INSTRUCTION

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External partners reporting to Kibion AB of adverse reactions and specific situations	10 2237/06	1 (12)

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Approved by (Function/Name/Sign)	Date	
QA/ Eva Kjaer /	2017-02-28	

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1 PURPOSE

This Standard Operating Procedure (SOP) defines the responsibility of external partners in handling adverse reactions and specific situations occurring in connection with the use of medicinal products, both for which Kibion AB and Kibion GmbH (hereafter called Kibion) is the marketing authorization holder (MAH) and distributor holds the MAH-responsibility.

The purpose of collecting and reporting information from safety reports occurring within external partner's territory is to make regulators and the MAH aware of new, important safety information. Regulations from Regulatory Authorities worldwide require reporting within specified time frames.

2 SCOPE

This SOP applies to adverse reactions and reports of specific situations, hereafter commonly called safety reports. Specific situations are described in section 4.8.

This SOP describes the external partner's responsibilities concerning handling of safety reports. The procedure for case handling at Kibion and TFS is described in SOP 10 5035 (ref 1) and the responsibilities for any employee concerning handling of safety reports is described in SOP 10 5023 (ref 2).

An external partner is a third party outside the organization, which for a payment or a fee provides products and/or services (ref. 3).

3 RESPONSIBILITY

3.1 Revision and maintenance

The PV Responsible holds the responsibility for the revision and maintenance of this SOP. This SOP is revised according to the latest regulations and guidelines and will be revised every third year or when needed.

3.2 Kibion's responsibilities

This SOP shall be distributed to all external partners (see section for distribution list).

The Quality Manager at Kibion is responsible for the distribution of current version to all concerned external partners.

The PV Responsible at Kibion is responsible for collecting safety reports from the external partners and having the primary contact with the external partners during the handling of the safety reports.

The PV Responsible at Kibion is responsible for distributing final CIOMS I forms (ref. 4) to the external partners in countries where Kibion is not the MAH.

It is the responsibility of Regulatory Affairs at Kibion to coordinate PSUR production and to submit PSURs to the Regulatory Authorities (only in countries within EEA) in accordance with SOP 10 5036 (ref 5).

It is the responsibility of Regulatory Affairs at Kibion to coordinate any request from Regulatory Authorities and to submit documentation related to the request (only in countries within EEA) in accordance with SOP 10 5036 (ref 5).

3.3 TFS Trial Form Support AB's responsibility

TFS Trial Form Support AB is responsible for:

Evaluating case reports and requesting follow-up information.

Producing final CIOMS I forms (ref. 4) and distributing them to Kibion and the external partners in countries where Kibion is the MAH.

Submitting adverse reaction reports to EudraVigilance and the Regulatory Authorities in EEA.

3.4 External partner's responsibilities

The External partner's responsibility is governed by each individual QAA agreement. Tasks that the external partner might be responsible for are:

- Having a system for receiving safety reports including retention safety report files. A designated individual shall be in charge of the system.
- Performing an initial review for ensuring that safety report information is legible, relevant and as complete filled in as possible.
- Making every effort to obtain information, as complete as possible, regarding the safety report. Assisting Kibion/TFS to obtain additional information from Customers.
- Reporting safety reports to Kibion (see section 4.3).
- Ensuring Customer satisfaction. Making sure that any claim of information or actions beyond the responsibility of the external partner is forwarded to Kibion, and that relevant information from Kibion or TFS is forwarded to the Customer.
- Submitting adverse reaction reports to the Regulatory Authorities in accordance with local legislation
- Performing screening of literature.
- Informing Kibion about PSUR requirements and information and requests from Regulatory Authorities.
- Submitting PSURs and other safety-related documentation to the Regulatory Authorities.
- Provide translation of safety information from local language to English or vice versa. Translations should always be verified and recorded by a second person.

4 PROCESS

4.1 Receiving safety reports

- The Customers may report adverse reactions and specific situations to an external partner external partner. Upon receipt of a safety report the external partner shall take appropriate action for ensuring Customer satisfaction.
- Use the CIOMS I Form (ref. 4) for filling in the safety report information.
- All safety reports shall at least contain the following minimum information for a valid case:
  - an identifiable patient
  - an identifiable reporter
  - a suspected adverse reaction or specific situation
  - a suspected medicinal product

  If any of the minimum information for a valid case is missing, at least one follow-up attempt should be performed to get the missing information (see section 4.6).
- All safety reports shall be logged and preferably given a unique local registration number. This number is to be added to the CIOMS I Form (ref. 4) and any attachment for assuring traceability.
- Safety report information shall be obtained from the responsible physician/ practitioner preferably on the CIOMS I Form (ref. 4).
- If original data received from Reporter is in other language than English or Swedish, or hard to read, the external partner shall translate the information into English and fill in a new form. Translations should always be verified and recorded by a second person.

4.2 Safety report evaluation

- All technical complaints shall be reviewed for any potential adverse reaction or specific situation.
- All adverse reactions should be checked for seriousness. The result shall be documented in sections 8-12 of the CIOMS I Form (ref. 4).

4.3 Sending safety reports to Kibion

- The CIOMS I Form (ref. 4) shall be completely filled in and dated before sending it to Kibion.
- Make a copy of the report to be kept at the external partner as a local safety report file.
- **All safety reports are to be sent to Kibion in a prompt manner.**
  - ~~**A report with any serious criterion checked for "Yes" shall be forwarded within 24 hours of awareness**~~
  - **All other safety reports shall be forwarded within 5 working days**

4.3.1 Contact information

Send the Adverse Reaction Report Forms either by:

Mail:	Kibion AB Box 303 SE-751 05 UPPSALA Sweden
e-mail:	complaints.kibion@mayoly.com
Phone:	+46 (0) 730622772

All new information (e.g. follow-up reports) or corrections shall be sent to the same address as the initial report and within the same given time-limits.

4.4 Processing at Kibion and TFS

Upon receipt of a safety report Kibion should acknowledge the receipt of the report.

The report will be handled in accordance with SOP 10 5035 (ref. 1). Kibion has contracted the main part of case handling of safety reports to the contract research organization TFS Trial Form Support AB (TFS). TFS will evaluate each case and create a final CIOMS I form (ref. 4) including the assessment of the case.

Distribution of the final CIOMS I form (ref. 4) will be performed according to the following:

- To external partners in countries where Kibion is MAH:
  TFS will distribute the final CIOMS I form (ref. 4) within 10 calendar days from day 0 for serious reports and within 35 calendar days from day 0 for non-serious reports.
- To external partners in countries where Kibion is not the MAH:
  Kibion will distribute the CIOMS I form (ref. 4) within 12 calendar days from day 0 for serious reports and within 40 calendar days from day 0 for non-serious reports.

If Customer or external partner has requested any specific investigation or action, Kibion will give a first answer within 30 days. The reply will be sent to the external partner and applicable information shall be forwarded to the Customer.

4.5 Reporting to Regulatory Authorities

TFS is responsible for the submission of adverse reaction reports to EudraVigilance and the applicable Regulatory Authorities within EEA.

For countries outside EEA, the external partner is responsible for the submission of adverse reaction reports to the Regulatory Authorities in its own territory. This is applicable for all external partners outside EEA, The submission shall be performed in accordance with local legislation.

4.6 Follow-up of safety reports

If any important information is missing for the assessment of the safety report, follow-up to receive additional information will be performed as follows:

- At least one follow-up attempt should be performed for all cases to get the minimum information for a valid case (see Section 4.1). This follow-up will be done by the distributor before the report is sent to Kibion.
- At least two follow-up attempts should be performed for serious adverse reactions and adverse reactions of special interest to get additional information about the case. This follow-up will be done by the distributor after a request has been received from TFS via Kibion.

For non-serious safety reports, usually no follow-up attempts will be performed.

Follow-up information is handled in the same manner as initial reports in accordance with the procedure described in sections 4.1-4.5.

4.7 Medical confirmation of consumer reports

If an adverse reaction reported by a consumer is judged to be serious or of special interest, at least one attempt should be performed to obtain consent from the consumer to contact the consumer's healthcare provider to get the adverse reaction medically confirmed. If consent is given, two attempts should be made to request medical confirmation and further information about the case from the healthcare provider. This follow-up will be done by the external partner after a request has been received from TFS via Kibion.

4.8 Reporting in specific situations

Pregnancy

Reports of the use of any of Kibion's medicinal products during conception or pregnancy must be collected and processed in accordance with sections 4.1 - 4.5. This applies where the embryo or fetus may have been exposed to a medicinal product either through maternal exposure or through transmission of a medicinal product via semen following paternal exposure.

For pregnancy reports from healthcare professionals, follow-up of the outcome of the pregnancy should be sought after the estimated due date by the distributor. At least two follow-up attempts should be performed.

For pregnancy reports reported directly by consumers, attempts to follow up the report via the consumer's healthcare provider should be made after obtaining consent from the consumer. Follow-up with the healthcare provider should take place after the estimated due date and be performed by the distributor. At least one attempt should be performed to obtain consent from the consumer and at least two follow-up attempts should be performed to get outcome information from the healthcare provider.

Pregnancies with abnormal outcomes are classified as serious adverse reactions and must be reported to the Regulatory Authorities in accordance with section 6.2. This especially applies to:

- congenital anomalies or developmental delay in the fetus or the child,
- fetal death and spontaneous abortions,

- adverse reactions in the neonate that are classified as serious.

If a pregnancy report does not include an adverse reaction, e.g. a pregnancy with a normal outcome or a report without outcome data, it shall be collected and processed in accordance with sections 4.1 - 4.4 but it should not be reported to the Regulatory Authorities.

Other specific situations

If any of Kibion's medicinal products is involved in any of the following specific situations, data must be collected and processed in accordance with sections 4.1 - 4.5:

- An adverse reaction in a breastfed child while the mother is exposed to a medicinal product
- Suspected transmission of an infectious agent (classified as serious adverse reaction)
- Lack of effect
- Abuse, overdose, misuse
- Off-label use
- Medication error
- Occupational exposure

If the specific situation does not involve or is not classified as an adverse reaction, it shall be collected and processed in accordance with sections 4.1 - 4.4 but it should not be reported to the Regulatory Authorities.

4.9 Safety reports received directly by Kibion

If a safety report is reported directly to Kibion by a customer, the external partner in the country of origin of the report has to support Kibion and TFS in the management of the report if needed, e.g. translate text in local language into English and collect complementary/follow-up information and medical confirmation.

4.10 Literature, media and conferences

The external partners in countries outside EEA are responsible for screening of the literature. The screening should search for case reports and other relevant safety information for Kibion's medicinal products and the active substances contained in Kibion's products. Any case report found in the literature should be handled in accordance with sections 4.1 – 4.8. Other relevant safety information should be sent to Kibion within 5 working days.

Any other safety reports related to any of Kibion's medicinal products or the active substances contained in Kibion's medicinal products received by the external partners within or outside EEA via medical journals, lay press, on TV, radio, digital media or in a conference should be handled in accordance with sections 4.1 – 4.8.

The external partners are responsible for providing translations of the relevant articles/texts. If the translation cannot be provided within the defined timelines, a summary of the information and the date when the translation will be available must be provided to Kibion.

4.11 Periodic Safety Update Report (PSUR)

The external partner is responsible for informing Kibion about any Periodic Safety Update Report (PSUR) needed for submission in its territory. However, for countries in EEA, the external partner only has to inform Kibion about Periodic Safety Update Report (PSUR) needed in addition to what is stated in the EU Reference Date (EURD) List.

The external partner has to inform Kibion no later than 35 days before data lock point (DLP).

For countries within EEA, Kibion is responsible for the submission of the PSUR to the Regulatory Authorities.

For countries outside EEA, the external partner is responsible for the submission of the PSUR to the Regulatory Authorities. The submission shall be performed in accordance with local legislation.

4.12 Other safety information and requests from Regulatory Authorities

The external partner is responsible for informing Kibion about any safety information received from the local Regulatory Authorities or any other source. Furthermore, the external partner is responsible for informing Kibion about any request related to safety information received from the local Regulatory Authorities. The external partner should inform Kibion as soon as possible after receipt of the information and/or request.

Kibion and TFS are responsible for compiling any safety-related documentation requested by Regulatory Authorities.

For countries within EEA, Kibion is responsible for the submission of the documentation to the Regulatory Authorities.

For countries outside EEA, the external partner is responsible for the submission of the documentation to the Regulatory Authorities.

If needed, the external partner have to provide translations of safety information. E.g. this applies to:

- Information in local language received from Regulatory Authorities. In this case, English translation should be provided to Kibion.
- Communication to healthcare professionals (Direct Healthcare Professional Communication; DHPC) and/or consumers. In this case, translation of English template text into local language should be provided to Kibion.

5 REFERENCES

Ref	Type	Doc ID	Doc Name
1	IN	10 5035	Management of adverse reactions and specific situations
2	IN	10 5023	Reporting adverse reactions on Kibion products
3	IN	10 3144	Control of supplier
4	Form	10 1041	CIOMS I form
5	IN	10 5036	Pharmacovigilance system

6 APPENDIXES

NA

7 DOCUMENT INFORMATION

7.1 Definitions

Term	Explanation
Abuse	Persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
Adverse reaction	A response to a medicinal product which is noxious and unintended. This includes adverse reactions which arise from: • the use of a medicinal product within the terms of the marketing authorisation; • the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors; • occupational exposure.
Day 0	The date when any employee at the MAH or employee at a company who acts on the behalf of the MAH first becomes aware of the adverse reaction or specific situation.
EEA	European Economic Area
MAH	Marketing Authorisation Holder
Medication error	Unintentional error in the prescribing, dispensing, or administration of a medicine while under the control of a healthcare professional, patient or consumer.
Misuse	Situation where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
Occupational exposure	Exposure to a medicinal product as a result of one's professional or non-professional occupation.
Off-label use	Situation where the medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
Overdose	Administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgement should always be applied.
PSUR	Periodic Safety Update Report
QPPV	Qualified Person responsible for Pharmacovigilance

Term	Explanation
Serious adverse reaction	An adverse reaction that: - results in death, - is (immediately) life-threatening, - requires hospitalisation or prolongation of existing hospitalisation, - results in persistent or significant disability or incapacity, - is a congenital abnormality/birth defect or - is an important medical event that may jeopardise the patient or may require an intervention to prevent one of the outcomes above.
SOP	Standard Operating Procedure

7.2 Submitted for comments

Function	Name
QPPV/TFS	Margareta Svensson
TFS	Charlotta Wängberg
QA	Eva Kjaer

7.3 Changes from previous version/document

Version	Point	Change
1	n/a	New document
2	9.1	Has been updated with the following text: At least two attempts must be performed and documented before the case can be considered closed.
3	General	Kibion template for steering documents
	General	Change Orexo to TFS
	General	Updated and reworked to fit both TFS and Kibion
4	4.3.1	Updated the phone number
5	General	Updated the SOP to reflect that the SOP is applicable to external partners. "Distributors" is now updated to "External partner". The name of the SOP is updated too.
	2	Section referring to SOP 10 3144 Control of supplier.
	3.4	Information added that responsibilities are covered in the business agreement.

	3.4 and 4.1	Added information about verified translation of safety report.
	Appendix 1	The appendix is removed and will be a separate form "Form 1041".
	7.4.2	Updated list of distribution- removed Orifice and added Idifarma.
6	4.3.1	Update of email address.

7.4 Distribution

7.4.1 Registered electronic copy (pdf with watermark)

Function	Name	No of copies
Doc.Handler	DocHandler.kibion@mayoly.com	1
External partner	Distributors via web page log in	1

7.4.2 Registered paper copy

Function	Name	Distributed by	No of copies
TFS	Margareta Svensson	Eva Kjaer	1
Idifarma	Paula Rivera Velasques	Eva Kjaer	1
Izotop	Gabor Korpas	Eva Kjaer	1