

## Omeprazole and discolouration of the gastric content

### Introduction

Omeprazole (Losec<sup>®</sup>), a substituted benzimidazole, belongs to the class of proton pump inhibitors (PPIs) which strongly reduce gastric acid secretion by the parietal cell [1]. PPIs are acid-activated prodrugs that require gastric acid secretion to be converted to the active sulfenic acids or sulfonamides [2]. The pharmacological mechanism of action is based on irreversible inhibition of the H<sup>+</sup>/K<sup>+</sup>-ATP-ase enzyme (the so-called proton pump) in the parietal cell of the stomach mucosa. Both the basal and the stimulated gastric acid secretion are dose dependently inhibited [1-3].

Omeprazole 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* [4].

Other PPIs available on the Dutch market are esomeprazole, lansoprazole, pantoprazole and rabeprazole [3].

The use of omeprazole in children under the age of 1 year is off-label. Nevertheless, omeprazole is regularly used by paediatricians to treat reflux symptoms in this group of patients. Omeprazole is not available in a liquid dosage form and patients who have difficulties swallowing, require extemporaneous liquid dispersion of solid dosage forms of omeprazole. According to the Dutch National Formulary for Children [5] the granules in omeprazole capsules can be dispersed in a slightly acid liquid (e.g. fruit juice, yoghurt or buttermilk). Tablets contain enteric-coated granules and can be disintegrated in water, and subsequently administered by probe.

The stability of omeprazole is pH dependent. Below pH 4 omeprazole rapidly degrades to a dark purple compound [6]. The available dosage forms of omeprazole contain an enteric coating that prevents the release of the drug before it reaches the intestine.

The current observation describes the association between omeprazole and gastric content discolouration.

### Reports

On August 6<sup>th</sup> 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports of gastric content discolouration associated with the use of omeprazole. The reports are listed in Table 1.

Table 1. Reports of gastric content discolouration associated with the use of omeprazole

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A 142718 M, 0 – 1 years general practitioner	omeprazole od 10mg gastroesophageal reflux		gastric content discoloured	1.5 month discontinued recovered
B 104943 M, 0 – 1	omeprazole od 10mg		gastric content discoloured	7 hours

years pharmacist	gastroesophageal reflux	eczema	1 day discontinued recovered	<i>Nederlands Bijwerkingen Centrum Netherlands Pharmacovigilance Centre</i>
C 103536 M, 0 – 1 years pharmacist	omeprazole od 10mg gastroesophageal reflux	gastric content discoloured eczema	7 hours  1 day discontinued recovered	
D 76097 M, 0 – 1 years pharmacist	omeprazole od 10mg gastroesophageal reflux	gastric content discoloured	5.5 weeks no change not recovered	

od = once a day

In case A omeprazole capsules were opened and the coated particles were inserted in the buccal space. After 45 days of treatment a purple discolouration of the sputum was reported. This case was strengthened by a photo of the purple discolouration of the sputum. After discontinuation of omeprazole the purple discolouration of the sputum disappeared.

Case B and C describe twins who were treated with omeprazole tablets. Before administration the tablets were dissolved in water. Seven hours after the first intake both of the twins spit out red granules. The twins also suffered from eczema located on the chest. After discontinuation of omeprazole the presence of red granules in the sputum disappeared. Eczema was recovering at the moment of reporting. These cases were also strengthened by a photo.

In case D the mother of the patient mentioned purple granules in the sputum of the patient 5.5 weeks after treatment with omeprazole capsules. The method of administration was not mentioned in this report. Considering the age of the patient, it is presumable that the capsule was opened before intake.

Three of the four cases describe a positive dechallenge. No rechallenge was performed in these cases.

Although sputum discolouration was reported as the reaction, it is likely and plausible that sputum discolouration was confused with the reflux of discoloured gastric content.

## Other sources of information

### SmPC

None of the Dutch SmPCs of omeprazole mention gastric content discolouration as a possible ADR [7-9]. The US SmPCs of Prilosec<sup>®</sup> and Zegerid<sup>®</sup>, both available as powder for oral administration, mention faecal discolouration as a possible adverse reaction. Gastric content discolouration is not mentioned [10,11].

### Literature

An association between omeprazole and gastric content discolouration has been previously published as a short report. Tuleu et al. [12] report the appearance of dark purple coloured 'poppy seed'-like structures found in the aspirated stomach contents and faeces of a 3-month-old infant receiving an omeprazole liquid via nasogastric tube, prepared by dispersing an omeprazole tablet (10 mg MUPS<sup>®</sup>) in water.

Beers et al. [13] report a case of a three-week-old boy who developed purple gastric juice discolouration after receiving omeprazole. Omeprazole capsules were opened and the coated particles were inserted in the buccal space, immediately followed by breastfeeding. After five weeks of treatment the boy's refluxed gastric

juice contained purple particles. The case was supported with a photo. The omeprazole administration regime was changed. After administration in the buccal space the boy sucked a dummy teat for a few minutes in order to swallow the administered particles. Consequently he was breastfed. The purple particles were then observed only twice in a couple of months.

## Databases

On August 6<sup>th</sup> 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports of gastric content discolouration in association with omeprazole. The reporting odds ratio (ROR) was 83.7 (95% CI: 20.9 – 334.9).

On August 6<sup>th</sup> 2013, the WHO database of the Uppsala Monitoring Centre contained 5 reports of gastric content discolouration associated with omeprazole. Three of the reports are from the Netherlands (one report is probably missing due to incorrect duplicate detection of the report concerning twins). The reporting odds ratio (ROR) was 0.9 (95% CI: 0.4 – 2.2), which is not disproportional.

On August 13<sup>th</sup> 2013, the Eudravigilance database contained 5 reports of gastric content discolouration associated with omeprazole. Four of the reports are from the Netherlands. The reporting odds ratio (ROR) was 3.3 (95% CI: 1.4 – 8.0), which is disproportional.

Table 2. Reports of gastric content discolouration associated with omeprazole in the databases of Lareb, WHO and EMA

Drug	Number of reports	ROR (95% CI)
Omeprazole	Lareb: 4	83.7 (CI 20.9 – 334.9)
	WHO: 5	0.9 (0.4 – 2.2)
	EMA: 5	3.3 (1.4 – 8.0)

## Prescription data

The number of patients using omeprazole in the Netherlands is shown in Table 3 [14].

Table 3. Number of patients using omeprazole in the Netherlands between 2008 and 2012

	2008	2009	2010	2011	2012
Omeprazole	1,220,000	1,376,000	1,596,000	1,690,000	676,600

## Mechanism

The postulated mechanism by which PPIs can cause gastric content discolouration is by degradation of omeprazole in the acidic stomach. Normally the enteric-coated pellets prevent omeprazole from degradation in the acidic stomach. It seems that dispersion in water or insertion of omeprazole coated particles in the buccal space can lead to degradation of the coating. In combination with delayed gastric emptying in critically ill children, this will lead to degradation when omeprazole contacts with the gastric acid. Degradation of omeprazole leads to dark purple discolouration of the drug, resulting in a reduced bioavailability and reduced effectiveness of the treatment [6,12].

Some literature reports suggest to avoid acid-induced degradation by preparing omeprazole in alkaline sodium bicarbonate solution. This will increase stomach pH sufficiently to prevent degradation of unprotected omeprazole. Nevertheless the neutralising and buffering capacity of bicarbonate has never been demonstrated [12]. Zegerid<sup>®</sup>, available in the US as powder for oral suspension, contains omeprazole and sodium bicarbonate. It is advised to take Zegerid<sup>®</sup> suspension on an empty stomach at least one hour before a meal [11]. Prilosec<sup>®</sup> powder for oral suspension, contains omeprazole magnesium [10].

Others suggest to use a tasty acidic (semi-)liquid product to decrease dissolution of the enteric coat and reduce oral retention [13].

## **Class effects**

Beside the described cases of gastric content discolouration associated with omeprazole, the Lareb database contains 1 case of gastric content discolouration with esomeprazole. This report from a paediatrician concerns a female aged 1 month, with spitting up purple granules following administration of esomeprazole for gastroesophageal reflux with a latency of 13 days after start. Initially it was thought there was blood in reflux. The drug omeprazole was withdrawn. The gastric content discolouration disappeared after 8 days. Concomitant medication was not reported. According to the reporter a colleague had experienced the same situation before.

## **Discussion and conclusion**

Lareb received four reports of gastric content discolouration associated with the use of omeprazole in young infants who require extemporaneous liquid dispersion of solid dosage forms of omeprazole. Three cases describe a positive dechallenge. The Lareb and Eudravigilance databases showed significant disproportionality of gastric content discolouration associated with the use of omeprazole. Nevertheless, the vast majority of the Eudravigilance and the WHO cases consists of reports from the Netherlands. Discolouration of the gastric content is not described in the SmPCs of omeprazole.

In addition to gastric content discolouration, the Lareb database also contains a report about purple discolouration of the faeces in a male aged 5 months, who was treated with omeprazole suppositories. The medical history of the patient indicates that he had possible cow's milk allergy and reflux esophagitis. Concomitant medication was macrogol. After withdrawal of omeprazole the patient recovered.

In contrast to young infants, most adults do not require an adjustment of the solid dosage form of omeprazole. Together with the fact that adults expectorate gastric content less often than young infants this may explain why the Lareb database does not contain any reports of gastric content discolouration in adults.

Clinicians should be aware of the possibility of gastric content discolouration and related reduced bioavailability of omeprazole when administered to infants using extemporaneous liquid dispersion of solid dosage forms of omeprazole. Although the red/purple discolouration itself will not be harmful it can decrease the effectiveness of the treatment. Patients should be informed about the possibility of gastric content discolouration during treatment with omeprazole.

An association between extemporaneous liquid dispersions of solid dosage forms of omeprazole administered to infants and gastric content discolouration is likely.

- Gastric content discolouration should be mentioned in the SmPC of omeprazole when administered by extemporaneous liquid dispersions of solid dosage

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*This signal has been raised on 31 October 2013. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB [www.cbgmeb.nl/cbg/en/default.htm](http://www.cbgmeb.nl/cbg/en/default.htm) or the responsible marketing authorization holder(s).*