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The Swedish Medical Products Agency (MPA) is in violation of the European rules regarding reporting of adverse reactions from ADHD drugs (N06BA)

An investigation has revealed that the Swedish MPA is in violation of the European rules regarding reporting of adverse reactions from ADHD drugs (N06BA), as put forward in the *Guideline on good pharmacovigilance practices (GVP)* from 28 July 2017, revision 2 (1).

The Agency should urgently correct its routines so that they are in accordance with the legal requirements applicable to the competent authorities in Member States.

According to the guidelines (p. 6) the definition of an *adverse reaction* is "a response to a medicinal product which is noxious and unintended", and (under *causality*) the definition of an adverse reaction "implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event". It is further stated that "an adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected". And for regulatory reporting purposes, "if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction".

According to the guidelines (p. 9) *a valid individual case safety report* (ICSR) "should include at least *one identifiable reporter*, *one single identifiable patient*, *at least one suspect adverse reaction*, *and at least one suspect medicinal product*".

Under ***Collection of individual safety reports*** (p. 11) we can read "the system [for this] should also be structured in a way that allows for reports of suspected adverse reactions to be validated … in a timely manner and exchanged between competent authorities and marketing authorisation holders within the legal submission time frame".

In the chapter ***Validation of reports*** (p. 14) we can read about the "four minimum criteria for ICSRs validation". They are:

- **a)** one or more identifiable reporter,
- **b)** one single identifiable patient,
- **c)** one or more suspected substance/medicinal product,
- **d)** one or more suspected adverse reaction.

In the chapter ***Follow-up of reports*** (p. 16) we can read that *a valid individual case safety report (ICSR)* can be *incomplete* and the requirement for the regulatory authority in this case. It is stated: "When first received, the information in suspected adverse reactions reports may be incomplete. *These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases*." (Emphasis added.)

In the chapter ***Submission of individual case safety reports (ICSRs)*** (p. 21) we can read about the submission of valid ICSRs to the EudraVigilance database (European Drug Regulatory Authorities Vigilance database): "The clock for the submission of a valid ICSR starts as soon as *the information containing the minimum criteria* has been brought to the attention of the national or regional pharmacovigilance centre of a competent authority…" (Emphasis added.) It is further stated (p. 41) that *serious* valid ICSRs should be submitted within 15 days and *non-serious* valid ICSRs should be submitted within 90 days.

The Swedish Medical Products Agency (MPA) is, in the case of ADHD drugs, violating these rules in the following way.

When healthcare professionals (in this case psychiatrists) submit an application to the MPA to prescribe a not approved ADHD drug (an "unlicensed medicine") they must clearly state the reasons why already approved drugs cannot be used. This means that psychiatrists must describe that the approved drugs are not having the intended effect and/or *give unacceptable adverse reactions*.

In order to approve applications for the short acting dexamphetamine drug Metamina (unlicensed) or the amphetamine drug Amfetamin (unlicensed) the requirement is also that (more than one) methylphenidate drug, (often) atomoxetine, the lisdexamphetamine Elvanse and the approved dexamphetamine Attentin should have been tried – and, as said, showed not to be working as intended and/or to *give unacceptable adverse reactions*.

For 2018 the MPA reports it has received 61 individual case safety reports (ICSRs) from doctors to its adverse events register, mostly describing the adverse reactions from *one* approved ADHD drug.

At the same time (2018) 22 license applications about Metamina and Amfetamin (approved and not approved) were received from psychiatrists, *clearly describing adverse reactions from approved ADHD drugs.* A*s explained above these adverse reactions did not only concern one ADHD drug but in most cases adverse reactions from three or four different drugs.*

A *comparison* with the reports to the adverse events register shows that *none* of the applying psychiatrists had submitted a *formal* individual case safety report (ICSR) to the adverse events register in 2018 for the adverse reactions described in the license applications.

We can see that the 22 license applications are fulfilling the *minimum criteria* for a *valid* individual case safety report, in that they contain "*one identifiable reporter*, *one single identifiable patient*, *at least one suspect adverse reaction*, *and at least one suspect medicinal product*". They are written with the purpose of getting the MPA to understand the seriousness of the *identified* adverse reactions. They are further written with the purpose of informing the MPA that often *more than three* identified approved drugs had been tried, all with *unacceptable* adverse reactions. As these (more than three) drugs were used and withdrawn (due to the adverse reactions) at *different* times, the formal individual case safety reports (ICSRs) that *should* have been written, at these different times, amount to around 60 reports – the same number of *formal* reports submitted to the MPA for ADHD drugs for the whole of 2018!

According to the guidelines (in chapter *Follow-up of reports*, p. 16) we can see the requirement for the regulatory authority in the case of receiving a valid adverse reaction report that "may be incomplete". In these cases the regulatory authority are supposed to do the following: "These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases." This is however not happening. The MPA is not treating these important reports as valid adverse reaction reports (fulfilling the minimum requirement listed above) and is *not acting* to obtain the necessary additional information.

I hope the information above is helpful for the European Medical Agency (PRAC) in correcting the Swedish MPA and getting its routines to be in accordance with the legal requirements applicable to the competent authorities in Member States.

The first action in this should most definitely be to require a follow-up of the incomplete valid adverse reaction reports described in this report. In order to make it easier to do this, and to get necessary coordination to happen, I have in the attachment given the necessary details about the adverse reactions listed in these 22 cases.

Respectfully submitted

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(1) EMA, Guideline on good pharmacovigilance practices (GVP), Module VI, 28 July 2017, Rev 2, https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf

Attachment

- **a)** one or more identifiable reporter,
- **b)** one single identifiable patient,
- **c)** one or more suspected substance/medicinal product,
- **d)** one or more suspected adverse reaction.

Identifiable reporter	**Identifiable patient** (available in application at the MPA)	**Suspected medicinal product**	**Suspected adverse reaction**
Serrano Toro Alexandra Sahlgrenska Universitetssjukhuset Göteborg	2018-03-20 (Amphetamine)	Concerta Ritalin	Concerta and Ritalin "feelings of unreality"; Ritalin "increased … suicidal thoughts"
Ahnland Marguerite, Psykiatri Lasarettsgatan 1, 88104 Sollefteå	2018-10-02 (Amphetamine)	Attentin	Attentin cannot be titrated upwards due to severe headache

Elverfors Anders, Läkarhuset Södra Vägen 27, 40015 Göteborg	2018-10-13 (Amphetamine)	Methylphenidate Dexamphetamine	"Patient has got a rash from Methylphenidate and Dexamphetamine
Berntsson Anders, Psykiatriska kliniken Sunderby sjukhus, 97180 Luleå	2018-11-30 (Amphetamine)	"Patient tested all medicines on the market … latest Focalin"	"in increasing doses as earlier adverse reactions (palpitation, anxiety, gastro-intestinal problems)"
Faltzis Vasileios, Närpsykiatri Boden Kungsgatan 25, 96161 Boden	2018-01-26 (Metamina)	Medikinet, Equasym, Concerta, Ritalin (depot), Ritalin (fast acting), Elvanse, Strattera, Voxra, Attentin	Medikinet, Equasym, Concerta, Ritalin (depot), Ritalin (fast acting) – "unacceptable adverse reactions (intestinal convulsions, diarrhea, problems with stomach, panic attacks" Elvanse – "increased tiredness" Attentin – "vomitin, diarrhea" Strattera and Voxra – "no real effect"
Lemanczyk Wojciech, Psykiatrimottagningen Parkgatan 19, 79131 Falun	2018-02-09 (Metamina)	Methylphenidate Elvanse Attentin	Methylphenidate – "strong anxiety and depression" Elvanse – "lost effect after a month" Attentin – "better result …but much worse than Metamina …which he earlier has taken on his own"
Lemanczyk Wojciech, Psykiatrimottagningen Parkgatan 19, 79131 Falun	2018-02-23 (Metamina)	Elvanse Attentin	Elvanse – "felt as if paralyzed" Attentin – "some similar experiences"
Severin Annika, Psykiatri Sydväst Röntgenvägen 3, 14152 Huddinge	2018-03-21 (Metamina)	Attentin	Attentin – "adverse reactions when … in adequate dose"
Hogner Maria Psyk klin Vrinnevisjukhuset 60182 Norrköping	2018-08-20 (Metamina)	Ritalin Elvanse Attentin	Ritalin – "in high dose (300 mg/day) developing tolerance" Elvanse – "blurred vision" Attentin – "tired and without energy" "has without doubt an drug dependency iatrogenically created, but no ongoing abuse … has sometimes psychotic symptoms, suspected to be triggered or maintained by the high methylphenidate dose"
Rydén Elenore, S:t Eriksplan, Norra Stockholms Psykiatri, Atlasmuren 3, 11321 Stockholm	2018-06-07 (Metamina)	Methylphenidate Elvanse Attentin	Methylphenidate – "clearly increased anxiety" Elvanse – "difficulties to sleep" Attentin – "effect on ability urinate, dry mouth and blood in stool"
Christensson Martina, Centrummottagningen Psykiatri Nordväst, Centralvägen 16, 17129 Solna	2018-09-10 (Metamina)	All stimulants Attentin	"tested all stimulants available with insufficient effect or adverse reactions" Attentin – "anxiety"
Adler Hans, Fosievägens psykmott, Fosievägen 17, 20502 Malmö	2018-09-25 (Metamina)	Stimulants Attentin	"vomiting on other stimulants including Attentin"
Gorgis Nada, PSS Tideliusgaan 26, 1 tr, 11869 Stockholm (not approved)	2018-01-08 (Metamina)	Concerta, Strattera, Elvanse, Ritalin	Concerta, Strattera – "not having effect" Elvanse – "not feeling good" Ritalin – "palpitation and pressure in the breast"

Arendarska Bozena, Uddevalla sjukhus, 45180 Uddevalla (not approved)	2018-02-09 (Metamina)	Different stimulants Elvanse	”clear adverse reactions especially heavy anxiety at high doses”
Juhnevica Vineta, Allmänpsyk mott2, 721 89 Västerås (not approved)	2018-02-13 (Metamina)	Methylphenidate Elvanse Attentin Voxra	Methylphenidate, Elvanse – “hair loss that cannot be tolerated” Attentin – “similar adverse reactions …also experiencing withdrawal symptoms”
Grantelius Christoffer, Norra Stockholms Psykiatri (Sll) ADHD I S:t Eriksplan, Atlasmuren 3, 11321 Stockholm (not approved)	2017-12-20 (Metamina)	Other stimulants Attentin	Other stimulants – ”glassy-eyed … heavy palpitation. Feel strange in the whole body” “nightmares”
Mircica Cecilia, SU Sahlgrenska, Rullagergatan 5, 415 26 Göteborg (not approved)	2018-03-02 (Metamina)	Concerta, Ritalin, Medikinet, Elvanse, Attentin	Concerta, Ritalin, Medikinet, Elvanse, Attentin – ”mostly anxiety …leading to close to suicide attempt”
Nyqvist Anders, Medicinska habenheten, 35188 Växjö (not approved)	2018-08-15 (Metamina)	Attentin	Attentin – ”with bad effect and adverse reactions”
Hagberg Johan, WeMind Unga Vuxna, Rudsjöterassen 7, 13640 Handen (not approved)	2018-10-17 (Metamina)	Elvanse	Elvanse – ”unacceptable adverse reactions”
Tiger Annika, Danderyds sjukhus, Psykiatri Nordväst, Sturegatan 2, 17231 Sundbyberg, (not approved)	2018-10-25 (Metamina)	Concerta, Ritalin, Elvanse, Attentin	Concerta, Ritalin – ”tiredness, depression” Elvanse – ”chills and tremor” Attentin – ”headache”
Berntsson Anders, Psykiatriska kliniken Sunderby sjukhus, 97180 Luleå (not approved)	2018-11-30 (Metamina)	Available drugs	Available drugs – ”increase of the approved drugs has only led to more of a feeling of entrapment”
Berntsson Anders, PRIMA Vuxenpsykiatri, Vrinnevi sjukhus, Skepparegatan 44, 60245 Norrköping (not approved)	2018-11-11 (Metamina)	Metylfenidat Elvanse Attentin	”Either too high a dose with adverse reactions, or no effect.”