

## Omeprazole and erectile dysfunction – an update

### Introduction

Omeprazole (Losec®) belongs to the class of proton pump inhibitors (PPIs) which strongly reduce gastric acid secretion by the parietal cell [1]. It has been registered since November 1988 and is indicated for use in gastroduodenal ulcer disease, acid relate dyspepsia, reflux-oesophagitis or reflux symptoms and in Zollinger-Ellison's syndrome [1,2].

Omeprazole is available as capsules (10, 20, and 40 mg), and also as MUPS (Multiple Unit Pellet System) tablets (10, 20, and 40 mg). Other PPIs available on the Dutch market are esomeprazole, lansoprazole, pantoprazole and rabeprazole [3].

Normal erectile function requires interactions among vascular, neurologic, hormonal and psychological systems [4]. Common causes of erectile dysfunction concern abnormalities in one of these systems [4,5] and mainly affects men older than 40 years [5]. In addition to age, the best predictors of erectile dysfunction are diabetes mellitus, hypertension, obesity, dyslipidemia, cardiovascular disease, smoking and medication use [4]. Drug that are associated with the onset of erectile dysfunction include antihypertensives, antidepressants, antipsychotics, antiandrogens and recreational drugs [6].

In Quarterly Report 2006-4, the Netherlands Pharmacovigilance Centre Lareb described erectile dysfunction associated with omeprazole [7]. This report gives an update of reports and literature about this association.

### Reports

In the period from July 21th 1992 until June 9<sup>th</sup> 2015, the Netherlands Pharmacovigilance Centre Lareb received seventeen reports of erectile dysfunction with the use of omeprazole [7]. The details of these reports are presented in table 1.

Table 1. Reports of erectile dysfunction associated with the use of omeprazole [7]

SRT ID Sex, age source	Drug, daily dose, indication	Concomitant medication	Suspected adverse drug reactions	Time to onset, action with drug, outcome
A. 5998 M, 61-70 years specialist doctor	omeprazole 20mg unknown use		erectile dysfunction libido decreased	2 weeks, drug withdrawn outcome unknown
B. 17769 M, 51-60 years general practitioner	omeprazole 20mg 2dd1 gastric ulcer tetracycline 250mg gastric ulcer bismutoxide 120mg metronidazole 250mg gastric ulcer	cimetidine	erectile dysfunction	omeprazole 3 days drug withdrawn bismutoxide 1 day drug withdrawn metronidazole drug withdrawn tetracycline 1 day drug withdrawn outcome unknown
C. 21907 M, 51-60 years general practitioner	omeprazole 10mg 1dd1 reflux esophagitis		erectile dysfunction	latency unknown drug withdrawn recovered
D. 26932 M, 41-50 years general practitioner	omeprazole 20mg 2dd1 reflux esophagitis	budesonide betamethasone miconazole	erectile dysfunction	unknown days drug withdrawn recovering
E. 28421 M, 41-50 years general practitioner	omeprazole 40mg 1dd1 celiprolol 200mg	amlodipine	erectile dysfunction	omeprazol 10 Weeks Drug withdrawn Outcome Unknown celiprolol latency unknown drug withdrawn not recovered

F. 31733 M, 51-60 years general practitioner	omeprazole 40mg 1dd1 diaphragmatic hernia		erectile dysfunction	1 month dose reduced recovering/resolving
G. 39136 M, 41-50 years specialist doctor	omeprazole 40mg 1dd1 dyspepsia		erectile dysfunction	2 Weeks drug withdrawn recovered/resolved
H. 50499 M, 41-50 years general practitioner	omeprazole 20mg unknown use dyspepsia		erectile dysfunction	1 day dose not changed recovering/resolving
I. 56154 M, 41-50 years general practitioner	omeprazole 10mg unknown use gastroesophageal reflux		erectile dysfunction	3 weeks drug withdrawn outcome unknown
J. 58187 M, 61-70 years pharmacist	omeprazole 20mg unknown use	colchicine diclofenac acenocoumarol	erectile dysfunction	latency unknown action Unknown outcome unknown
K. 99336 M, 61-70 years consumer	omeprazole 20mg 1dd1 barrett's esophagus		erectile dysfunction	unknown days dose not changed not recovered/not resolved
L. 103570 M, 61-70 years pharmacist	omeprazole 40mg 1dd1 dyspepsia		erectile dysfunction dandruff	2 months drug withdrawn recovered/resolved
M. 118053 M, 51-60 years general practitioner	omeprazole 40mg 2dd1 barrett's esophagus	metformine tolbutamide simvastatin	erectile dysfunction	2 weeks dose not changed outcome unknown
N. 123625 M, 61-70 years general practitioner	omeprazole 40mg 1dd1 dyspepsia	fluticasone	erectile dysfunction visual acuity reduced rash presyncope	6 months drug withdrawn recovering/resolving
O. 168492 M, 21-30 years pharmacist	omeprazole 40mg 1dd1 stomach discomfort		erectile dysfunction	1 week drug withdrawn recovered/resolved
P. 184511 M, 21-30 years general practitioner	omeprazole 40mg 1dd1 gastric disorder		erectile dysfunction	1 day drug withdrawn recovered/resolved
Q. 199382 M, 21-30 years consumer	omeprazole 20mg 1dd1 reflux oesophagitis		erectile dysfunction	4 weeks after start (after a dosage increase), dose not changed not recovered/not resolved

The latency for the described cases varied from one day to six months, in twelve cases the erectile dysfunction presented <one month after start of omeprazole.

For three cases the outcome is unknown (A, I and J). There are eight positive dechallenges (C, D, F, G, L, N, O and P). Case D describes a positive rechallenge and case C describes a similar reaction to another PPI lansoprazole.

Two reports have multiple suspect drugs (B and E). In case B, omeprazole was used for three days and then the other suspect drugs were started at the same moment and all suspect drugs were withdrawn at the same moment. For the concomitant medication cimetidine erectile dysfunction is also a labelled ADR [8]. Cimetidine was started almost two months later than the other suspect drugs, making it an unlikely cause of the ADR. In case E first celiprolol was withdrawn where after the erectile dysfunction worsened, then omeprazole was withdrawn and the patient started to use ranitidine that is associated with impotence as well [9]. The outcome is unknown. Concomitant medication amlodipine is known to cause erectile dysfunction as well [10], the date this concomitant was started is unknown. Confounding factors were known for three patients (F, H and M). These include smoking (F)

depression (H) and diabetes (M). For case H the reporter mentioned the erectile function problems decreased after withdrawal of omeprazole.

The erectile dysfunction was treated in three patients (F, M and L). Two patients were treated with sildenafil (F and M) and one patient with a homeopathic formulation (L).

Time to recover was reported in three cases (G, O and P) and varied from <2 days to >2 weeks.

For three patients the dose of omeprazole was not changed (K, M and Q). In Case K and Q the patient did not recover, in case M the patient was treated with sildenafil, but the outcome is unknown. For case Q the reporter mentioned the complaints started after a dose increase of omeprazole (10 to 20 mg).

Three cases (O, P and Q) concern young men who do not have any known risk factors for erectile dysfunction.

## Other sources of information

### SmPC

Erectile dysfunction has not been described in the Dutch SmPCs of omeprazole tablets, capsules or MUPS [1,11], nor in the US SmPC [11]. It is also not labeled for esomeprazole, the S-isomer of omeprazole [12], the US SmPC of esomeprazole mentions impotence with an incidence <1% [13]. For other proton pump inhibitors impotence is only mentioned for lansoprazole in both the Dutch and the US SmPCs [14,15].

### Literature

Several studies describe case reports of erectile dysfunction associated with the use of omeprazole. Carvajal et al. [16] describe three patients who developed impotence, unilateral gynaecomastia or anorgasmia in relation to omeprazole treatment. In 1992 Lindquist et al. [17] discussed 15 cases of impotence during the use of omeprazole reported at the WHO. In most cases the complaints started within a few days after start and in 7 cases positive dechallenge occurred. In 2012 the *arznei-telegram* also published a case of erectile dysfunction in a 51 year old man several weeks after start of esomeprazole, the S-isomer of omeprazole. His sexual function normalised after discontinuing the proton pump inhibitor [18].

Rosenshein et al. [19] describe a case report of loss of libido in a 42 year old women that had a heterozygous polymorphism for CYP2C19\*2 variant (\*1/\*2), the enzyme that metabolizes omeprazole. The loss of libido was related to a lowered testosterone concentrations of her serum. She experienced a positive dechallenge and her testosterone levels increased after withdrawal of omeprazole as well.

### Databases

Table 2. Reporting odds ratios of omeprazole and erectile dysfunction in the database of the Netherlands Pharmacovigilance Centre Lareb and the WHO [7,20,21]

Drug and ADR	Number of reports	ROR (95% CI)
Omeprazole and Erectile dysfunction	Lareb: 17	2.1 (1.3-3.4)
	Eudravigilance: 35	1.40 (1.0 – 2.0)
	WHO: 225	2.0 (1.7-2.3)

### Prescription data

Table 3. Number of omeprazole users in the Netherlands between 2010 and 2014 [22]

Drug	2010	2011	2012	2013	2014
Omeprazole	1,596,000	1,690,000	980,240	1,029,000	1,078,000

### Mechanism

A suggested mechanism for omeprazole to cause erectile dysfunction is the interference with the metabolism of hormones. Omeprazole was seen to induce the enzyme CYP3A4, in high serum levels (high dosed or in a specific population with a polymorphism for poor omeprazole metabolism). A role of CYP3A4 had been postulated, converting testosterone to beta-hydroxytestosterone. Increased CYP3A-mediated testosterone metabolism decrease levels of testosterone in some patients [17,19,23,24]. Deepinder et al. [25] reviewed drugs that potentially cause gynecomastia. They suggest

omeprazole at high concentrations has some properties of inhibiting the estradiol catalytic enzyme, cytochrome P450 in the liver. This can lead to inhibition of estradiol metabolism possibly causing elevated estrogen/androgen ratio leading to breast tissue growth. The elevated ratio might also influence erectile function. Gynaecomastia is labelled in the SmPC of omeprazole [1].

Another hypothesis is that omeprazole directly interacts with and significantly inhibits human dimethylargininase (DDAH) activity, thereby increasing endothelial and serum asymmetric dimethylarginine (ADMA) levels. The increase in ADMA levels would be anticipated to impair vascular nitric oxide synthase activity, to increase oxidative stress, to reduce vasodilator function in vitro [26]. Since nitric oxide has a role in erectile function, this could be a mechanism omeprazole causes erectile dysfunction. Contradictory, other studies suggest omeprazole to alter the function of calcium channels and thereby effectively inhibit the spontaneous contraction of the corpus cavernosum and induce relaxation of corporal smooth muscle precontracted in vitro [27,28].

### Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 17 reports of erectile dysfunction associated with the use of omeprazole. Erectile dysfunction was mostly presented within 1 month after start of omeprazole. The Lareb case reports include eight positive dechallenges and two positive rechallenges. An additional four cases were reported for esomeprazole, the S-isomer of omeprazole. The association is supported by cases described in literature. Also, the association is supported by a possible pharmacological mechanism and a statistically significant disproportionality in the databases of Lareb and WHO. The age of the patients could be a possible confounder in this association, however the last three reports Lareb received were about young men (two 26 year-olds and one 28 year-old) and no other causes for the erectile dysfunction were described in the reports. In the last received report (Q), the patient mentions the reaction occurred after a dosage increase and the erectile dysfunction led to a loss of sex drive.

In conclusion, Lareb has received several new cases on erectile dysfunction associated with omeprazole in addition to those cases described in Quarterly Report 2006-4. Among the new cases are also young patients in their twenties. Based on the available information this could be a signal for omeprazole and further investigation of the information of the marketing authorization holders and other national centres is needed to strengthen the signal.

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