

## Overview of drug-interactions between coumarin derivatives and Over the Counter (OTC) Drugs

### Introduction

The availability of medicinal products is divided into two main groups: medicines available only on Prescription from doctor or specialist (PO) and medicines available without prescription (over-the-counter: OTC). Over-the-Counter drugs are extensively used in the Netherlands. These OTC drugs are categorized into three categories of legal status of supply, based on a mild to very low potential risk for the user. These categories are 'Pharmacy only (PH)' (medicines with a relatively mild potential risk), 'Pharmacy and Drugstore only (PDO)' (medicines with a relatively low potential risk) and 'Without Restriction (GS)' (medicines with a relatively very low potential risk). However, there is always a certain risk of undesirable effects like adverse drug reactions (ADRs) at an effective dose of a medicinal product [1], which also includes a risk of drug-interactions.

A drug group where it is particularly important to monitor for drug-interactions are the coumarin-derivatives. Phenprocoumon (Marcoumar<sup>®</sup>), acenocoumarol and warfarin are vitamin K antagonists (VKA) indicated for *prophylaxis and therapy of thromboembolic diseases*. The anticoagulant effects of these drugs are mediated by inhibiting the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X. The VKA have a narrow therapeutic range and are known to have many drug interactions which may lead to an increase or decrease in their serum levels leading to an increased risk of bleeding or increased risk of thromboembolic events, respectively [2,3]. The anticoagulant effect is monitored with the International Normalized Ratio (INR). Warfarin is not used in the Netherlands, but is largely prescribed in Europe and North America.

The purpose of this overview is to bring attention to potential risky interactions between OTC drugs and coumarin-derivatives, as reported to the Netherlands Pharmacovigilance Centre Lareb. A search of the Lareb database revealed reports of the following OTC drugs and interactions with coumarin-derivatives acenocoumarol and phenprocoumon: glucosamine (n=1), acetylcysteine (Fluimucil<sup>®</sup>) (n=1), the NSAID diclofenac (Voltaren<sup>®</sup>) (n=1), noscapine (Roter Noscapept<sup>®</sup>) indicated for *cough* [4], and the imidazoles, topical miconazol (Daktarin<sup>®</sup> cream and powder, nailpolish) and topical clotrimazole (creams and powder), both indicated for *mycotic infections of the skin and nails caused by dermatophytes and candida* [5,6]. Clotrimazole (Canesten<sup>®</sup> gyno crème) indicated for *mycotic infections of the vagina caused by candida* [7] became an OTC in April 2012 and will also be discussed.

Reports received by Lareb on interactions with coumarin-derivatives are regularly sent to the 'Commissie Interacterende Medicatie Cumarines' after causality assessment.

In 2009 Lareb published a Quarterly Report on topical imidazole [8] derivatives and drug interactions wherein eight reports from the Lareb database were described concerning an interaction between topical miconazole and a coumarin-derivative which led to an increase in the INR [8]. In addition to the reports concerning miconazole, Lareb received four reports of OTC clotrimazole and increased INR as a result from an interaction with coumarin-derivatives. The SmPCs of clotrimazole in topical and vaginal formulations do not describe interactions between coumarin-

derivatives and clotrimazole [5,7]. Clotrimazole is an imidazole derivative with a broad antimycotic spectrum. It inhibits the sterol synthesis of fungi, specifically by inhibiting the synthesis of ergosterol in the cytoplasmic membranes of fungi thereby causing a change in its permeability. Depending on its concentration it is fungistatic or fungicidal (up to 1000ug/cm<sup>3</sup>) [5,9].

The current observation will focus primarily on interactions of coumarin-derivatives with noscapine and clotrimazole.

## Reports

The Netherlands Pharmacovigilance Centre Lareb received six reports of possible interaction of coumarin-derivatives with noscapine between April 2007 and September 2014. Five reports concerned acenocoumarol and one report concerned phenprocoumon (case A). All patients had been using the coumarin-derivatives for months to years and had stable INRs before the OTCs were started. These reports are listed in Table 1.

Table 1. Reports of acenocoumarol and phenprocoumon and drug interaction with noscapine

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 163642 F, 61-70 pharmacist	phenprocoumon 1mg indication unknown noscapine 15mg indication unknown	mesalazine, ezetimibe, ciclesonide, formoterol, salbutamol, paracetamol, atorvastatin, isosorbide mononitrate, glyceryl trinitrate, bumetanide, desloratidine, carvedilol, valsartan, pantoprazole, spironolactone, potassium chloride, acetylcysteine	drug interaction haemorrhage	8 days phenprocoumon discontinued unknown
B 64831 M, 71 years and older pharmacist	noscapine 15mg cough acenocoumarol 1mg indication unknown	folic acid, metformin, enalapril, simvastatin, hydrochloro- thiazide, plantago ovata	INR increased (6.2)	6 days noscapine discontinued recovered within 1 week
C 126740 F, 31-40 pharmacist	acenocoumarol 1mg indication unknown noscapine 15mg dry cough		drug interaction potentiation, INR increased	2 days noscapine discontinued unknown
D 138649 F, 71 years and older pharmacist	acenocoumarol 1mg indication unknown noscapine 15mg dry cough	hydrochloro- thiazide, digoxin, losartan	INR fluctuation	3 weeks noscapine discontinued recovered
E 166204 F, 71 years and older pharmacist	acenocoumarol 1 mg indication unknown noscapine 15mg cough		drug interaction eye haemorrhage	2 days acenocoumarol discontinued not recovered

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
G 181095 M, 71 years and older pharmacist	acenocoumarol 1 mg thrombosis noscapine 15mg cough	ticagrelor	eye haemorrhage	3 days noscapine discontinued recovered

All cases concerning noscapine were reported by pharmacists. In patient A the indication for use of phenprocoumon was unknown, however the patient had a medical history of thromboembolism and angina pectoris. The time between the start of noscapine and drug interaction with the phenprocoumon and acenocoumarol ranged from 2 days till 3 weeks. In case D a latency of 3 weeks was reported, perhaps because the patient's INR had not been controlled at an earlier moment. Cases B and C reported an increase in INR (in case B the INR was 6.2). In case D a dysregulation of the anticoagulant effect was reported, however the actual INR value was unknown. In the other three cases hemorrhage was reported. Patient G was treated with ticagrelor for 10 months, which can also cause bleeding, as a common ADR. In patients B, D and G the INR normalized after noscapine was discontinued.

After publication of the Quarterly Report on topical imidazole derivatives in 2009 [8], Lareb received an additional two reports of topical miconazole resulting in a fluctuation or increase in INR (Table 2).

Table 2. Reports of acenocoumarol and drug interaction with miconazole.

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
H 97625 M, 71 years and older consumer	acenocoumarol 1mg atrial fibrillation miconazole cream 20mg/g mycosis of the glans penis	not reported	drug interaction potentiation, INR fluctuation (4.2)	33 months acenocoumarol was discontinued temporarily recovered
I 115734 F, 71 years and older pharmacist	acenocoumarol 1mg indication unknown miconazole/zink cream 20/576mg/g decubitus ulcer		drug interaction INR increased	2 days miconazole discontinued recovered

Lareb received case H from a consumer who originally reported fluctuations in his INR due to dietary margarine and the cause of these fluctuations remained unexplained for more than 2 years. Patient I had a decubitus ulcer thereby probably facilitating systemic absorption of miconazole cream. The patient was treated with phytonadion (vitamin K1) and prothrombincomplex.

Between August 2009 and September 2014 the Lareb database received four reports of coumarines and drug interaction potentiation with topical and vaginal cream formulations of clotrimazole. These reports are listed in table 3.

Table 3. Reports of acenocoumarol and phenprocoumon and drug interaction with clotrimazole

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
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Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
J 159820 F, 71 years and older specialist doctor	clotrimazole cream fungal infection, acenocoumarol 1 mg atrial fibrillation	non specified drug	drug interaction, international normalized ratio increased	13 days acenocoumarol dose reduced recovered
K 166602 M, 61-70 general practitioner	clotrimazole cream 10mg/g intertrigo, phenprocoumon 3mg Cerebrovascular accident	sotalol, baclofen, magnesium hydroxide, plantago ovata, omeprazole, methotrexate, solifenacine, fucidin/triam- cinolone	drug interaction, INR increased	3 days phenprocoumon dose reduced recovering
L 175923 M, 61-70 specialist doctor	clotrimazole cream 10mg/g dermatomycosis phenprocoumon 3mg atrial fibrillation	candesartan	drug interaction, INR increased (up to 8)	16 days phenprocoumon and clotrimazole discontinued recovered
M 119627 F, 71 years and older specialist doctor	acenocoumarol 1mg indication unknown clotrimazole vaginal cream 10mg/g vaginal mycosis	not reported	drug interaction, INR increased	1 day acenocoumarol discontinued recovered

All four reports were from physicians. All patients had stable INR values under treatment with coumarines. Patient K received treatment with phenprocoumon and the other three patients were treated with acenocoumarol. The time between the start of the imidazole and drug interaction with the phenprocoumon and acenocoumarol ranged from 1 day till 16 days. In patients J and K the coumarine dose was reduced leading to normalization of INR values. Acenocoumarol was discontinued in case M and the patient recovered. Patient J used clotrimazole cream over a large surface area which may have influenced the absorption. Patient K had omeprazole as co-medication, which may be a confounding factor as omeprazole has a drug interaction potentiation effect on phenprocoumon [10,11]. In case L the increased INR values were frequently measured, with the first measurement being 7.5 (16 days after start), and then fluctuating between 4.2 and 8.1 and accompanied with ecchymosis. During this time the patient was treated with phytomenadion and this resulted in fluctuating INR values. The physician treating the patient was unaware of what caused this INR increase and started treatment with vitamin K. After 37 days phenprocoumon and clotrimazole were withdrawn and the INR normalized. Patient M was treated with clotrimazole vaginal cream and after 1 day there was an INR increase. After acenocoumarol was withdrawn the INR normalised.

## Other Sources of Information

### SmPC

The SmPC of noscapiene states in section 4.5 (Interactions) that noscapiene may increase the effects of warfarin and may possibly increase the effects of acenocoumarol and phenprocoumon [4]. The SmPCs of OTC vaginal and topical formulations of clotrimazole do not describe interactions with coumarin- derivatives. [5,7] The SmPCs of OTC miconazole describe possible interactions with warfarin [6].

## Literature

The Federation of Dutch Thrombosis Services has noscapine on its "Attention List" as the relevance of coumarine interactions with noscapine is yet uncertain. However, the Commissie Interacterende Medicatie Cumarines confirms that the Swedish adverse drug reactions register (SWEDIS) ascertains that noscapine can increase the effect of warfarine.

To the best of our knowledge, the literature does not describe any case reports of acenocoumarol and phenprocoumon interactions with noscapine. In the literature there are several reports of warfarin and interactions with noscapine. Sixteen cases have been reported of a drug interaction between noscapine and warfarin which lead to an INR increase in 15 cases and bleeding in one case. One patient developed an INR higher than 8 [12]. In 2006 SWEDIS received a report of a noscapine and warfarin interaction concerning an 82-year-old man who was stabilized on warfarin therapy, who, after 6 days of noscapine treatment for cough, developed an INR of 7.2 (3 weeks earlier his INR had been 3.0). Noscapine was withdrawn, warfarin was discontinued for one day, and the patient was treated with vitamin K. The INR normalized to 2.3 [13].

It is well known that systemic azole antifungals, miconazole, ketoconazole, and itraconazole are metabolized by hepatic cytochrome P450 enzymes and via a dose-dependent mechanism interfere with the metabolism of coumarin-derivatives [14,15]. However, also topical formulations of miconazole are systemically absorbed (when used on large areas of warm, moist, skin (intertrigo) or under occlusion) and through inhibition of CYP2C9 may cause an increase in INR when taken with coumarin-derivatives [16]. To date there have been no case-reports describing an interaction between clotrimazole and coumarines.

The Commissie interacterende medicatie cumarines describes in their '*Standaard afhandeling coumarine-interacties*' that when under treatment with coumarines, miconazole vaginal cream or ovules should be substituted for clotrimazole or butoconazol vaginal cream or ovules and miconazole cutaneous/topical should be substituted for clotrimazole cutaneous/topical. With miconazole there's a risk for high INR increases and therefore the risk of bleeding is deemed higher than with the use of clotrimazole [15].

## Databases

Table 4. Reports of INR changes associated with noscapine, miconazole and clotrimazole in the Lareb-, WHO- and Eudravigilance databases [17,18]

Database	Drug	Adverse Drug Effect	Number of reports	ROR (95% CI)
Lareb	Noscapine*	INR increased	2	-
		INR fluctuation	1	-
	Clotrimazole	INR increased	3	200.0 (56.0-714.3)
		INR fluctuation	1	-
WHO	Noscapine	INR increased	19	47.3 (29.6-75.4)
		INR fluctuation	1	-
	Miconazole	INR increased	168	10.6 (9.1-12.4)
		INR decreased	2	-
	Clotrimazole	INR increased	7	2.0 (1.0-4.25)

Database	Drug	Adverse Drug Effect	Number of reports	ROR (95% CI)
Eudravigilance	Noscapine	INR increased	27	48.3 (32.2-72.5)
		INR fluctuation	1	-
	Miconazole	INR increased	262	106.6 (92.5-122.8)
		INR fluctuations	2	-
	Clotrimazole	INR increased	7	4.1 (2.0-8.7)
		INR fluctuation	1	-

\* Reports of Eye Haemorrhage (n=2) and Hemorrhage (n=1) not included in this table

Due to differences in encoding drug interactions in MedDRA, with miconazole and the coumarines it is not possible to determine the reporting odds ratio.

For the WHO database of the Uppsala Monitoring Centre and the Eudravigilance database all dosage-forms of miconazole and clotrimazole were taken into account, including oral dosages.

For the reports in the WHO database the number of patients using coumarines was checked. Of the 19 reports of noscapine in association with increased INR and 1 report of noscapine and INR fluctuation, in 16 reports warfarin was a comedication and in 4 cases acenocoumarol was used. For the 7 reports of clotrimazole and INR increase; in 5 cases warfarin was used as comedication and in 1 case both acenocoumarol and phenprocoumon were used. The reporting odds ratio (ROR) is disproportional for INR increased in all databases for miconazole and clotrimazole, The ROR could not be calculated for noscapine in the Lareb database, however, the ROR was disproportional in the WHO and Eudravigilance databases.

## Prescription Data

Noscapine, miconazole and clotrimazole are readily available as OTC-medications. Because of their OTC status the number of users cannot be obtained through the GIP-database of the National Health Care Institute (Zorginstituut Nederland). The number of patients using acenocoumarol and phenprocoumon in the Netherlands is shown in table 5.

Table 5. Number of patients using phenprocoumon and acenocoumarol in the Netherlands between 2009 and 2013 [19]

Drug	2009	2010	2011	2012	2013
phenprocoumon	71,207	75,616	78,773	82,227	86,914
acenocoumarol	292,070	299,790	311,430	328,450	344,990

## Mechanism

The anticoagulants warfarin, acenocoumarol and phenprocoumon exist as two enantiomers that are metabolized by different cytochrome P450 (CYP) isoenzymes in the liver. The S-enantiomers are mainly metabolized by CYP2C9. The R-enantiomers are mainly metabolized by CYP2C9, but also by CYP1A2 and CYP3A4 [2,3,20]. Many drugs are inhibitors or inducers of these isoenzymes causing an increase or decrease in plasma concentrations of coumarines resulting in a high or low INR, respectively.

Ohlsson *et al.*, did an in vitro experiment to elucidate the drug interaction between noscapine and warfarine and found that noscapine inhibits in vitro CYP2C9 and

CYP3A4 leading to higher warfarin plasma concentrations and an increase in INR [14]. Recently, Zhang *et. al.* determined that nospapine is a competitive inhibitor of the (S)-warfarin 7-hydroxylation reaction by CYP2C9 and established a mechanism-based inactivation of CYP2C9 by nospapine. Spectral tests of the reaction between CYP2C9 and nospapine showed a metabolite-intermediate complex. (S)-warfarin exposure may increase up to 7 times during therapy with nospapine [21].

The systemic absorption of topical clotrimazole is less than 2% and that of vaginal tablets is 3-10% [5,7]. Imidazole antimycotic agents and their induction and inhibition of hepatic cytochrome P450 enzymes have been extensively studied. Zhang *et. al.*, performed in vitro studies of five imidazole derivatives in order to be able to predict possible drug-drug interactions in vivo, using cDNA-expressing microsomes from human lymphoblast cells or human hepatic liver microsomes. They concluded that clotrimazole strongly inhibits CYP2A6, 2B6, 2C9, 2C19 and 3A4 [21]. Inhibition of CYP2C9 and 3A4 may lead to increased plasma concentrations of coumarines with a corresponding increase in INR [14,21].

Furthermore, the imidazole, clotrimazole, miconazole, sulconazole, ketoconazole and tioconazole are all potent inhibitors of CYP2C9 and 3A4 [21]. There may be evidence supporting a possible class effect due to the chemical structure as both an N-substituted group at the imidazole moiety and the lipophilicity of the side chains affect inhibition of CYP3A4 [21,23,24].

## Discussion

Lareb received 6 reports of INR increase or fluctuation and bleeding with patients stabilized on coumarines and administered nospapine for cough. In one case the INR was greater than 6. The WHO database is also disproportional for this association. In the literature there are well documented case reports on nospapine interactions with warfarine. Given the reports in literature describing nospapine interactions with warfarine and the proposed mechanism that nospapine is a strong CYP2C9 inhibitor, it is reasonable to assume that acenocoumarol and phenprocoumon interact in the same way.

Lareb received 4 reports of clotrimazole and an increase in INR. To date, information is lacking on the systemic absorption of topical imidazoles. Patient J used clotrimazole over a large surface area and it is probable that mycosis of the skin may cause sufficient skin damage enabling easier absorption of clotrimazole. As clotrimazole is a strong inhibitor of CYP2C9 and 3A4 [25] an interaction may be expected. In case L, the physician was unaware that there was an interaction between topical miconazole and phenprocoumon and treated the patient with Vitamin K before discontinuing the miconazole more than a month later. It is possible that these interactions are underreported as they are not described in the referral literature frequently used by physicians and the Federation of Dutch Thrombosis Services recommends substituting OTC miconazole for clotrimazole during treatment with coumarines.

## Conclusion

It is advisable to include an interaction with coumarine derivatives in the SmPC of OTC clotrimazole. SmPCs of imidazoles could advise monitoring the INR in patients who are on coumarine therapy. Information about acenocoumarol and phenprocoumon and interactions with OTC-drugs is sparse. Given the extensive use of readily available OTC drugs and supplements it is important to recognize the risks involved for patients on coumarine prophylactic therapy.

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*This overview was published in November 2014. 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.cbqmeb.nl](http://www.cbqmeb.nl)*