

## 1.1. Noscapine and abdominal pain, chest pain and headache

### Introduction

In October 2016, Pharmacovigilance Centre Lareb and Uppsala Monitoring Centre performed a collaborating signal detection sprint. This sprint had a focus on patient reports. One of the goals of this process, was to detect adverse drug reactions (ADRs) that were not fully covered in the patient information leaflets (PILs). During this joint Lareb / Uppsala Monitoring Centre signal detection sprint, noscapine and various adverse drug reactions (ADRs) were highlighted. The most notable ADRs to emerge from this were abdominal pain (upper), headache, chest pain and chest discomfort, in all a total of 130 individual case safety reports [1].

Noscapine is indicated for treatment of non-productive cough. It is an opium alkaloid, which is derived from the opium poppy [2]. Noscapine has a central mechanism of action which blocks the antagonizing receptors in the reflex centres of the medulla oblongata [3], although the exact mechanism is not clear. It is possible that cough is actually suppressed or just better tolerated [4]. It has also been proposed that noscapine's antitussive effect is caused by the  $\mu$ -opioid receptor agonist activity [4]. In contrast to codeine, noscapine lacks analgesic, sedative, hypnotic and addictive effects [4]. Dry cough is associated with an accumulation of bradykinin which can stimulate bronchoconstriction and mucous production. Noscapine is a non-competitive bradykinin receptor antagonist [4], and therefore can also have a mild bronchodilator effect.

Noscapine was granted a marketing authorization in 1974 [3]. Worldwide, noscapine is marketed in many countries [5]. Noscapine is mostly available as a combination product [5].

Cough is a physiological mechanism that serves to clear the respiratory tract of foreign material and excessive secretions. The cough reflex is a complex mechanism which involves the central and peripheral nervous systems and the smooth muscles of the airway [6]. Therefore, drugs that act on one of these three components of the cough reflex may reduce coughing.

It is important to note that noscapine is an over-the-counter (OTC) drug in many countries, so it is available without prescription.

### Reports

From 1 May 1991 until 28 February 2017 the Netherlands Pharmacovigilance Centre Lareb received nine reports concerning abdominal pain, six reports of abdominal pain upper, four of chest pain, two of chest discomfort and two concerning headache associated with the use of noscapine, with a total of 21 individual case safety reports (ICSRs) [7]. Cases I and S represent one report, in which both abdominal pain and chest discomfort was reported. Also cases T and W represent one report, both chest discomfort and headache were reported. Eight cases concerned male and thirteen female patients. The ages varied from eight until 76 years and in four cases age was unknown. The mean age was 40 years. Time to onset varied from 30 minutes until one week after start, with a median of two hours. Time to onset was unknown in three cases. In thirteen cases, after withdrawal the patient recovered or was recovering at the time of reporting. In the other cases the outcome or action with the drug was unknown. Appendix A gives an overview of the reports received by the Netherlands Pharmacovigilance Centre Lareb.

### Other sources of information

#### *SmPC*

The Dutch SmPC of noscapine does not mention headache, (upper) abdominal pain or chest pain [3]. In Europe, the Swedish, Norwegian and German SmPCs, do mention all three adverse drug reactions [8-10]. In addition, the label information of the Swedish SmPC and the PIL outlines that a patient can experience severe abdominal pain and/or chest pain with a latency of half an hour to four hours after administration. These symptoms decrease after one to three hours [8,11].

#### *Literature and mechanism*

Noscapine and its possible adverse drug events are little discussed in the literature. A proposed mechanism for the chest pain and chest discomfort is that noscapine is a potent histamine releasing drug and large doses may cause bronchoconstriction [12].

## Databases

Table 1. Reports of abdominal pain, abdominal pain upper, chest pain, chest discomfort and headache associated with noscapine, in the Lareb and WHO database at 28-2-2017 [1,7].

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Abdominal pain	9	4.1 (2.1-8.2)
WHO	Abdominal pain	80	15.3 (12.0-19.6)
Lareb	Abdominal pain upper	6	8.9 (3.9-20.3)
WHO	Abdominal pain upper	22	8.1 (5.3-12.5)
Lareb	Chest pain	4	4.8 (1.8-13.0)
WHO	Chest pain	60	16.7 (12.7-22.0)
Lareb	Chest discomfort	2*	
WHO	Chest discomfort	7	2.2 (1.0-4.5)
Lareb	Headache	2*	
WHO	Headache	7	0.5 (0.2-1.0)

\*For this association in the Lareb database no reliable ROR can be calculated because of the small number of reports.

In VigiBase®, the WHO international database of suspected adverse drug reactions, as of 13 November 2016 there were 130 individual case safety reports (ICSRs) for noscapine, which consisted of 74 reports of *Abdominal pain*, 20 of *Abdominal pain upper*, 58 of *Chest pain*, 7 of *Chest discomfort* and 7 of *Headache*. A single ICSR can consist of multiple ADRs. The cases concerned 79 females and 41 males; the patient's sex was unknown in 10 cases. Most of these ICSR's affected patients in the 18 to 44 age group (81 ICSR's, 62.3% of the total). 129 (99.2% of the total) originated from Europe, from five countries; Sweden, Norway, Denmark, Germany and the Netherlands; only one report came from the Americas.

For abdominal pain and upper abdominal pain reports (with a total of 94 reports), there were 41 positive dechallenges and six positive rechallenges. One patient experienced the same events before. One ICSR described recurrence upon administration, co-reported adverse effects in this report were male breast pain and restlessness. Seven patients were hospitalized or visited a doctor because of the symptoms. One patient almost called a doctor, but at that moment the symptoms decreased. A number of reports mentioned the severity of the symptoms. The most commonly co-reported term in these reports is chest pain (30 ICSR's, 31.9%).

74 ICSR's give noscapine as the only drug used, in 19 reports the patient used concomitant medication. Some concomitant medication was used for the patient's comorbidity. In other reports the indication of the concomitant medication is unknown but it is most likely that this concomitant medication is taken for the same indication as noscapine; such as paracetamol, ibuprofen and bromhexine. In one case, the patient was diagnosed with constipation one week after starting the noscapine, which could explain his abdominal pain.

Concerning the chest pain and chest discomfort (65 reports in total), there were 35 positive dechallenges and eight positive rechallenges. Two reports gave both chest pain and chest discomfort. Five mentioned that the patient had visited the hospital or a doctor. The chest discomfort was described as 'pressure' in five reports and as 'tightness' in two. The chest pain symptoms were characterized as a peaking, sharp, stinging or cramping pain of the chest.

In 52 reports noscapine is the only reported drug. In 11 reports the patient used multiple drugs, but noscapine was the single suspect drug. Regarding these concomitant medications, some were prescribed for a patient's comorbidity. One ICSR had pulmonary medication (budesonide and ipratropium) which could be confounding.

The seven headache reports included six with positive dechallenge. In five ICSRs, noscapine was the only reported drug.

For all the ADRs described above, the symptoms started within a few hours after administration (mostly between 30 minutes and four hours) and the symptoms decreased or disappeared within a few hours after start of the symptoms.

In respect of the chest pain, chest discomfort and abdominal pain, there is some confounding by indication. In most ICSRs the noscapine was indicated for (dry) cough or common cold. Persistent and severe cough can lead to myalgia and contusion of the costal and abdominal muscles. One report mentioned that the patient was diagnosed with pleurisy and in another the patient had peribronchitis. Furthermore, the chest pain and chest discomfort could be a manifestation of oesophageal spasms, which would be consistent with the abdominal pain and stomach cramps described earlier. Abdominal pain has a high background incidence and it is often listed as an adverse event for a variety of medicines.

### Discussion and conclusion

During this signal detection sprint 130 ICSRs for noscapine were identified. These concerned the adverse events abdominal pain, upper abdominal pain, chest pain, chest discomfort and/or headache. Of these reports, 21 ICSRs originated from the Netherlands Pharmacovigilance Centre Lareb (nine reports concerning abdominal pain, six reports of abdominal pain upper, four of chest pain, two of chest discomfort and two concerning headache). From the total of 130 ICSRs, there were 41 positive dechallenges and six positive rechallenges for the abdominal pain and upper abdominal pain. For the chest pain and chest discomfort, there were 35 positive dechallenges and eight positive rechallenges. Concerning the chest pain, chest discomfort and abdominal, there is some confounding by indication. As severe cough can lead to myalgia and therefore to chest pain or abdominal pain. For headache there were six positive dechallenges. For all the described ADRs, the symptoms started within a few hours (mostly between 30 minutes and four hours) after administration, and the symptoms reduced or disappeared within a few hours after starting. Most of the reports (62.3%) concern relatively young patients (between 18 and 44 years) with hardly any comorbidity.

Although the Dutch SmPC doesn't mention these adverse events and the literature on ADRs related to noscapine is scarce, headache, (upper) abdominal pain and chest pain are labelled in the Swedish, Norwegian and German SmPCs. Therefore, it is advisable that these adverse events are also mentioned in the Dutch SmPC. The reports also point to a degree of severity which is relevant to mention in the patient information leaflet. Hence, a description of the possible seriousness of these adverse reactions in the SmPC and PIL is recommended.

### References

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5. Martindale: The Complete Drug Reference. (version date: 2017, access date: 16-1-2017) <https://www.medicinescomplete.com/mc/martindale/current/> (access restricted).
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7. Lareb database. (version date: 2017, access date: 28-2-2017) <https://www.lareb.nl/nl/databank/>.
8. Swedish SmPC Nipaxon<sup>®</sup> 50 mg tabletter. (version date: 2016, access date: 13-1-2017) <https://lakemedelsverket.se/LMF/Lakemedelsinformation/?nplid=19791116000111&type=product>.
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10. German SmPC Capval<sup>®</sup> Dragees 25 mg Überzogene Tabletten. (version date: 2015, access date: 13-1-2017) <https://portal.dimdi.de/amispb/doc//2015/03/10/0554655/Oc2fd7b9669304b75817da0f5c24e4269.pdf>.
11. Swedish PIL Nipaxon<sup>®</sup> 50 mg tabletter. (version date: 2016, access date: 13-1-2017) <https://lakemedelsverket.se/LMF/Lakemedelsinformation/?nplid=19791116000111&type=product>.
12. Relis: Manufacturer-independent drug information for healthcare. (version date: 2015, access date: 17-1-2017) [https://relis.no/sporsmal\\_og\\_svar/2-750?source=relisdb](https://relis.no/sporsmal_og_svar/2-750?source=relisdb).

**Appendix A, reports received by the Netherlands Pharmacovigilance Centre Lareb concerning abdominal pain, abdominal pain upper, chest pain, chest discomfort and headache associated with the use of noscapine**

Table 1 Reports of abdominal pain in the Lareb database

<b>ID, sex, age, source</b>	<b>Drug, daily dose, indication</b>	<b>Concomitant medication</b>	<b>Suspected adverse drug reactions</b>	<b>Time to onset, action with drug, outcome</b>
A 232 F, unknown, General Practitioner	noscapine dragee 15mg, 3dd2, unknown	metoprolol, enalapril	abdominal pain	2 hour, unknown, unknown
B 1531 M, unknown, General Practitioner	noscapine capsule 30mg, 3dd1, unknown		abdominal pain	1 hour, unknown, unknown
C 2737 M, unknown, General Practitioner	noscapine capsule 20mg, 3dd1, unknown		abdominal pain	90 minute, unknown, unknown
D 4403 M, unknown, General Practitioner	noscapine dragee 15mg, 4dd1, unknown	cimetidine	abdominal pain	2 hour, dose not changed, unknown
E 49108 M, 8-10 years, Pharmacist	noscapine dragee 15mg, 3dd1, cough	amoxicillin, valproic acid, non specified insulin, salbutamol aerosol, fluticason aerosol	abdominal pain, nausea	For the abdominal pain: unknown, drug withdrawn, recovered/resolved  For the nausea: 2 day, drug withdrawn, recovered/resolved
F 53246 M, 71 years and older, Pharmacist	noscapine capsule 15mg, 2dd1, cough	lisinopril/hydrochlorothiazide	abdominal pain, constipation	1 week, unknown, recovered/resolved
G 99625 M, 51-60 years, Pharmacist	noscapine stroop 1mg/ml, 2dd30ml, dry cough	metoprolol, acetylsalicylic acid	abdominal pain	8 hour, drug withdrawn, recovered/resolved
H 203235 M, 8-10 years, Pharmacist	noscapine stroop 1mg/ml, 2-4dd10ml, cough	methylphenidate	abdominal pain	day, drug withdrawn, recovered/resolved
I 214258 F, 31-40 years, Consumer	noscapine tablet 15mg, 1dd1, cough		chest pain, abdominal pain	3 hour, drug withdrawn, recovered/resolved

Table 2 Reports of abdominal pain upper in the Lareb database

<b>ID, sex, age, source</b>	<b>Drug, daily dose, indication</b>	<b>Concomitant medication</b>	<b>Suspected adverse drug reactions</b>	<b>Time to onset, action with drug, outcome</b>
J 28535 F, 71 years and older, Pharmacist	noscapine stroop 1mg/ml, 1dd1	paracetamol	abdominal pain upper	unknown, drug withdrawn, unknown
K 90931 M, 31-40 years, Specialist doctor	noscapine dragee 15mg, 1dd30mg, dry cough		abdominal pain upper	2 hour, not applicable, recovered/resolved

L 157771 F, 11-20 years, Pharmacist	noscipine tablet 15mg, 1dd30mg, nonproductive cough		abdominal pain upper	3 hour, drug withdrawn, recovered/resolved
M 165395 F, 41-50 years, Consumer	noscipine capsule 15mg, 1dd30mg, dry cough	paracetamol	abdominal pain upper, vomiting	2 hour, drug withdrawn, recovered/resolved
N 205064 F, 11-20 years, Pharmacist	noscipine tablet 15mg, 1dd1, dry cough	methylphenidate	pharyngeal oedema, abdominal pain upper	1 hour, drug withdrawn, recovered/resolved
O 206368 F, 21-30 years, Consumer	noscipine stroop 1mg/ml, 30 ml, dry cough		abdominal pain upper	1 hour, drug withdrawn, recovering/resolving

Table 3 Reports of chest pain in the Lareb database

ID, sex, age, source	Drug, daily dose, indication	Concomitant medication	Suspected adverse drug reactions	Time to onset, action with drug, outcome
P 27140 F, 51-60 years, Pharmacist	noscipine stroop 1mg/ml, 3dd15ml	metoprolol succinate	chest pain	unknown, drug withdrawn, unknown
Q 49150 F, 31-40 years, Consumer	noscipine stroop 1mg/ml, 15 ml, cough	budesonide, fexofenadine, ipratropium	chest pain	hour, drug withdrawn, recovered/resolved
R 105253 F, 31-40 years, Pharmacist	noscipine dragee 15mg, cough	levonorgestrel iud, hydrocortisone butyrate, carbomer (980)	chest pain	2 hour, drug withdrawn, recovered/resolved
S 214258 F, 31-40 years, Consumer	noscipine tablet 15mg, 1dd1, cough		chest pain, abdominal pain	3 hour, drug withdrawn, recovered/resolved

Table 4 Reports of chest discomfort in the Lareb database

ID, sex, age, source	Drug, daily dose, indication	Concomitant medication	Suspected adverse drug reactions	Time to onset, action with drug, outcome
T 183634 F, 61-70 years, Consumer	noscipine tablet 15mg, 1dd30mg, dry cough		dyspnoea, chest discomfort, headache	30 minute, drug withdrawn, recovered/resolved
U 202994 F, 41-50 years, Consumer	noscipine tablet 15mg, 1dd1, dry cough	pyridostigmine	myasthenia gravis, head discomfort, chest discomfort, somnia, nausea	1 hour, drug withdrawn, recovering/resolving

Table 5 Reports of headache in the Lareb database

ID, sex, age, source	Drug, daily dose, indication	Concomitant medication	Suspected adverse drug reactions	Time to onset, action with drug, outcome
V 179472 F, 51-60 years, Consumer	noscipine tablet 15mg, dry cough		sleep disorder, abnormal dreams, amnesia, headache, crying	For sleep disorder and abnormal dreams: hour, drug withdrawn, recovered/resolved  For amnesia, headache and crying: 1 day, drug withdrawn, recovered/resolved

W 183634  
F, 61-70  
years,  
Consumer

noscapine tablet 15mg,  
1dd30mg, dry cough

dyspnoea,  
chest discomfort,  
headache

30 minute,  
drug withdrawn,  
recovered/resolved

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*This signal has been raised on April 26 2017. 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](http://www.cbg-meb.nl)*