Iomax® and adulteration

Introduction
Iomax® is an illegal product in the Netherlands, without a marketing authorization. The product can be bought online. Iomax® was developed as a successor to Ionamin Forte®, a very popular weight loss drug product approved in 1959 by the Food and Drug Administration (FDA). Ionamin Forte® was withdrawn from the market due to the side effects. Iomax® was not approved by the FDA and EMA. This is a potential risk, because it may contain components that may not normally be allowed. The active ingredient of Iomax® should be phentermine, unfortunately it often contains other ingredients such as speed (1). Generic phentermine is still available by itself in most countries, including the US. Complaints about Iomax® have been known for several years. The National Poisons Information Center (NVIC) has received serious complaints from people who use Iomax® as a slimming aid (2). In 2013 NIVC and the Netherlands Food and Consumer Product Safety Authority (NVWA) have issued a warning about the risks of this product (3). However, the recently received report by Lareb shows that the product is still illegally used.

Report
Pharmacovigilance centre Lareb received in October 2020 one serious report of the suspected adverse drug reaction (ADR) related to the use of Iomax®.

Case NL-IRB-00417663
This serious spontaneous report sent by a specialist doctor concerns a female aged 30-40 years, who used Iomax® for weight loss. After an unknown period she started to behave strangely. Therefore a CT-scan of cerebrum was made in the hospital. This revealed a subaracnoid hemorrhage. It is unknown for how long the slimming supplement Iomax® was used. The neurologist suspects a reversible vasocnstrictive syndrome have caused the hemorrhage. No other medication, beside the Iomax® was reported.

Sample Analysis
2 samples of the supplement used by the patient were collected and sent to the National Institute for Public Health and the Environment (RIVM) for analysis. Analysis by UPLC-QTOF-MS/MS revealed 300.6 mg of amphetamine and 326,4mg caffeine per gram powder in sample 1 and 335.4 mg of amphetamine and 303.6 caffeine in sample 2. In addition, the contaminant was determined: di-(beta-phenylisopropyl)amine (DPIA). DPIA is a common adulterant of amphetamine and being a close analogue to amphetamine could therefore have similar pharmacological activity (4, 5).

Table 1 Products received with (in gray) the pharmacologically active substances found therein.

<table>
<thead>
<tr>
<th>Order</th>
<th>Product description</th>
<th>Identity of substances found</th>
<th>Amount / content</th>
</tr>
</thead>
<tbody>
<tr>
<td>A181501</td>
<td>White powder in a transparent bag with Iomax sticker.</td>
<td>Caffeïne¹, Amphetamine¹, di(β-phenylisopropyl)amine³</td>
<td>326.4 mg/gram², 300.6 mg/gram², Not measured</td>
</tr>
<tr>
<td>A180502</td>
<td>Capsules with white powder</td>
<td>Caffeïne¹, Amphetamine¹, di(β-phenylisopropyl)amine³</td>
<td>303.6 mg/gram², 335.4 mg/gram², Not measured</td>
</tr>
</tbody>
</table>

¹ The presence of the reported compound has been confirmed with a reference standard. ² The content is determined semi-quantitatively (± 20%). ³ A strong indication of the presence of the substance, so the presence has not been confirmed with a reference standard.

The capsule of the first sample (sample1) got damaged during the sending, therefore the powder/content from the capsule was analysed. The analyse results are therefore given as mg active substance /g powder.
Product information Iomax®
Information found on the website iomax.nl do not mention the active substance in the product, it is just classified as: “strong fat burner which ensures that you can lose an average of 6 kg per 3 weeks. Iomax reduces your appetite & provides a lot of energy during the day.”

Mechanism
Presuming that the supplement Iomax® resembles the product Ionamin®, the information from the product label of Ionamin®, with the active substance phentermine, has been consulted for the mechanism. Actions include central nervous system stimulation and elevation of blood pressure. It has not been established, however, that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions, or metabolic effects may be involved. Amines cause vasoconstriction and a rise in blood pressure due to the release of noradrenaline from sympathetic neurones and that they may also exert direct vascular effects independent of a noradrenergic mechanism.

ADRs of phentermine
The Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Agency concluded in 1999 that there are concerns about the safety profile of phentermine-containing medicines, in relation to the potential risk of heart valve defects in monotherapy with phentermine, the risk of primary pulmonary hypertension and other serious ADRs of a cardiovascular nature or ADRs related to the central nervous system such as dependence.

ADRs of amphetamine
Anorexia, weight loss and insomnia are predictable and frequent adverse events associated with the use of amphetamine-based medications. Other adverse events evoked by the amphetamines include nausea, vomiting, abdominal cramps, increases in blood pressure and heart rate and possibly also the exacerbation of motor tics. The use of amphetamine can lead to hyperthermia, neurotoxicity, hepatotoxicity, nephrotoxicity and cardiotoxicity. Case-reports of intracranial haemorrhage related to amphetamine and amphetamine-like stimulants have been described in literature.

ADRs of caffeine
The available literature suggests that cardiovascular effects experienced by caffeine consumers at levels up to 600 mg/day are in most cases mild, transient, and reversible, with no lasting adverse effect. The point at which caffeine intake may cause harm to the cardiovascular system is not readily identifiable in part because data on the effects of daily intakes greater than 600 mg is limited.

Other sources of information
The Dutch National Poisons Information Centre (NVIC) received a total of 41 information requests for Iomax® between June 2009 and October 2020. After occasional reports in June 2009, September 2011 and May 2012, the number of incidents increased from November 2012 onwards, rising to seven inquiries in 2013. After the warning issued in 2013, in 2014, no reports were received. But since 2015 the number of received reports increases again each year from two 2015, to seven in 2019 and six until October 2020 (Lareb case not included). The common reported symptoms in those reports were agitation, hypertension, tachycardia, palpititations, headache, chest pain, nausea, vomiting, abdominal pain, sweating; few muscle cramps and dizziness and singe reports of hallucinations, nightmares, liver function disorders, QT time extension, dyspnea, ringing in the ears and dry mouth.

Discussion and conclusion
Dietary supplements are widely available over the counter as well as through the internet. The illegal dietary supplements often contain substances which are not mentioned on the label and may cause serious ADRs. Products intended for losing weight, increasing energy and athletic performance are notorious for this. The recent case report to Lareb concerns a serious suspected ADR of slimming pill Iomax®. The reporting neurologist suspects that the subarachnoid haemorrhage was caused due a reversible vasoconstriction syndrome, possibly triggered due to the use of Iomax®. The sample analysis determined that the pills contain amphetamine, caffeine and also the di-(beta-phenylisopropyl)-amine (DPIA) which is a common adulterant of amphetamine. It is a close analogue to amphetamine and could therefore have a similar effect. Vasoconstriction and intracranial haemorrhage have been previously described with amphetamine and amphetamine-like stimulants.
The Dutch Food and Consumer Product Safety Authority (NVWA) posted a warning against slimming pills with the name Iomax® in 2013 for the public on their website and encouraged users to report ADRs (3).

It is warranted to remind the public again of the potential risks of these types of products.

References

6. website iomax. p. iomax.nl
7. FDA label Ionamin. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/011613s027lbl.pdf

This signal has been raised on March 4, 2021. It is possible that in the meantime other information became available.