

## Flucloxacillin and oesophageal complaints

### Introduction

Flucloxacillin (Floxapen®) is a narrow spectrum isoxazolyl penicillin. This  $\beta$ -lactam antibiotic has bactericidal activity against many strains of gram-positive organisms, including streptococci and  $\beta$ -lactamase producing staphylococci. Flucloxacillin inhibits crosslinking of peptidoglycans in the cell wall, resulting in lysis and cell death. It is mainly used to treat *respiratory infections (e.g. pharyngitis, tonsillitis, sinusitis, pneumonia, pulmonary abscess) and infections of skin and soft tissue (e.g. impetigo, abscesses)* [1]. Flucloxacillin is registered in the Netherlands since 1971 as Floxapen® and is nowadays mostly dispensed as generic brands [2].

Oesophageal pain is a non-specific symptom which can indicate various underlying illnesses, like gastroesophageal reflux disease or oesophagitis [3]. The neurophysiological mechanisms causing oesophageal pain are not well understood. It is suggested that activation of thermoreceptors (hot/cold food), mechanoreceptors (distension, contractions) and chemoreceptors (acid, hyperosmolar agents) result in oesophageal pain [4].

### Reports

Between October 29<sup>th</sup> 2007 and October 23<sup>th</sup> 2019 Pharmacovigilance Centre Lareb received 22 reports of oesophageal pain or similar complaints associated with the use of flucloxacillin. Included MedDRA Preferred Terms (PT) were oesophagitis (n=1), oesophageal pain (n=7), burn oesophageal (n=3), throat irritation (n=5), oropharyngeal pain (n=4) and oral pain\* (n=2).

Table 1. Reports of oesophageal related pain complaints associated with flucloxacillin

Patient, Lareb ID, Sex, Age (year), Reporter	Suspect drug, Dosage, Indication	Concomitant medication	Reported adverse drug reactions (ADR)	Time to onset, Action taken, Outcome
A, NL-LRB-00292929, F, 60-70, consumer	flucloxacillin (Floxapen®), 500mg 3 times per day, erysipelas	ranitidine, rosuvastatin	oesophagitis, black stools	1 day, drug withdrawn, not recovered
B, NL-LRB-00347691, M, 40-50, consumer	flucloxacillin, 500mg 4 times per day, bursitis		burning oesophagus, burning sensation of stomach	1 day, not applicable, recovered
C, NL-LRB-00296756, F, 71 years and older, physician	flucloxacillin, 500mg 4 times per day, orbital cellulitis		oesophageal pain	10 minutes, dose not changed, unknown
D, NL-LRB-00293859, F, 50-60, consumer	flucloxacillin, 500mg 3 times per day, insect bite NOS	lercanidipine, pravastatin, tiotropium, beclomethasone, cholecalciferol, magnesium	burning oesophagus, dyspepsia	2 minutes, drug withdrawn, not recovered
E, NL-LRB-00283907, F, 71 years and older, other health professional	flucloxacillin of brand Mylan, 500mg 4 times per day, Infection (non-specified)		oesophageal pain, oesophageal spasm	3 days, dose not changed, recovering 1 day after the reaction started
F, NL-LRB-229668, F, 60-70, consumer	flucloxacillin, 500mg 4 times per day, infected finger		oesophageal pain	5 minutes, dose not changed, recovered with sequelae (not further specified)
G, NL-LRB-212637, F, 40-50, consumer	flucloxacillin of brand Mylan, 500mg 3 times per day, wound infection	phenprocoumon	oesophageal pain, cough, burping	20 hours, dose not changed, unknown

H, NL-LRB-180983, F, 71 years and older, pharmacist, pharmacist	flucloxacillin, 500mg 3 times per day, inflammation		oesophageal pain	2 days, drug withdrawn, recovered 1 day after withdrawal
I, NL-LRB-00293278, F, 20-30, consumer	flucloxacillin, 500mg 4 times per day, prophylactic antibiotic therapy		oesophageal burn, vaginal mycosis, stool black	1 hour, not applicable, recovered after 8 days
J, NL-LRB-219975, M, 30-40, pharmacist	flucloxacillin, unknown dose 3 times per day, infection	non specified insulin	oesophageal burn	10 minutes, dose not changed, not recovered
K, NL-LRB-71570, M, 50-60, physician	flucloxacillin, 1000mg 4 times per day, erysipelas		oesophageal burn	3 hours, drug withdrawn, recovered
L, NL-LRB-00344032, M, 10-20, consumer	flucloxacillin, 500mg 3 times per day, bacterial infection		burning in throat, nauseous	2 days, unknown, not recovered
M, NL-LRB- 00257752, F, 50-60, consumer	flucloxacillin, 500mg 4 times per day, boil in nose		throat burning sensation of, swallowing difficult	1 minute, drug withdrawn, recovered after 11 days
N, NL-LRB-245093, M, 50-60, consumer	flucloxacillin, 500mg 4 times per day, skin infection		burning in throat, dyspepsia	5 minutes after administration of the 3 <sup>th</sup> capsule, not applicable, unknown
O, NL-LRB-226635, F, 30-40, consumer	flucloxacillin, 500mg 4 times per day, breast inflammation	levothyroxine, ferrofumarate, acetaminophen	burning in throat, gastroesophageal reflux	2 days, unknown, not recovered
P, NL-LRB-194062, F, 50-60, consumer	flucloxacillin, 500mg 4 times per day, infection bacterial	metformin, glimepiride, amlodipine	throat irritation, vaginal candidiasis, fatigue	2 days, not applicable, recovered 1 week after withdrawal
Q, NL-LRB-00344212, F, 40-50, consumer	flucloxacillin, 500mg 4 times per day, infection localised	acetaminophen	throat pain, pyrexia, musculoskeletal pain	5 days, drug withdrawn, recovering 3 days after withdrawal
R, NL-LRB-00333535, M, 20-30, consumer	flucloxacillin (Floxapen®), unknown dose 4 times per day, infected toe	methylphenidate	oropharyngeal pain, fatigue, somnolence	4 days, dose not changed, not recovered
S, NL-LRB-00289656, F, 71 years and older, pharmacist	flucloxacillin of brand Mylan, 500mg 4 times per day, jaw infection	acetylsalicylic acid, clomipramine omeprazole, darbeoetin alfa	oropharyngeal pain, pharynx strangled sensation of	circa 5 minutes after administration of the 2 <sup>nd</sup> capsule, drug withdrawn, recovering a few hours after withdrawal
T, NL-LRB-244090, F, 50-60, consumer	flucloxacillin, 500mg 4 times per day, postoperative wound infection	fusidic acid (cream)	throat pain, respiration labored	1 day; after administration of the 4 <sup>th</sup> tablet, drug withdrawn, not recovered
U, NL-LRB-00358369, F, 50-60 years, consumer	flucloxacillin of brand Mylan, 500mg 4 times per day, erysipelas		oral pain*, lip burning sensation of, nausea, headache, diarrhoea	30 minutes, not applicable, recovered

V, NL-LRB-111061, F, 40-50, pharmacist	flucloxacillin, 3dd1000mg, foot infection  clindamycin, unknown, foot infection	macrogol 4000, oxazepam, dexamethasone, levetiracetam, acenocoumarol, esomeprazole	oral pain*	5 minutes, both drugs withdrawn, unknown
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Additional information on cases

A: described as if the oesophagus was on fire.

B: burning sensation of oesophagus and stomach. It seemed like the capsule dissolved too quickly. According to the consumer, it was stated that the capsule should be taken with half a glass of water. But when using half a glass of water, it felt like the capsule was stuck to the oesophagus and the shell of the capsule dissolved, resulting in a burning sensation. After administration with a big glass of water, the event did not reoccur.

C: the pain lasted for several hours after administration

D: burning sensation of oesophagus and stomach, lasting for at least 15 minutes. The patient was treated with pantoprazole 40mg. One day the patient forgot the pantoprazole, after which the complaints returned immediately.

F: terrible oesophageal pain after administration of flucloxacillin. The severity of the burning pain fluctuated.

G: felt like the tablet was stuck in the throat and caused a painful wound. In the past, when the patient used flucloxacillin, oesophageal pain (and coughing and burping) also occurred as adverse events.

H: described as burning sensation of the oesophagus.

I: burning pain of oesophagus and stomach. The patient was treated with ranitidine.

J: burning pain felt like pyrosis. The patient was treated with calcium carbonate/ magnesium carbonate (Rennie®) and milk. The events reoccurred every time after taking a new capsule. The patient felt it burning through his entire gastrointestinal tract.

K: described as a local etching effect of flucloxacillin capsules. Two capsules were taken in the evening with a little amount of water. After administration, the patient laid down and woke up several hours later due to pain retrosternal. The patient took some milk and was treated with omeprazole and sucralfate.

L: burning sensation in throat and chest, lasting for 30 minutes. The patient took the capsules with water 1 hour before a meal or 2 hours after a meal.

M: the patient had difficulty swallowing food the whole day. The complaints occurred particularly in the morning. Due to the complaints, the patient did not finish the last day of her treatment.

N: the burning sensation in throat diminished after drinking a lot of water and raising the headboard of the bed.

P: described as an annoying feeling in the throat when breathing.

Q: described as mild throat pain.

R: in the past, the patient used flucloxacillin (Floxapen®) and experienced no adverse event.

S: described as sharp pain in throat and oesophagus and a constricted sensation, resulting in swallow difficulty.

T: the pain was treated with ibuprofen (1 tablet) and the patient switched to another antibiotic.

U: painful and irritated palate and tongue and burning sensation of lips. The patient was treated with a non-specified stomach protector. The first day, the patient took the capsules according to the intake instruction in the leaflet. Since the second day, the patient took the stomach protector first and then the capsules with water or juice. The patient did not take eating times into account. The capsules were not opened.

V: described as a burning and tingling sensation in mouth which lasted for circa 10 minutes. Medical history included emphysema, COPD, pulmonary carcinoma, brain metastasis, chemotherapy and radiation therapy.

## Other sources of information

### SmPC

The intake instructions described in the Dutch SmPCs of flucloxacillin differ from each other. All SmPC's of flucloxacillin capsules state that the absorption of flucloxacillin is influenced by taking food simultaneously. Therefore, flucloxacillin should be taken on an empty stomach, for example 1 hour before or 2 hours after a meal [5-7]. In addition, the SmPC of brand Apotex and the SmPC and patient information leaflet of brand Mylan indicate that the patient should place the capsule on the back of tongue and swallow the capsule with a lot of water (preferably a full glass) [5,7,8]. In contrast to the SmPC, the patient information leaflet of brand Apotex, does not mention the specific intake instruction with a lot of water [9]. Furthermore, the SmPC and patient information leaflet of brand Aurobindo and the patient information leaflet of brand Eureco-Pharma (parallel product) also lack the specific instruction about taking the capsule with plenty of water [6,10,11].

### Website [www.apotheek.nl](http://www.apotheek.nl)

This Dutch website is an initiative of the Royal Dutch Pharmacists Association. This website provides clear information to patients. Regarding flucloxacillin, this website instructs to take the capsules with half a glass of water or other drink [12].

### Website [www.meldpuntmedicijnen.nl](http://www.meldpuntmedicijnen.nl) (IVM)

On this website patient can share their experiences with medicines. Between April 14<sup>th</sup> 2019 and July 26<sup>th</sup> 2019 five patient described comparable complaints to the reports Lareb received, like oesophageal pain, a burning sensation and the feeling like the capsule was stuck in the throat [13].

### Databases

Table 2. Reports of oesophageal related pain associated with the use of flucloxacillin in the Lareb, WHO and Eudravigilance database (only shown when 3 reports or more were available) [14, 15]

Database	Drug	ADR	Number of reports	ROR (95% CI)
Lareb	flucloxacillin	oesophageal pain	7	18.9 (8.8 – 40.6)
	flucloxacillin	burn oesophageal	3	20.1 (6.3 – 64.5)
	flucloxacillin	throat irritation	5	3.9 (1.6 – 9.5)
	flucloxacillin	oropharyngeal pain	4	1.2 (0.5 – 3.2)
WHO*	flucloxacillin	oesophagitis	6	1.1 (0.5 – 2.4)
	flucloxacillin	oesophageal pain	15	8.9 (5.4 – 14.8)
	flucloxacillin	burn oesophageal	4	10.0 (3.8 – 26.8)
	flucloxacillin	throat irritation	29	1.6 (1.1 – 2.3)
	flucloxacillin	oropharyngeal pain	20	0.6 (0.4 – 0.9)
Eudravigilance*	flucloxacillin	oral pain	9	1.2 (0.6 – 2.4)
	flucloxacillin	oesophagitis	3	0.4 (1.3 – 4.0)
	flucloxacillin	oesophageal pain	8	4.9 (9.8 – 19.7)
	flucloxacillin	throat irritation	15	1.4 (2.4 – 4.0)
	flucloxacillin	oropharyngeal pain	8	0.3 (0.7 – 1.3)
	flucloxacillin	oral pain	5	0.7 (1.6 – 4.0)

\*The WHO and Eudravigilance data include the number of reports of Pharmacovigilance Centre Lareb

### Prescription data

Table 3. Number of users of flucloxacillin [16]

Drug	2014	2015	2016	2017	2018
flucloxacillin	290,260	287,690	306,540	308,000	322,810

### *Mechanism*

The oesophageal complaints could be caused by either a mechanic effect, where the capsule does not sink well in the oesophagus, or a direct toxic effect of flucloxacillin itself on the oesophagus. Since flucloxacillin has a regular capsule size 2, a mechanic cause for the complaints is less likely [7]. Furthermore, inadequate intake instructions could play a role for the oesophageal pain complaints in the patients using flucloxacillin, since some reporters described a relation with too little fluid intake. However, since Lareb also received two reports in association with the Floxapen® oral suspension of flucloxacillin, a direct harmful effect of flucloxacillin itself seems more plausible. In addition, the received reports of flucloxacillin concern at least two brands (Floxapen® which contains no further excipients [1] and flucloxacillin Mylan®) which also indicates that flucloxacillin itself causes the complaints and not an excipient.

### **Discussion and conclusion**

Pharmacovigilance Centre Lareb received 22 reports of oesophageal related complaints of pain associated with the use of flucloxacillin. The complaints were reported as oesophagitis, oesophageal pain, oesophageal burn, throat irritation, oropharyngeal pain or oral pain. Remarkably, 13 patients specifically described a burning type of pain in the oesophagus or throat. Six patients took medication for their complaints. Five of them were treated with a proton pump inhibitor, H2-receptor blocker, antacid, mucosal protective agent and/or a non-specified stomach protector, which indicates the severity of the complaints. In addition, seven patients recovered or were recovering after withdrawal of flucloxacillin (including 3 reports of which the action was not applicable; suggesting the treatment was finished). In most reports, the time to onset was short after starting with flucloxacillin or after administration of a capsule, suggesting a direct association between the administration of flucloxacillin and the start of the oesophageal pain. Possibly, these events are related to the amount of fluid with which flucloxacillin was administered. However, in only two reports information about the used amount of fluid was available. Furthermore, the two reports concerning Floxapen® argue against this theory and support a harmful effect of flucloxacillin itself.

Attention for this association is warranted, including the intake instructions.

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*This signal has been raised on March 5, 2020. 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.cbq-meb.nl](http://www.cbq-meb.nl)*