Guidance document
Authorisation of antivenin

Identification number:	ZL000_00_033
Version:	2.1
Valid from:	24.05.2023

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1 Terms, definitions, abbreviations

1.1 Definitions and terms

1.1.1 Antivenom

In this Instruction, antivenoms are understood to be human medicinal products comprising immune sera developed especially for treating bites inflicted by venomous animals.
Numerous snake, spider, scorpion, fish and amphibian venoms are mixtures of enzymes that have a toxic action on structures including nerve cells, blood vessel cells, the coagulation cascade or blood platelets. Corresponding antibodies are used as antivenoms against these toxins. These antibodies are usually manufactured by immunising horses or sheep with the toxins in question. The antibodies formed are then obtained from the animals' plasma, purified and concentrated. This is why the term animal sera is also used in this context[1].
The European Pharmacopoeia contains a general monograph for immune sera from animals for use in humans (01/2008:0084); for snake venom immune serum (Europe), it contains a single monograph relating to immune sera for humans (01/2008:0145).

1.1.2 Basic company dossier for antivenoms

The basic company dossier for antivenoms is specific to the entire antivenom range of a market authorisation holder (MAH) and describes aspects that are specific to the company and applicable to all preparations, such as the addresses and contact data for the qualified antivenom depots (see section 1.1.3) and their responsible persons (RP), a description of their valid Swissmedic authorisations and information regarding collaboration (regarding procurement, storage, labelling, market release, purchase authorisations, dispensing of antivenoms, etc.) between the MAH and qualified antivenom depots and with Tox Info Suisse (see section 7.3). A list of the relevant venomous animal species and the corresponding antivenoms (antivenom list) can be found on the website of Tox Info Suisse.
The basic company dossier for antivenoms is produced by the MAH in collaboration the aforementioned bodies.

1.1.3 Qualified antivenom depot

A qualified antivenom depot is an institution that procures, stores, manages and supplies antivenoms from marketing authorisation holders. A cooperation agreement between the depot and the marketing authorisation holder regulates the corresponding responsibilities and activities in writing.
The depot has the necessary cantonal and national establishment licences for the distribution and dispensing of these preparations and complies with the relevant GDP requirements. Ideally, the qualified antivenom depots belong to the national Antivenin-CH network.

[1] cf. also the WHO website and Guideline *on Production, Control and Regulation of Snake Antivenom Immunoglobulins* at http://www.who.int/bloodproducts/snake_antivenoms/en/

1.2 Abbreviations

AApot	Armeeapotheke, Armed Forces Pharmacy
ADR	Adverse Drug Reaction
CoA	Certificate of Analysis
FeeO-Swissmedic	Ordinance on the Fees charged by the Swiss Agency for Therapeutic Products of 14 September 2018 (SR 812.214.5)
ff.	and following
GDP	Good Distribution Practice
GSASA	Swiss Association of Public Health Administration and Hospital Pharmacists
MAH	Marketing authorisation holder
MPLO	Ordinance of 14 November 2018 Licensing in the Medicinal Products Sector (SR 812.212.1)
NAS	New active substance
Tox Info Suisse	Swiss toxicology information centre (previously: STIZ)
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, SR 812.21)
TPLO	Ordinance of the Swiss Agency for Therapeutic Products of 22 June 2006 on the Simplified Licensing of Therapeutic Products and the Licensing of Therapeutic Products by the Notification Procedure (SR 812.212.23)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (Therapeutic Products Ordinance, TPO) (SR 812.212.21)

2 Introduction

This Instruction describes the procedure for authorisation of antivenoms in Switzerland; it defines terms and specifies the requirements and the documentation necessary for authorisation of this group of medicinal products. As this is a guidance document aimed at administrative bodies, it does not directly specify the rights and obligations of private individuals.

2.1 Legal framework

The procedure for the authorisation of antivenoms is based on the following:
TPA:

- Art. 10 Conditions for granting a marketing authorisation
- Art. 11 Application for a marketing authorisation
- Art. 14 Simplified authorisation procedure
- Art. 17 Official batch release
- Art. 59 Mandatory reporting, reporting system and the right to report

MPLO:

- Art. 3ff. Establishment licences
- Art. 44 License for importing individual batches

TPO:

- Art. 3 Application for a marketing authorisation

- Art. 21 to 25 Variation of the authorisation
- Art. 61 to 66 and Annex 3 Vigilance

TPLRO:

- Art. 3 to 5 Documentation requirements
- Art. 12 to 17 Labelling and product information requirements
- Art. 18 to 22 Official batch release and exceptions

TPLO:

- Art. 4 to 7 Recognition of the status of an important medicinal product for rare diseases (human medicinal products, orphan drugs)
- Art. 24 to 26 Requirements for the authorisation of important medicinal products for rare diseases

FeeO-Swissmedic:

Art. 12 Fee reduction in the public interest

3 Objective

Swissmedic uses this document first and foremost as a resource for applying the legal provisions on the authorisation of antivenoms in a uniform and equitable manner. The intention of publishing this Instruction is to show private individuals what requirements have to be fulfilled under Swissmedic practice to ensure that corresponding authorisation applications are processed as quickly and efficiently as possible.

Various exotic venomous snakes, scorpions, venomous spiders etc. are kept publicly and privately in Switzerland, and there are also native venomous animals (particularly snakes) that live in the wild. Antivenoms are available nationwide through a network of antivenom depots, which together make up the Antivenin-CH network[2], for the emergency medical care of individuals bitten by venomous animals. Tox Info Suisse and the Antivenin-CH network together coordinate antivenom requirements, compile a joint antivenom list, provide medical and scientific advice and maintain contact with treating physicians.

According to Art. 4 para. 1 a of the Therapeutic Products Act (TPA), antivenoms are considered to be medicinal products subject to authorisation. As immunological medicinal products, antivenoms also require a license to import individual batches (Art. 44ff. MPLO) and, as animal sera, are subject on principle to official batch release in accordance with Art. 18ff. TPLRO. However, Swissmedic generally waives the requirement for batch release for antivenoms on the basis of Art. 18 para. 3 TPLRO (cf. point 8).

Venomous animal bites, and thus the need for the corresponding antisera to treat life-threatening conditions, are very rare occurrences in Switzerland (roughly 40-55 bites per year). This category of medicinal products can therefore be accorded orphan drug status in accordance with Art. 4 TPLO. The conditions for a simplified authorisation procedure in accordance with Art. 14 para. 1 f TPO are therefore fulfilled. Appropriate account is taken of the requirements that the scientific documentation has to fulfil in terms of quality, safety and efficacy in order to ensure the availability of life-saving specific antivenoms. Since scant quality documentation and limited data from preclinical and clinical studies are generally available for antivenoms, it is necessary to compensate for this situation with intensive monitoring each time an antivenom is administered (pharmacovigilance, cf. point 9.2).

[2] Antivenin-CH is the network of Swiss antivenom depots and is organised within the Antidotes working group of the Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA) and Tox Info Suisse. Tox Info Suisse coordinates the network's collaborative activities. Link: www.toxinfo.ch: For physicians and pharmacists > Antidotes > Antivenin-CH.

The authorisation application contains administrative data, medicinal product-specific data submitted on the form *New authorisation variation antivenin HMV4* and associated attachments, and data applicable to all medicinal products that is summarised in a “basic company dossier for antivenoms” and is specific to an individual holder of a marketing authorisation (MAH) for antivenoms.

4 Scope

This Instruction applies to the authorisation of antivenoms (cf. point 1.1.1), extensions of these authorisations and major variations, type II.
Swissmedic may also apply this Instruction to immune preparations obtained from animal sera that are intended to treat rare forms of poisoning (e.g. by poisonous plants, bacterial toxins) and are not subject to other requirements.
This Instruction does not apply to antivenom preparations manufactured using biotechnological processes.

5 Description

5.1 Fees

Orphan drug status is granted for all antivenoms in accordance with Art. 4 to 7 TPLO and there is an overriding public interest in the fee waiver. For this reason Swissmedic does not levy a fee for applications for recognition of the status of an important medicinal product for rare diseases or for applications for a license to import single batches in accordance with Art. 32 para. 1 MPLO for antivenoms under the terms of Art. 12 FeeO-Swissmedic.

5.2 Authorisation of antivenoms

Applicants who fulfil the conditions for authorisation stated in Art. 10 TPA should submit the documentation as described in section 6.1. Swissmedic will review the submitted documentation in accordance with the criteria stipulated for this group of medicinal products and will notify the applicant of the outcome in an official decision. An authorisation certificate will be issued on request (subject to payment of a fee) or may be printed by the authorisation holder from the Swissmedic portal. The authorisation will be published in the Swissmedic Journal.
Once a year the MAH must send Swissmedic an updated basic company dossier for antivenoms, updated statistics for venomous animal bites and a list of antivenom movements in the past 12 months.
The MAH must submit to Swissmedic variation applications for its antivenoms should any come to its attention (cf. point 6.4).

5.2.1 Authorisation documents

5.2.1.1 Mandatory documents

a) Covering letter
b) Form *New authorisation variation antivenin HMV4* with the additional documents required, including mandatory submission of:

Form *Full declaration HMV4* stating the full composition, manufacturer's certificate(s) of analysis, copy of the foreign product information, copy of the foreign packaging texts and manuscript of additional labels (cf. point 6.2);

c) Basic company dossier for antivenoms (as an attachment to the form *New authorisation variation antivenin HMV4*):
If Swissmedic has already received a corresponding and current (not more than 1 year old) AV-MD, the applicant may make reference to this.

5.2.1.2 Optional documents

Where available, other documents should be submitted as optional attachments to the form *New authorisation variation antivenin HMV4*, e.g.

- Form *Manufacturer information HMV4*;
- Form *Status of authorisation applications abroad HMV4*;
- Copies of official batch release certificates;
- Other quality documentation (information about the manufacturing process, viral safely, specifications, stability, etc.);
- Preclinical documentation;
- Clinical documentation.

5.2.2 Product information, additional labels and packaging

The MAH must send Swissmedic a copy of the foreign product information (package leaflet).
If this is available in German, French, Italian or English, the following information must be provided in German and French on an additional label:

- Marketing authorisation holder (company and domicile as stated in the entry in the Commercial Register);
- Authorisation number for Switzerland;
- Dispensing category A.

If the antivenom destined for the Swiss market contains a package leaflet that is not in German, French, Italian or English, the following information must be provided in German and French on an additional label:

- Marketing authorisation holder (company and domicile as stated in the entry in the Commercial Register);
- Authorisation number for Switzerland;
- Dispensing category A;
- Indication* (with the exact name of the species of venomous animal in Latin) and
- recommended dosage*

The last two items (*) may appear in English only.
The additional label must be attached to every item of external packaging (secondary packaging) used for antivenoms destined for the Swiss market.
A copy of the foreign packaging texts used for the other packaging elements (secondary packaging, vial labels, etc.) must be sent to Swissmedic with the application for first authorisation and the corresponding variation applications. If these are not available when the application is submitted, they may be submitted subsequently.

5.2.3 Dispensing category

Antivenoms are classified as dispensing category A (stricter prescription-only status).

5.2.4 Variations, updates and list of antivenom movements

The MAH must send the following documents to Swissmedic:

- Medicinal product-specific variation applications with the form *New authorisation variation antivenin HMV4* (including any updated documentation that has to be submitted additionally).
- Annual update of the basic company dossier for antivenoms (if the current dossier in Swissmedic's possession has not been changed, reference may be made to this);
- List of the batches of antivenom imported and supplied during the last 12 months and the medicinal products used during this period (turnover statistics, list of antivenom movements).

5.3 Responsibility of the parties involved

5.3.1 Responsibility of the marketing authorisation holder

This is determined by the requirements of the therapeutic products legislation. The following requirements must be observed for antivenoms:

- A license to import single batches must have been issued for each import shipment of antivenoms in accordance with Art. 44 para. 1 MPLO:
- Documented release of each batch of antivenom imported for the Swiss market:
  Release of antivenoms for the market is based on a number of factors including a review of the available quality documentation comprising certificates of analysis (technical release by the manufacturer, batch release certificates issued by other authorities, etc.), batch identification and examination of the correct labelling of the antivenoms with the additional labels specific to Switzerland (showing at least the authorisation number, the MAH and dispensing category A).
- **Written agreements (cooperation agreements) delegating the activities listed below – which are the responsibility of the MAH – to qualified antivenom depots:**
- Applying for the licenses to import single batches for each import shipment of antivenoms on behalf of the MAH in accordance with Art. 44 para. 1 MPLO;
- Ordering, storing, delivering (24-hour on-call service), logistics and labelling of the antivenoms with the appropriate additional labels;
- Sending the forms for pharmacovigilance reports (ADR) with every shipment of antivenoms to treating physicians; as an alternative to using the postal service, treating physicians may be given the link to the form on the Swissmedic website;
- Reporting each delivery of antivenoms to Tox Info Suisse, stating the medicinal product and the recipient.

5.3.2 Responsibility of the qualified antivenom depots

- Provision of information on the antivenoms imported and supplied each year to the corresponding MAH;
- Possession of the necessary licenses (wholesale, retail, etc.) to enable antivenoms to be exchanged through the antivenom network;
- Responsibility for the GDP-compliant storage and supply of the authorised antivenoms;
- A 24-hour on-call service in cooperation with the Antivenin-CH network which guarantees that the antivenoms can be supplied without delay for every emergency.

5.3.3 Responsibility of Tox Info Suisse

- Medical and scientific guidance in cases of poisoning in cooperation with the treating physicians;
- Processing pharmacovigilance requirements for antivenoms in cooperation with the MAH and Swissmedic;
- Provision of the required data on the antivenoms used each year to Swissmedic and the MAH so that the turnover statistics can be drawn up (list of antivenom movements);
- Production of annual statistics on venomous animal bites and the related treatment, and incorporation of this data into the toxicovigilance report sent to Swissmedic, or else the publication of this report so that Swissmedic has access to it.

5.4 Official batch release

In accordance with Art. 18 para. 3 TPLRO, the requirement for official batch release is waived for antivenoms.

5.5 Conditions

5.5.1 General

To compensate for the fact that applications for authorisation of antivenoms are exempt from the obligation to submit comprehensive quality documentation and preclinical and clinical trial data, every administration of an antivenom must be closely monitored (even if no adverse drug reaction (ADR) has occurred), and incidents of poisoning must be documented accordingly.
A report should be sent to Tox Info Suisse every time an antivenom is administered.
In addition to the reporting obligation pursuant to Art. 59 TPA, dispensing of the antivenom is closely monitored.

5.5.2 Pharmacovigilance

- A copy of the pharmacovigilance form[3] that must be filled out by the user and sent to Swissmedic (may also be e-mailed to vigilance@swissmedic.ch) is enclosed with every pack of antivenom supplied. Tox Info Suisse may assist the submitting bodies with pharmacovigilance.

The issuing offices notify Tox Info Suisse of which antivenom was dispensed and to whom.

6 Transitional regulations

Until the official authorisation decision has been issued, Swissmedic will – subject to application – extend temporary authorisations to distribute medicinal products without authorisation in accordance with Art. 9*b* TPO.

[3] The reporting form is available in German and French and can be obtained as a printed form from Swissmedic or downloaded from the Swissmedic website: www.swissmedic.ch, Market surveillance, Report adverse drug reactions, Forms. It can also be completed online and sent to Tox Info Suisse by e-mail.

Change history

Version	Change	sig
2.1	New layout, no content adjustments to the previous version.	dei
2.0	Implementation of new pharmacovigilance rules, details regarding distribution of work between AApot, Swissmedic and the regional centres, and deletion of the flow chart (Annex, section 11)	fufa
1.0	Implementation of TPO4	stb