Temporary Authorisations for Use (ATU)

The “Autorisations Temporaires d’Utilisation” (“Temporary Authorisations for Use”) or ATU procedure is an exceptional measure making available medicinal products that have not yet been granted a Marketing Authorisation (MA).

The aim of ATUs is to provide early access to new promising treatments where a genuine public health need exists, i.e. in the treatment of patients suffering from serious disease and having reached a situation of therapeutic impasse.

This regulatory provision, stipulated in the French Public Health Code, has actually been applied in France since 1994.

ATUs have made it possible to treat tens of thousands of patients per year, several months before MA. The diseases most frequently concerned are cancers, infectious diseases such as AIDS, and neurological diseases. For example, all the new antiretroviral drugs have been available in France by ATU an average of 12 months before the MA decision, for around 6000 patients per medicinal product.

Since 1994, more than 400 medicinal products have been the subject of applications for an ATU and a benefit/risk ratio assessment. These may concern medicinal products already authorised abroad or drugs that are still under development.
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INTRODUCTION

1. Purpose of ATUs

The sole purpose of temporary authorisations for use (ATUs) is to provide access to some promising medicinal products that do not have a marketing authorisation (MA) where there is a public health need, i.e. for patients suffering from serious or rare diseases in the absence of any suitable therapeutic alternative and when there is presumed to be a benefit.

An ATU may concern medicinal products that already have a MA abroad or drugs under development.

The ATU system was actually set up in France in 1994. It has made it possible to use new drugs to treat several tens of thousands of patients in a situation of treatment failure, several months before these drugs have obtained a MA.

2. ATUs and clinical trials

- ATUs are not clinical trials and are not for investigative purposes. The decision to award an ATU must not slow down the implementation or continuation of clinical trials intended to provide detailed and essential answers relative to the benefit/risk ratio of a medicinal product.

- Clinical trials (which are governed by the law of 20th December 1988 relative to the protection of subjects involved in biomedical research), whilst providing access to medicinal products without a MA, are the only means of obtaining reliable data, particularly in terms of efficacy, safety, drug interactions and therapeutic strategies, and with a view to future marketing authorisations.

- Whether a medicinal product is made available according to the ATU procedure or in the context of clinical trials depends on the level of information available on the drug. In general, at an early stage of drug development, clinical trials must be favoured, since they alone can provide new knowledge valuable for the medical and scientific community as a whole and for patients.
I. **ATU – General principles**

The use of medicinal products that do not have a marketing authorisation in France and outside the context of a clinical trial is dependent on prior ATU issued by the Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps) (article L.5121 of the French Public Health Code and decree No. 98-578 of 9th July 1988 relative to temporary authorisations for use).

ATUs are granted as an exceptional and temporary measure, when the following conditions are met:
- for the treatment of serious or rare diseases,
- in the absence of a suitable therapeutic alternative (with a MA) available in France,
- and when there is presumed to be a positive benefit/risk ratio.

In practice, there are two types of temporary authorisation for use:

- **the named patient ATU**, issued for a single, named patient, at the request of and under the responsibility of the prescribing physician.
  This type of ATU concerns medicinal products presumed to be effective, and to have an acceptable drug safety profile in the light of the data available.
- **the so-called cohort ATU**, which concerns a group or sub-group of patients, treated and monitored according to criteria fully defined in a protocol for therapeutic use and information collection.
  A cohort ATU is issued at the request of the holder of the licensing rights, which must commit to submit a marketing authorisation application within a determined period.
  This type of ATU concerns medicinal products strongly presumed to be effective and to have an acceptable safety profile, having reached an advanced stage of development, for example with a marketing authorisation dossier currently being compiled or registered.

II. **Regulations**

2.1. **Law relative to ATUs:**

As an exception to the marketing authorisation for medicinal products, article L.5121-12 of the French Public Health Code, resulting from law No. 92-1729 of 8th December 1992, amended by law 96-452 of 28th May 1996, provides for the rules for the use, for therapeutic purposes and as an exceptional measure, of medicinal products without a MA in France, intended to treat serious or rare diseases, where no suitable treatment exists and:

a) these medicinal products are strongly assumed to be effective and safe in view of the results of clinical trials conducted with a view to submitting a marketing authorisation application, and that this application has been submitted or that the applicant undertakes to submit it within a determined period ("cohort" ATU);

b) or that these medicinal products are prescribed to named patients and, if applicable, imported for this purpose, under the responsibility of their attending doctor, as long as they are presumed to be effective and safe on the basis of current scientific knowledge and are likely to offer a real benefit ("named patient" ATU).

The use of these medicinal products is authorised by the Afssaps, for a limited period, at the request of the holder of the licensing rights in the case of a cohort ATU or at the request of the attending doctor in the case of a named patient ATU.

A cohort ATU is applied for in the context of a protocol for therapeutic use and information collection, established by the Afssaps with the assistance of the holder of the licensing rights.

The authorisation may be suspended or withdrawn if the conditions having led to it being granted are no longer met or for public health reasons.

2.2. **Decree relative to ATUs:**
Decree No. 94-578 of 9th July 1988 relative to temporary authorisations for use for certain medicinal products for human use and amending the French Public Health code provides for:
- the conditions for granting ATUs,
- the contents of the ATU application dossier,
- the procedure for assessment of dossiers,
- the duration of the ATU,
- the provisions in terms of pharmacovigilance,
- the conditions for renewal, withdrawal, suspension and expiry of ATUs.

2.3. **Decree relative to the import of medicinal products that are the subject of an ATU**

The conditions for importing medicinal products that are the subject of an ATU are stipulated in decree No. 98-578 of 9th July 1998 relative to the import and export of medicinal products (articles R.5142-12, R.5142-14 and R.5142-15).

2.4. **Decree relative to pharmacovigilance**

Decree No. 95-278 of 13th March 1995 relative to pharmacovigilance applies to medicinal products that are the subject of an ATU (article R.5144-3).

### III. Medicinal products concerned and prescribing and dispensing conditions

Any use of a medicinal product without a marketing authorisation in France and outside the context of a clinical trial is subject to an ATU, irrespective of whether or not the medicinal product has a marketing authorisation abroad.

The continuation of treatment at the end of a clinical trial must be the subject of an amendment to the initial protocol and does not generally involve an ATU.

The use of a medicinal product in any indication other than those stipulated in its MA is the responsibility of the prescribing physician and is not the subject of an ATU.

Due to their without-MA status, medicinal products with an ATU are not available in public pharmacies and may only be dispensed by hospital pharmacies. Their prescription may be restricted to a particular category of prescribing physicians.

### IV. Identity of the ATU applicant

Named patient ATU applications are made by the prescribing doctor and transmitted to the Afssaps by the hospital pharmacist by fax. The prescribing physician is the holder of the named ATU.

Cohort ATU applications are made by the holder of the licensing rights for the medicinal product, which is also the holder of the ATU.

### V. To whom should ATU applications be sent?

ATU applications should be sent by the applicant to:

Afssaps
Autorisations Temporaires d’Utilisation Unit
143-147, boulevard Anatole France
93285 SAINT-DENIS CEDEX
FRANCE
Fax: (33) 1.55.87.36.12
Tel.: (33) 1.55.87.36.11
VI. Named patient ATUs

6.1. Named ATU application dossier

Named ATU applications are made on Cerfa form No. 10058 01 (Appendix A). In particular, they include information concerning the scheduled treatment (name, dosage, treatment duration), the patient (initials of surname and first name), the exact indication and justification of the use of a medicinal product without a MA. This form must be completed, dated and signed by the prescribing doctor and the hospital pharmacist. Their respective contact details are indicated in full.

In the event that any information relevant for assessment of the application cannot be indicated on the Cerfa form, one or more separate documents are attached, indicating the references of the application (name of the prescribing physician, patient’s initials, name of the medicinal product). When additional information is required by the Afssaps, this should be sent as soon as possible, if possible attaching a copy of the Cerfa form for the initial application.

6.2. Evaluation of named patient ATU applications and Afssaps decisions

The evaluation concerns the medicinal product, its pharmaceutical quality (viral safety if applicable), its safety and efficacy in the indication claimed in the ATU, along with the absence of any therapeutic alternative. Each named ATU application is studied by the Afssaps, assisted by experts.

To do this, the agency notably relies on a dossier on the medicinal product supplied by the pharmaceutical company at its request and, if necessary, by the ATU applicant and including, in particular:
- a copy of the authorisation obtained abroad, if applicable;
- any available information relative to the pharmaceutical quality, efficacy and safety (bibliography, investigator’s brochure, etc.);
- a list of ongoing or scheduled clinical trials in France.

The decisions are as follows:
- granted: an ATU is granted, repeating the following information in particular: name of the medicinal product, contact details of the prescribing physician, patient’s initials, treatment duration, contact details of the hospital pharmacist.
- rejected, for the following reasons notably:
  - existence of a therapeutic alternative with a MA and available on the market.
  - and/or absence of convincing data suggestive of a real benefit for the patient.
  - and/or use requested for investigative purposes.

The rejection is sent by fax to the pharmacist, who informs the prescribing physician, and by recorded delivery mail with acknowledgment of receipt to the prescribing physician and the pharmacist. A reapplication may be made to the Director General of the Afssaps and/or the matter may be referred to the relevant administrative court within a period of 2 months from notification of the decision.

The response times for ATU applications depend, first of all, on the therapeutic emergency and, secondly, on how much knowledge the Afssaps has about the medicinal product. Consequently:
- when the medicinal product has already been evaluated by the Afssaps, the decision is quick, generally being made within 24-48 hours.
- when the medicinal product has never been evaluated, the response time takes into account the time taken to compile the dossier and to complete the assessment.

6.3. Procedure to obtain or to import a medicinal product with a named ATU

If a distributor exists in France, the hospital pharmacist makes the order using an order form accompanied by the ATU issued by the Afssaps. It is the responsibility of the pharmacist to take receipt of the medicinal product and to dispense it.
If the product is not available in France, the pharmacist must import it. The named ATU serves as an import authorisation.

In order to optimise the time taken to dispense medicinal products, drugs for which the import or order times can be long, should be available in hospital pharmacies. The building of stocks by hospital pharmacists may be authorised by the Afssaps in order to respond to situations of extreme therapeutic urgency or for other clinical situations occurring frequently in the same hospital.

In both these cases, duly justified applications to build stocks are made to the Afssaps on the hospital pharmacy's headed paper. In particular, the indication for which the medicinal product will be used must be mentioned.

6.4. Duration of named ATU and treatment continuation

The duration of a named ATU must be specified on the authorisation. This corresponds to the treatment duration and cannot exceed one year.

If it is necessary to prolong treatment, an application for an ATU renewal is submitted to the Agency. This application is made in the same way (Cerfa form) indicating the nature of the application (renewal) and the number of the initial ATU and any other information justifying the continuation of the treatment, its efficacy and its safety.

6.5. Patient information and role of the prescribing physician in the case of a named ATU

The patient must be informed by the prescribing physician about the characteristics of the medicinal product and the exact scope of the exceptional authorisation to which it is subject.

The prescribing physician must:
- undertake to inform his/her patients;
- ensure that the patients treated are monitored;
- comply with pharmacovigilance requirements;
- keep the pharmacist at his/her healthcare establishment informed.

6.6. Role of the hospital pharmacist in the case of a named ATU

The hospital pharmacist sends the named ATU application to the ATU Unit of the Afssaps. He/she collects any additional information requested by the Afssaps. He/she takes receipt of the ATU, informs the prescribing physician and transmits the latter copies of any letters enclosed by the Afssaps. He/she orders, imports if necessary, takes receipt of and dispenses the medicinal product. He/she manages stocks in accordance with good practices. He/she complies with pharmacovigilance requirements (cf. 7.9.1).

6.7. Labelling in the case of a named ATU

It must include at least the name of the medicinal product or, if applicable, its code name, the manufacturing batch number and the expiry date.

6.8. Information about named ATU medicinal products

The information available relative to medicinal products subject to a named ATU is diverse:
- Summary of product characteristics (SPC) of a marketing authorisation granted abroad
- Investigator’s brochure
- Project of a summary of product characteristics proposed by the pharmaceutical company (core data sheet)
- Data from the literature.

The Afssaps will endeavour to enclose a note for information to the prescribing physician and the pharmacist relative to the medicinal product and summarising its main characteristics with each ATU.
Pharmaceutical companies responsible for medicinal products can also send information about the medicinal product, on condition that said information has first been transmitted to the Afssaps.

VII. "Cohort" ATU

A "cohort" ATU application can be submitted:
- either simultaneously with a marketing authorisation application;
- or prior to submission of a marketing authorisation application, as long as the applicant undertakes to subsequently submit a MA application.

Any "cohort" ATU is accompanied by a summary of product characteristics for the medicinal product, a patient leaflet, labelling conditions and, generally, a protocol for therapeutic use and information collection.

The use of these medicinal products is subject to regular monitoring by the Afssaps, mainly focusing on compliance of the indications and the analysis of adverse reactions provided by the pharmaceutical company.

7.1. Cohort ATU application dossier

The dossier contains all the pharmaceutical and pharmaco-toxico-clinical documentation and data available at the time of the application (even if the studies are ongoing). The format of the cohort ATU dossier is as close as possible to that required for a MA dossier:
- cohort ATU application (alone or accompanied by a copy of the MA application), duly justified
- part I, summary of the dossier (50 copies) with, notably, draft summary of product characteristics, package leaflet and labelling in French (paper and electronic versions)
- part II, chemical, biological and pharmaceutical documentation (5 copies)
- part III, toxicological and pharmacological documentation (5 copies)
- part IV, clinical documentation (10 copies).

If expert reports are available, these must also be provided.

In addition, the following documents must be supplied:
- the titles and aims of ongoing trials with their current progress status and scheduled trials, the identity of the investigator(s), indication of the study site(s) concerned;
- when the medicinal product has been given an authorisation abroad, a copy of this authorisation issued by the relevant authority;
- an undertaking to submit a marketing authorisation application and the approximate date on which this will be filed;
- a draft protocol for therapeutic use and information collection in French (10 copies of the paper version + one copy in electronic format);
- the conditions for supply of the medicinal product, free of charge or in return for payment;
- the estimated number of patients to be treated;
- if applicable, the "orphan medicinal product" designation.

A complete copy of the dossier, known as "dossier A" must be supplied for archiving, in orange elasticated folders; the other copies are parts B, intended for evaluation.

The dossier may be written in French or English. Any dossier must be submitted in the form of a bound document.

7.2. Protocol for therapeutic use and information collection. Where this is required, it is drawn up by the licence holder and the Afssaps.

The purpose of this protocol is to provide physicians and pharmacists with any information on the medicinal product and its prescribing conditions and on the conditions for monitoring the patients treated.
A protocol model can be provided by the Afssaps (on request to the ATU Unit).

In particular, this protocol includes:
- a review of the general principles of the ATU.
- the summary of product characteristics.
- a description of the practical prescribing conditions for the medicinal product.
- a description of the dispensing conditions for the medicinal product.
- a description of the conditions for providing patients with information.
- a description of the conditions for monitoring patients.
- a description of the conditions for collection of information relative to follow-up of patients by prescribing physicians and by the ATU holder (in particular, the characteristics of the patients treated, the effective use of the medicinal product, serious or unexpected adverse reactions).
- a description of pharmacovigilance conditions.
- a description of the conditions for the compilation and circulation of summary reports by the ATU holder.

7.3. Evaluation of cohort ATU applications

Each cohort ATU dossier is studied by the MA Committee. In particular, the evaluation concerns the pharmaceutical quality (and viral safety if applicable), safety and efficacy of the medicinal product in the indication claimed.
The drug’s position in the therapeutic arsenal available on the French market is also assessed.

If the application is accepted, the ATU is granted for the use of the medicinal product in a precise indication that must be respected. It is accompanied by the summary of product characteristics, the patient information leaflet and the labelling, along with the protocol for therapeutic use and information collection if necessary.

7.4. Duration of cohort ATU and renewal

A cohort ATU is granted for a duration of one year and may be renewed if necessary.

This renewal must be the subject of a specific application 2 months prior to expiry of the ATU. The dossier submitted is evaluated by the MA Committee. It includes:
- a summary report describing all the data gathered in the context of the ATU;
- any new information obtained on the medicinal product during the validity period of the ATU;
- the quantities of medicinal product dispensed in France during this period;
- a summary of ongoing and scheduled trials;
- a copy of authorisations (foreign marketing authorisation) obtained during the ATU period, if applicable.

7.5. Patient information in the context of a cohort ATU

Prior to instigating the treatment, each patient must be informed by the prescribing physician about:
- the conditions providing exceptional access to the medicinal product;
- the characteristics of the medicinal product.

An information sheet available in the protocol for therapeutic use is given to the patient, along with verbal explanations. An information leaflet is also available in each pack of medicinal product.

The patients will also be informed that the prescribing physician will collect data, particularly relative to safety, concerning the treatment and that this data will be passed on to the ATU holder and the Afssaps and may be computerized. In application of the French data protection law of 6th January 1978, the patient may exercise his/her right to correct this information at any time.

7.6. Role of the prescribing physician in the context of a cohort ATU
The prescribing physician must:
- comply with all the conditions for use described in the summary of product characteristics and the protocol for therapeutic use;
- ensure monitoring of the patients treated and collection and transmission of the information gathered to the ATU holder according to the conditions described in the protocol for therapeutic use;
- inform his/her patients (cf. 7.4);
- inform the hospital pharmacist about the implementation of treatment of patients included in the ATU;
- inform the pharmacist and the ATU holder of any treatment discontinuations;
- comply with the pharmacovigilance requirements (Cf. VIII).

7.7. Role of the hospital pharmacist in the context of a cohort ATU

The hospital pharmacist:
- studies the protocol for therapeutic use and ensures that it is complied with;
- ensures that he/she has all the information relative to the implementation of treatment of patients included in his/her hospital;
- orders, takes receipt of and dispenses the medicinal product and manages stocks in accordance with good practices.

7.8. Procedure to instigate treatment and obtain medicinal products in the context of a cohort ATU

Cohort ATU medicinal products are dispensed by hospital pharmacies, with, if necessary, prescription restricted to certain prescribing physicians.

The conditions for obtaining medicinal products are described in the protocol for use. Generally the doctor and/or the pharmacist first of all contacts the cohort ATU holder to obtain a protocol for therapeutic use and forms for instigation of the treatment in the cohort.

To instigate treatment for a patient, the prescribing physician generally sends a treatment instigation form, accompanied by an order form, to the pharmaceutical company holding the ATU via the hospital pharmacist, after having first studied the protocol.

The application to instigate treatment is validated by the pharmaceutical company, in accordance with the criteria indicated in the protocol.

Once the application has been validated, the pharmaceutical company honours the order for medicinal products issued by the pharmacist.

7.9. Responsibilities of the holder of the licensing rights in the context of a cohort ATU

The holder of the licensing rights circulates the protocol for therapeutic use along with the summary of product characteristics to the prescribing physicians and pharmacists concerned, to the Regional Pharmacovigilance Centres and to Antipoison Centres.

The temporary authorisation for use granted implies that the licence holder must check the inclusion criteria defined in the protocol for therapeutic use and the summary of product characteristics and also that procedures for information and prospective follow-up of patients treated must be set up.

The ATU holder gathers the data passed on by the prescribing physicians and pharmacies and analyses them.

It is required to comply with pharmacovigilance obligations (cf. VIII).

It establishes a periodic report for the Afssaps (ATU and Pharmacovigilance Units) including an analysis of all the data collected in the context of the protocol for therapeutic use and information collection (cf. 7.10.) If requested by Afssaps, it sends prescribing physicians and pharmacists a summary of this report, validated by the Afssaps.
7.10. Periodic reports in the context of a cohort ATU

Periodic reports are sent to the Afssaps (5 copies to the ATU Unit and 2 copies to the Pharmacovigilance Unit) and to the designated Regional Pharmacovigilance Centre if applicable, according to a schedule set by the Afssaps.

It contains a description of all the data collected throughout the period of ATU, i.e. data collected during the period covered since the previous report and cumulative figures) in the context of the protocol for therapeutic use, as established by the Afssaps and the ATU holder.

In particular, these reports contain:
- a description of the actual conditions of use of the medicinal product in the context of the ATU (population, dosages, criteria for use, contraindications, etc.) on the basis of all the information collected by the prescribing physicians in the forms provided for this purpose.
- a pharmacovigilance part (cf. VIII)

At the request of the Afssaps, these reports are accompanied by a summary which, when validated by the Afssaps, must be sent to prescribing physicians and user pharmacists and also to the Regional Pharmacovigilance Centres for information purposes.

7.11. Import of medicinal products in the context of a cohort ATU

Any import of a medicinal product by the cohort ATU holder requires that an import authorisation issued by the Afssaps first be obtained (Import and Export Authorisations Unit, fax: 01.55.87.36.32; tel.: 01.55.87.36.31) in application of articles R.5142-12, R.5142-14 and R.5142-15.

7.12. Labelling in the context of a cohort ATU

Labelling includes at least the following information:
- the name of the medicinal product or, if applicable, its code name;
- the name and address of the company distributing the medicinal product;
- the manufacturing batch number;
- the route of administration and, if necessary, the method of administration of the medicinal product;
- the active substance composition;
- the expiry date;
- if applicable, the instructions required for proper storage of the medicinal product.

The information stipulated above must be written in French. It may also be written in other languages as long as the same information is given in all the languages used.

7.13. List of cohort ATU medicinal products

The list of medicinal products available in the context of a cohort ATU can be accessed on the Afssaps web site (http://afssaps.sante.fr).

VIII. Pharmacovigilance of ATUs

8.1. Regulatory aspects

The following texts concern ATU medicinal products:
- the provisions defined in the decree relative to the pharmacovigilance of medicinal products No. 95-278 of 13th March 1995 apply for medicinal products subject to a temporary authorisation for use (Art. R.5144.3). A certain number of definitions and recommendations will soon be amended in this decree to take into account the new directive 2000/38/EC of 5th June 2000.

For medicinal products that are the subject of a protocol for therapeutic use and information collection (cohort ATU medicinal products), the obligations for notification of serious or unexpected adverse reactions by health professionals and by pharmaceutical companies and for transmission of a periodic report apply according to the conditions defined in said protocol.
- the pharmacovigilance of plasma-derived medicinal products is subject to the general regulations concerning medicinal products but also to specific rules stipulated by decree No. 95-566 of 6th May 1995.

- the notice to marketing authorisation applicants published in volume IX of the Rules Governing Medicinal Products in the European Union states that: “in the period between the submission of the marketing authorisation application (irrespective of the procedure: national, mutual recognition or centralised) but prior to authorisation, any information which may have an impact on the benefit/risk evaluation must be submitted by the future MA holder or the Member State where the medicinal product is already marketed (on a compassionate use basis, as an ATU, etc.) to the competent authority of the Member States where the application is under assessment and, in the case of a European centralised application to the EMEA, rapporteur and co-rapporteur”.

- at the justified request of the Director General of the Afssaps, the pharmaceutical company must carry out all the investigations and studies concerning the risks of adverse reactions that these drugs or products could present. The information, investigations or studies must be necessary for the application of pharmacovigilance procedures (article R.5144-6).

8.2. Role of parties

8.2.1. Health professionals

- Who declares?
  Any doctor, pharmacist, dental surgeon or midwife having observed a serious or unexpected adverse reaction suspected of being related to the use of the medicinal product subject to the ATU must immediately declare it. Any member of a health profession having made such an observation must also report it.

- What is declared?
  By the terms of article R.5144-4 of the French Public Health Code and European Directive 2000/38/CE, the various definitions are as follows:
  - adverse reaction: harmful and unintended reaction, occurring at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of a physiological function or resulting from misuse of a drug or product.
  - serious adverse reaction: fatal or potentially life-threatening reaction or one that results in disability or incapacity or requires hospitalisation or prolongation of hospitalisation or results in a congenital anomaly/birth defect. According to the Directive, health professionals can also report any reaction they deem to be serious (outside the definitions above) or any reaction that jeopardise the patient without, however, having been immediately life-threatening or having led to the hospitalisation or death of the patient.
  Any serious reaction resulting from the use of the medicinal product not in accordance with the summary of product characteristics (SPC) must also be included (for example, use at supra-therapeutic doses, overdose or abuse).
  - unexpected adverse reaction: reaction for which the nature, severity or frequency are not consistent with the summary of product characteristics. For named patient ATUs, the investigator’s brochure for an ongoing trial should be taken as the reference, or the SPC of the exporting country, or the Core Data Sheet. These texts may be supplied to users by the pharmaceutical company along with the medicinal product (cf. 6.8).

- How?
  The declaration is formulated on the reporting form provided in appendix C (Cerfa form No. 10011*01), always specifying the ATU number. This form is available in Regional Pharmacovigilance Centres or a similar form is provided in the protocol for therapeutic use for medicinal products subject to cohort ATUs.
- To whom?
With respect to adverse reactions that could be due to a medicinal product subject to a named patient ATU, declarations must be made to the Regional Pharmacovigilance Centre on which the notifier is geographically dependent.
For medicinal products subject to a cohort ATU, the recipient of serious or unexpected reaction declarations is specified in the protocol for therapeutic use and it is usually the pharmacovigilance department of the pharmaceutical company holding the ATU.
In exceptional cases in which there is no protocol for therapeutic use, adverse reactions are declared to the Regional Pharmacovigilance Centre.

8.2.2. The company or the organisation distributing the medicinal product

In practice, there are two possible situations:
* There is a distributor in France who can import the product if necessary and it is this pharmaceutical establishment that is responsible for ensuring pharmacovigilance of the medicinal product.
* There is no distributor in France and it is the hospital pharmacist who imports the medicinal product: it is the holder of the licensing rights in the country of origin of the medicinal product that is the contact for pharmacovigilance.

The requirements of article R.5144.20 of the Public Health Code must be applied:
1°) – immediately notify (within a maximum of 15 calendar days from the date of receipt) to the Afssaps any serious adverse reaction (unexpected and/or expected) occurring in France, and any unexpected serious adverse reaction occurring outside the European Union which he/she has knowledge of.
This declaration is made by fax to the Pharmacovigilance Unit of the Afssaps using form CIOMS-1A Suspect adverse reaction report (fax: 01 55 87 35 32). Declarations are written in French or English and the term “Named or cohort ATU” is indicated in full on the form. For serious adverse reactions occurring in France, the unexpected nature of the reaction along with the causal relationship (according to the French method) must be indicated on the declaration.
In the case of a serious reaction occurring in France or another country and irrespective of the context of use (clinical trial, post-MA, ATU or compassionate use) requiring information to be sent to users rapidly (doctors, pharmacists, patients), it is essential to contact the ATU Unit at the Afssaps, which will contact the pharmacovigilance unit and the clinical trials unit if necessary.
If applicable, the adverse reactions are also reported to the Regional Pharmacovigilance Centre appointed by the Afssaps to be responsible for national pharmacovigilance monitoring for the medicinal product.

2°) – establish a periodic safety update report presenting an assessment of the information relative to all adverse reactions declared or reported and all the information useful for evaluation of the risks and benefits related to the use of the medicinal product:
- immediately on request
- every 6 months for the first two years, every year for the next 3 years, etc.
However, the submission calendar may be different and revised at the time of the first ATU and subsequently.
The birth date of this report is the date of the first named ATU or granting of the cohort ATU.
These reports are sent to the Afssaps (ATU Unit and Pharmacovigilance Unit) and to the designated Regional Pharmacovigilance Centre if applicable.

This report must have the format of the PSUR (Periodic Safety Update Report): in this report, the summary of the adverse reactions notified in France in the context of the ATU will be isolated. This French report will include the following for a given period and also in a cumulative manner:
- an estimate of the number of patients treated,
- the total number of cases and adverse reactions and a breakdown of this number by seriousness and expectedness (tables),
- a list of adverse reactions classified by body system, presented in tabulation,
- a synthetic analysis of all the adverse reactions (irrespective of seriousness) for each organ system, in particular specifying their time to onset, their time to regression and their outcome;
- the number of treatment discontinuations related to adverse reactions, including a table by organ system;
- the number of cases with a fatal outcome;
- the number of cases of use of the medicinal product during pregnancy;
- and, appended, a summary of cases, with the causal relationship with each medicinal product (using the French method) or a copy of the CIOMS format form.

If the PSUR format summary report cannot be submitted by the company within the period defined, the company must supplement the French summary with:
- cumulative data relative to the status of the medicinal product internationally and, for the period considered:
- collection of publications related to pharmacovigilance for the period considered,
- an assessment of measures taken for safety reasons by the regulatory authorities or by the company or organisation distributing the medicinal product (modification of an investigator's brochure, a summary of product characteristics for another country, sending of a letter to prescribing physicians (“Dear Dr letter”), foreign press release, etc.)
- the nature of the modifications to the reference medical information related to safety (Company Core Data Sheet).

The conclusion will enable comparative evaluation of the benefit/risk ratio relative to the previous period.

3°) SPECIFIC situations

a) Cohort ATU
For medicinal products subject to a cohort ATU, the periodic safety update report will represent the second part of the cohort ATU periodic report, with the first part describing the actual conditions of use of the medicinal product (cf. 7.10). All these data will be presented for the given period and also cumulatively.

b) When the product is used in France as a cohort ATU and a named patient ATU, the French summaries will be supplied in the same report, but analysed separately.

c) ATU in France and MA in one or more other countries
The periodic safety update reports (PSUR) produced for these countries will be supplied to the Afssaps whenever they become available throughout the period during which the product is used in France as an ATU or on request for documents prior to the ATU application. Either the calendar coincides with the schedule planned in France and these reports will contain a summary of the information gathered in the context of the ATU in France, or it does not coincide and the international PSUR and the France summary will be supplied separately.

8.2.3. Role of Regional Pharmacovigilance Centres

In particular, Regional Pharmacovigilance Centres are responsible for:
- collecting any information relative to the adverse reactions of medicinal products, including those subject to an ATU
- collecting declarations made by health professionals,
- transmitting the above information to the Afssaps, without delay in the case of serious effects
- fulfilling the role of expert, conducting studies and surveys at the request of the authorities.

If necessary, a Regional Pharmacovigilance Centre may be appointed by the Afssaps to be specifically responsible for the national pharmacovigilance monitoring of a medicinal product, working closely with the company or organisation distributing the medicinal product. It will be sent a copy of serious reactions notified to the Afssaps and summary reports and will play the role of expert for the analysis of these documents (inform the Afssaps of any data that it deems should be rapidly evaluated, ensure that the evaluation made by the pharmaceutical company makes it possible to compile an adverse reaction profile, calculate the incidence, position the risk observed or estimated relative to the risks of other medicinal products in the same therapeutic or pharmacological class, in comparison with other treatments or the absence of treatment, etc.) It may ask for additional information, propose actions relative to the prevention of the risk of an adverse reaction and evaluate proposals made by the
pharmaceutical company (cf. Good pharmacovigilance practices – Appendix 1: pharmacovigilance survey procedure).

8.2.4. Role of the Afssaps and the pharmacovigilance unit
The Afssaps studies the information sent to it by the company or organisation distributing the medicinal product and the Regional Pharmacovigilance Centres and takes all necessary measures to ensure correct use of the medicinal product.
The Afssaps informs the company or organisation distributing the medicinal product of any serious adverse reaction declared or notified to it (article R.5144-8 of the French Public Health Code).

IX. Withdrawal and suspension of an ATU
The authorisation may be withdrawn or suspended by the Afssaps if the conditions of article L.5121-12 of the French Public Health Code are not longer met or for public health reasons. These decisions are justified.
A suspension decision cannot be made for a period of more than three months.
A withdrawal decision may only be made after the holder of the authorisation has been invited to provide its comments and, for the cohort ATU, following the opinion of the marketing authorisation committee (French Commission d'AMM).

X. Approval for hospital use of ATU medicinal products
The DSS (French Government Department for Social Security) circular – 1C/DGS/DH/96 No. 710 of 21st November 1996 lays down the conditions according to which medicinal products subject to an ATU are approved for hospital use.

Medicinal products subject to a cohort ATU are included in the list of medicinal products approved for hospital use; this inclusion is automatic, with the approval of the cohort ATU issued by the MA commission being equivalent to a proposal for inclusion on the list.

Medicinal products subject to a named ATU are deemed to be approved for hospital use.

During the temporary period between the time a cohort ATU is obtained and publication of approval for hospital use under these conditions, internal pharmacies of healthcare establishments are authorised to purchase the medicinal products concerned. Pharmacies are authorised to purchase medicinal products with a named ATU throughout the duration of these ATUs.

For medicinal products subject to a cohort ATU or a named ATU, the approval granted as an ATU remains valid until a decision is made relative to the application for approval by the terms of the MA, on the condition that the latter is filed within 2 months following notification of the MA to the holder.

A copy of the application for inclusion of the medicinal product on the list of medicinal products approved for hospital use by the terms of the MA must be sent to the ATU Unit of the Afssaps.

XI. Change from ATU to MA
Article R.5142-29 of the French Public Health Code stipulates that when a medicinal product subject to an ATU obtains a MA, the Director General of the Afssaps sets the date on which the ATU ceases to be applicable, on the basis of the date of notification of the MA and the time required to make the authorised medicinal product available according to the MA conditions.

This date is set with the pharmaceutical company and is the subject of notification from the Afssaps.

This date is mainly dependent on the time required to ensure compliance of the package leaflet and labelling with the MA and thus the supply of the medicinal product in accordance with the MA.
In no case does it take into account the time required to publish the decision of approval for hospital use made by the terms of the MA or inclusion of the medicinal product in the list of reimbursable products, which are texts related to reimbursement of the product and not to the marketing authorisation itself.

Indeed, concerning this point, circular No. 710 of 21st November 1996 stipulates that public healthcare establishments and private healthcare establishments participating in the public service may continue to purchase the medicinal product until publication of the decision of approval for hospital use made by the terms of the marketing authorisation. These provisions make it possible to prevent any break in treatment availability.

The period must be as short as possible and may not exceed three months, apart from exceptional cases. The ATU holder must therefore work with the Afssaps (ATU Unit) from as early a stage as possible in order to limit these deadlines.

XII. Advertising

A medicinal product with an ATU cannot be the subject of any advertising, in accordance with article L.551-2 of the Public Health Code, which specifies that only medicinal products that have obtained a marketing authorisation may be advertised.

If information is sent by the pharmaceutical companies to prescribing physicians and users of the medicinal product, this must comply with the summary of product characteristics validated by the Afssaps in the case of cohort ATUs and, in all cases, must first be sent to the Afssaps (ATU Unit) for its opinion.
APPENDICES

- A. Named patient ATU Cerfa application form
   This form is available on the Afssaps website:
   www.afssaps.sante.fr in the practical information section,
   or directly from the French Ministry of Health’s website:
   www.sante.gouv.fr/cerfa/autotemp/atu.pdf

- B. Cerfa form for notification of an adverse reaction that could be due to a medicine or product mentioned in article R.5144-1
   This form is available on the Afssaps website:
   www.afssaps.sante.fr in the practical information section,
   or directly from the French Ministry of Health’s website:
   www.sante.gouv.fr/cerfa/efindes/abvitot.pdf

- C. Roles of the various parties
### “Roles of the various parties”

<table>
<thead>
<tr>
<th>Named ATU</th>
<th>Cohort ATU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescribing physician</strong></td>
<td></td>
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<tr>
<td>The use of the Medicinal product is under his/her responsibility.</td>
<td>He/she must comply with the protocol for therapeutic use: (prescribing criteria, conditions for monitoring and informing patients; data collection; pharmacovigilance procedures) or with the SPC where there is no protocol for therapeutic use.</td>
</tr>
<tr>
<td>The medicinal product may only be used after having obtained an ATU from the Afssaps.</td>
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<tr>
<td>He/she must provide the Afssaps with an ATU application detailed on a Cerfa form, justifying the application.</td>
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<tr>
<td>He/she must transmit the application via the pharmacist of his/her hospital, who sends it to the Afssaps.</td>
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<tr>
<td>He/she must inform the patient about the status of the medicinal product and provide him/her with all the information relative to the medicinal product.</td>
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<tr>
<td>He/she must notify adverse reactions to the Regional Pharmacovigilance Centre.</td>
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<tr>
<td>He/she keeps the Afssaps informed about the efficacy/safety of the treatment if he/she wants to renew the ATU.</td>
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<tr>
<td><strong>Company</strong></td>
<td></td>
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<tr>
<td>Labelling.</td>
<td>Labelling.</td>
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<tr>
<td>Distribution by the terms of the ATU issued by the Afssaps.</td>
<td>Package leaflet.</td>
</tr>
<tr>
<td>Distribution to an internal pharmacy or an authorised structure.</td>
<td>Distribution only to an internal pharmacy or authorised structure.</td>
</tr>
<tr>
<td>Pharmacovigilance report to the Afssaps.</td>
<td>Compliance with protocol for therapeutic use.</td>
</tr>
<tr>
<td>Submission to the Afssaps, for its opinion, of any information relative to the medicinal product, before its circulation.</td>
<td>Monitoring of users' compliance with the protocol.</td>
</tr>
<tr>
<td><strong>Hospital pharmacist</strong></td>
<td></td>
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<tr>
<td>He/she sends the ATU application to the Afssaps.</td>
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<tr>
<td>He/she takes receipt of the ATU and informs the prescribing physician.</td>
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<tr>
<td>He/she orders, imports if necessary, takes receipt of and dispenses the medicinal product after having obtained the ATU.</td>
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<tr>
<td>He/she manages stocks in accordance with good practices.</td>
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</tr>
<tr>
<td>He/she must notify the Regional Pharmacovigilance Centre of any adverse reactions.</td>
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