijst		1: Abdominal pain upper	1: 1 Day Drug withdrawn Recovered/resolved
49- 00299784 F, 61-70, Consumer	Rode gist rijst Arcosterol	sotalol losartan venlafaxine	1: Oedema peripheral	1: 4 Hours Dose reduced Recovered/resolved
50- 00304019 F, 61-70, Consumer	Rode gist rijst		1: Muscle spasms 2: Myalgia	Drug 1&2 1,2: 2 Days Drug withdrawn Not recovered/not resolved/ongoing

51-00307060 M, 51-60, Pharmacist	Rode gist rijst Atorvastatine	pantoprazole metformin cholecalciferol clopidogrel acetylsalicylic acid nitroglycerine perindopril diclofenac tramadol with paracetamol	1: Muscle spasms 2: Interaction	Drug 1 1: 190 Day Action unknown Recovering/resolving Drug 2 1 Year Drug withdrawn Recovering/resolving
52-00307417 F, 71 years and older, Specialist doctor	Puro rode gistrijstcomplex		1: Blood folate increased	1: 22 Months Drug withdrawn Outcome unknown
53-00308185 F, 71 years and older, Consumer	Rode gist rijst Golden Naturalis		1: Condition aggravated 2: Gait disturbance	1,2: 1 Month Drug withdrawn Not recovered/not resolved/ongoing
54-00308704 F, 0-1, Consumer	Rode gist rijst	calcium carbonate metoprolol perindopril budesonide formoterol with budesonide	1: Headache 2: Hypertension	1,2: 2 Weeks Drug withdrawn Recovered/resolved
55-00311831, M, 61-70, Consumer	Rode gist rijst	carbasalate calcium	1: Post procedural haemorrhage	1: 1 Day Not applicable Recovered/resolved
56-00312824 F, 61-70, Consumer	Rode gist rijst	ranitidine omeprazole cholecalciferol ascorbic acid bupropion	1: Arthralgia 2: Headache 3: Muscular weakness	1 t/m 3: 2 Days Drug withdrawn Not recovered/not resolved/ongoing
57-00313954 F, 71 years and older, Consumer	Rode gist rijst extra sterk Vitalis	magnesium citrate cholecalciferol losartan levothyroxine acetylsalicylic acid	1: Arthralgia 2: Myalgia	1,2: 10 Months Drug withdrawn Recovering/resolving
58-00314517 F, 51-60, Consumer	Rode gist rijst Its pure		1: Abdominal pain 2: Vomiting	1,2: 6 Days Drug withdrawn Recovering/resolving
59-00315832 M, 61-70, Consumer	Rode gist rijst Arkosterol	amlodipine paroxetine	1: Myalgia	1: 2 Weeks Drug withdrawn Outcome unknown
60-00316334 F, 61-70 Hospital Pharmacist	Rode gist rijst Holland&Barrett	magnesium citrate cholecalciferol calcium carbonate methylprednisolone levothyroxine alendronate artificial tears	1: Acute hepatic failure 2: Jaundice	1,2: 1 Week Drug withdrawn Recovering/resolving
61-00316526 M, 71 years and older, Consumer	Rode gist rijst Lucovital		1: Abdominal pain 2: Blood pressure increased 3: Dizziness 4: Malaise	1 t/m 4: 2 Weeks Drug withdrawn Recovered/resolved

62-00319932 F, 51-60 Consumer	Rode gist rijst	fosinopril venlafaxine	1: Myalgia of lower extremities	Unknown Drug Withdrawn Recovered
63-00321987 M, 41-50 Consumer	Red Rice 1,5% Monacoli K	losartan benzbromaron alfacalcidol vitamin b complex cholecalciferol	1: Myalgia 2: Skin disorder NOS	1,2: 10 Months Drug Withdrawn Recovering
64-00324940 M, 71 years and older Consumer	Rode gist rijst Lucovital		1: Stomach discomfort	8 Days Drug Withdrawn Not Recovered
65-00327400 F, 61-70 Consumer	Rode gist rijst		1: Stomach ache	8 Hours Drug Withdrawn Recovered
66-00327633 M, 61-70 Consumer	Rode gist rijst Lucovitaal		1: Muscle stiffness 2: Orientation disturbed 3: Headache 4: Muscle weakness lower limb	1 t/m 4: Unknown Drug Withdrawn Not Recovered
67-00328414 F, 61-70 Consumer	Rode gist rijst		1: Myalgia 2: Joint pain	1,2: Unknown Drug Withdrawn Recovered
68-00330107 F, 51-60 Consumer	Rode gist rijst capsules		1: Palpitations 2: Heart rate irregular	1,2: 3 Days Drug Withdrawn Recovering
70-00338065 F, 71 years and older Consumer	Arkosterol		1: Malaise 2: Fatigue 3: Somnolence 4: Appetite absent 5: Energy decreased 6: Nausea	1 t/m 6: 4 Years Drug Withdrawn Recovering
69-00338297 M, 51-60 Consumer	Rode gist rijst Arterin Omega Pharma		1: Myalgia of lower extremities 2: Muscle stiffness 3: Muscle weakness	1 t/m 3: 2 Years Dose Not Changed Not Recovered
71-00343144 F, 61-70 Physician	Rode gist rijst		1: Cramps of lower extremities	5 Months Drug Withdrawn Recovered
72-00343147 F, 51-60 Pharmacist	Rode gist rijst capsules	levodopa/carbidopa levetiracetam	1: Palpitations	11 Days Dose Not Changed Not Recovered
73-00349466 M, 71 years and older Consumer	Rode gist rijst	pantoprazole clopidogrel cyanocobalamin enalapril adalimumab salbutamol salmeterole/fluticasone tiotropium atenolol	1: Myalgia	4 Months Unknown Recovered with sequel

74- 00348388 F, 61-70 Consumer	Rode gist rijst Plus met Q10 and clopidogrel	melatonin mizolastine Losartan budesonide/formoterol	1: Muscle cramps	2 Months Unknown for RYR / Dose clopidogrel not changed Not recovered
---	--	---	------------------	---