Agence nationale de sécurité du médicament et des produits de santé

Notice to applicants for marketing

for Temporary Authorisation for Use (ATU)

July 2015

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CONTENTS

I. GENERAL PRINCIPLES AND LEGISLATION

1.1 Legislative and regulatory provisions relating to ATUs

At European community level, Article 5 (1) of Directive 2001/83/EC, duly amended, introducing a community code relating to medicinal products for human use provides an option for Member States to authorise, in some specific cases, the exceptional use of medicinal products that have not been granted marketing authorisations (MA).

In France, the exceptional use of pharmaceutical proprietary products that do not have MA and are not used in clinical trials is covered by obtaining a Temporary Authorisation for Use (ATU) in advance. The ATU is issued by the French National Agency for Medicines and Health Products Safety (ANSM).

In fact, by way of derogation from the MA procedure, Article L.5121-12 of the French Code of Public Health sets exceptional regulations governing the use for therapeutic purposes of medicinal products without a MA in France and intended to treat serious or rare diseases when no appropriate treatment exists and the initiation of treatment cannot be deferred.

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

Cohort ATU (cATU) covers medicinal products of which the efficacy and safety of use are strongly presumed and intended for a group or sub-group of patients treated and monitored in accordance with criteria defined in a protocol for therapeutic use and collection of information (PTU).
It is issued at the request of the holder of the distributing rights who has filed or is in the process of filing a MA request within a set timescale;

Nominative ATU (nATU) – this is issued for a single named person who cannot participate in a clinical trial, at the request and under the responsibility of the prescribing physician where the medicinal product is expected to be of benefit for the patient.
These are medicinal products with an efficacy/safety ratio presumed to be favourable for these patients based on available data.

The nominative ATU can only be issued by the ANSM if there has been a request for a cohort ATU or MA for the medicinal product concerned (or if the pharmaceutical company is in the process of filing such a request within a set timescale) or if a clinical trial is ongoing in France (or an authorisation application has been submitted).

However, by way of derogation, a nominative ATU can also be issued in one of the 3 following hypothetical situations even if the afore-mentioned requirements have not been met:
- given the treatments available, the patient will most likely experience serious consequences
- Where the medicinal product has been withdrawn from the market, the therapeutic indication requested differs from the one authorised and the medicinal product is definitely assumed to be safe and effective in the therapeutic indication requested;
- a request for a cohort ATU or application for clinical trial authorisation was rejected in the therapeutic indication requested but there is an individual benefit for the person for whom a nominative ATU has been requested, and the prescriber and the patient have been informed of the reasons why the application was rejected.

A Protocol for Therapeutic Use and the collection of information (PTU) drawn up between the ANSM and the holder of the distributing rights of the medicinal product must set up for all ATUs except nominative ATUs issued by way of derogation. This PTU specifies in particular the monitoring procedure for treated patients and the collection of data relating to efficacy, adverse events, actual conditions of use and the characteristics of the population benefiting from the authorised medicinal product. It also contains information compiled specifically for patients and which must be issued by the prescribers.

The use of proprietary medicinal products with an ATU cannot replace a clinical trial and serves no investigational purpose. The decision to grant an ATU must not hamper the initiation or continuation of clinical trials which can provide essential, accurate answers to questions regarding the benefit/risk

ratio of a medicinal product. In fact, patients can only receive treatment for which no MA has been granted when taking part in a clinical trial. The latter will provide reliable data on the product in question, essentially in terms of efficacy and safety in use, interactions with other medicinal products and therapeutic strategies, etc.
The choice of methods used to make medicinal products without MAs available (within the scope of an ATU or clinical trial) depends primarily on the amount of information available on the product in question. Generally and especially in the early stages of drug development, preference must always be given to clinical trials.

Similarly, n ATU is not a means to continue treating a patient with a drug introduced during a clinical trial. To do this, the clinical trial in question must be extended within the scope of a protocol amendment or a clinical trial of continuing treatment.
The ATU can be amended, suspended or withdrawn on public health grounds or if the conditions that led to the granting of the ATU are no longer met.

Articles R.1521-168 et seq. of the French code of Public Health set the guidelines for the presentation, instruction and content of ATU applications, conditions for granting and rejecting an ATU together with related publicity and follow-up strategies.

1.2 Provisions relating to the importing of medicinal products subject to ATUs

In accordance with Articles L.5124 -13 and R.5121-108 of the French code of Public Health, the nominative and cohort ATUs are equal to importation authorisation. Consequently, there is no need to submit an import authorisation request to the ANSM for medicinal products with an nominative ATU or cohort ATU.
However, specific importation of a medicinal product subject to nominative ATU for stockpiling in a pharmaceutical establishment or hospital pharmacy require prior authorisation by the ANSM Director General (see chapter 5.3).

1.3 Provisions relating to pharmacovigilance

Pharmacovigilance, as provided for in Articles R. 5121-150 et seq. of the French code of Public Health applies to medicinal products covered by an ATU.

Pharmacovigilance rules for medicinal products for which an ATU has been granted are the same as those governing MA-approved medicinal products. Nevertheless, certain specific measures may apply since Article R.5121-172 of the French code of Public Health provides that:

- in the case of medicinal products for which a ATU has been granted with PTU: this PTU sets procedures for implementing the obligations specified in Articles R.5121-161 and Articles R.5121-166 to R. 5121-170.
- In the case of medicinal products for which a nominative ATU without PTU has been granted: periodical safety update reports follow a specific template set out by decision of the ANSM Director General.

1.4 Regulatory provisions relating to conditions of prescription, dispensing and retrocession of medicinal products

The provisions provided for in Articles R.5121-77 to R.5121-95 and R.5126-102 to R.5126-115 of the French code of Public Health apply to medicinal products for which a ATU has been granted.

1.5 Provisions relating to ATU cost

For information purposes, it should be highlighted that Article L.162-16-5-1 of the French code of Social Security outlines the terms and conditions according to which the pharmaceutical company with the distributing rights for a medicinal product subject to ATU reports to the Comité Economique des Produits de Santé (CEPS) – the French Health Care Products Pricing Committee the amount of the payment it requests from hospital pharmacies and, in the absence of a distributing pharmaceutical company, the terms and conditions via which the hospital pharmacies report the amount payable.

1.6 Other European provisions

Article 83 of EC Directive No. 726/2004 dated 31 March 2004 provides Member States with an opportunity to make available a medicinal product covered by the centralised MA procedure (either as an obligation or as an option) "for compassionate use" provided that this medicinal product is either the object of a MA application submitted to the European Medicines Agency (EMA) or clinical trials. This applies to the following medicinal products:

- Obligatory field:
  - medicinal products obtained using one of the following biotechnological processes: recombinant DNA technology; controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells; methods based on hybridomas and monoclonal antibodies;
  - advanced therapy products, as defined in Article 2 of EC Regulation No. 1394/2007
  - medicinal products containing a new active substance, which on 20 November 2005 was not authorised within the Community and indicated in the treatment of one of the following diseases: AIDS, cancer, neurodegenerative disease, diabetes and, as from 20 May 2008, auto-immune diseases and other immune deficiencies and viral diseases.
  - Medicines referred to as orphan drugs, in accordance with (EC) Regulation No. 141/2000.

- Optional field:
  - medicinal products containing a new active substance, which on 20 November 2005 was not authorised within the Community;
  - Medicinal products for which the applicant shows that they are significantly innovative on a therapeutic, scientific or technical level or that the granting of an authorisation in accordance with the centralised procedure is of interest for patients on a community level.

In terms of "compassionate use", the afore-mentioned regulation makes one of the afore-mentioned medicinal products available on compassionate grounds to a group of patients who cannot be treated satisfactorily with an authorised medicinal product and who are suffering from a debilitating, chronic, serious or life-threatening disease. In France, this procedure corresponds to the provisions previously referred to in relation to cohort ATUs.

This regulation does not apply to compassionate use on individual grounds (nominative ATU in France).

Essentially, this regulation ensures that:
- Member States (MS) notify the EMA of their intention to introduce a compassionate use programme,
- The EMA Committee for Medicinal Products for Human Use (CHMP) may adopt opinions on the conditions of use and distribution of the medicinal product concerned and the patients targeted.

In order to implement the procedure covered in this article a Guideline on the Compassionate Use of Medicinal products, pursuant to Article 83 of (EC) Regulation No. 726/2004/July 2007 was drafted by the CHMP and is available on the EMA website (www.ema.europa.eu).
This guideline specifies in particular:
- the scope of application of the procedure (see above),
- the initiation of a CHMP opinion and the scope of that opinion,
- Transparency measures implemented by the EMA.

Furthermore, it should be remembered that:
- the implementation of a compassionate use programme lies within the competence of the Member States (MS),
- The enrolment of patients in clinical trial must be promoted before compassionate use program is offered.
- The opinion of the CHMP is required either when expressly requested by a MS or when two MSs report a compassionate use programme for the same medicinal product, even if these MS have not specifically requested an opinion from the CHMP.

II. MEDICINAL PRODUCTS CONCERNED AND CONDITIONS GOVERNING PRESCRIPTION, DISPENSING AND RETROCESSION

2.1 Medicinal products concerned

The ATU allows the use, outside the scope of clinical trials, of pharmaceutical proprietary products with no MA in France, regardless of whether or not a MA has been granted for these products abroad.

The following situations in particular do not fall within the ATU framework:

- continuing treatment at the end of a clinical trial – this is subject to an amendment to the initial protocol or the introduction of a clinical trial of continuing treatment,
- The use of a medicinal product with a MA in France for an indication other than the one provided for in its MA. The prescriber is responsible for this off-label use. This may be recommended by ANSM within the scope of a recommendation for temporary use (RTU),
- The use of a hospital or pharmaceutical preparation obtained from a proprietary product with no MA in France.
- Medicines for which an import authorisation has been granted by ANSM given the fact that the product is unavailable in France (due to a shortage of supplies, no longer being marketed or removal from the market in particular).

2.2 Conditions governing prescription, dispensing and retrocession

The provisions provided for in Articles R.5121-77 to R.5121-95 and R.5126-102 to R.5126-115 of the French code of Public Health apply to medicinal products subject to ATUs.

In accordance with Article R.5121-83 of the code of public Health, the classification of a medicinal product for which an ATU has been granted in the category of medicinal products reserved for hospital use implies that the prescription, dispensing and administration are carried out within a health care establishment.

Moreover, in some cases, the prescription can be restricted to certain categories of prescribers and may depend on regular tests carried out by the patient.

Medicinal products with ATUs are not available from retail pharmacies and can only be dispensed by pharmacists of hospitals, or internal health establishment pharmacies or by the responsible person referred to in Article L5126-6 (Article R.5121-71-1 of the French code of Public Health).

When the medicinal product with an ATU is not reserved for hospital use, it is:

- in the case of a nominative ATU – entered in the list provided for in Article L.5126-4 of the Public Health Code (retrocession list),
- In the case of a cohort ATU – entered in the afore-mentioned list by the Minister for Health after having obtained an opinion from ANSM, except in an emergency, or a recommendation from this body.

In practical terms, the medicinal products included in the retrocession list can be sold to the general public by hospital (public or private) pharmacies authorised to carry out this activity and reimbursed by the health insurance fund under the terms and conditions provided for in Article R.5126-110 of the French code of Public Health.

III. IDENTITY OF THE ATU APPLICANT

Requests for nominative ATUs are initiated by the prescribing physician and faxed to ANSM by the health establishment pharmacist. If approval is granted, this physician will be the holder of the nominative ATU.

Requests for cohort ATUs are submitted to ANSM by the holder of the distributing rights for the medicinal product subject to the cohort ATU or someone appointed on his/her behalf.

IV. RECIPIENT OF ATU APPLICATIONS

Holders of the distributing rights submit their cohort ATU applications to:

ANSM
DQFR – PGF Code enveloppe: 510
143 – 147 boulevard Anatole France
93285 SAINT-DENIS Cedex. FRANCE
Fax: (33) 1 55 87 36 12
Tel.: (33) 1 55 87 36 11

Requests for nominative ATUs are faxed by the hospital pharmacy to 01 55 87 36 12.

V. NOMINATIVE ATUs

5.1 Dossier of requests for nominative ATUs

Requests for nominative ATU are submitted using a form (Appendix A) available on the ANSM website: www.ansm.sante.fr (ATU).

In accordance to Article R.5121-69 of the French code of Public Health, they mainly contain information about the treatment planned (name of the medicinal product, dosage, pharmaceutical form, posology and possibly duration of treatment), the patient (initials of first name and surname, age, weight and gender), the precise therapeutic indication and the reasons for the request.
This form must be completed legibly, preferably directly online, by the pharmacist of the health establishment concerned and then dated and signed by the prescribing physician. Accurate contact details are provided.

In cases where any information relevant for the assessment of the request cannot be transcribed on the form, one or more separate documents can be attached, specifying references for the request (prescriber's name, patient's initials, name of the medicinal product).
If additional information is required by ANSM, this must be submitted as soon as possible, enclosing a copy of the initial request form, if possible.

5.2 Nominative ATU application assessment and ANSM's decisions

Each request is assessed by the Product Division for the therapeutic range concerned (see organogram available online on the *ansm.sante.fr* website), clicking the "ATU" link relating to the ANSM Evaluation Division.

This assessment focuses on the medicinal product, its pharmaceutical grade, safety in use and efficacy in the indication claimed in the ATU request and the absence of any appropriate treatment alternative.
Each nominative ATU request is assessed individually by ANSM.

To this end, ANSM relies on a dossier submitted at its request by the holder of the distributing rights for the medicinal product for which the ATU is requested. This dossier mainly comprises:

- a copy of the Summary of Product Characteristics (SmPC) when the medicinal product is authorised abroad or otherwise an equivalent document;
- Any information available relating to the pharmaceutical quality, efficacy and safety of use [bibliography, investigator's brochure, investigational drug dossier, PSUR (periodic safety update report) and DSUR (development safety update report or clinical trial annual safety report, etc.];
- if necessary, the option for the holder of the distributing rights to have this medicinal product available early in France;

- If applicable, the list of ongoing clinical trials and clinical trials scheduled in France and abroad.

The prescribing physician requesting an ATU may also supply a list of references justifying the ATU request, if asked to do so by ANSM.

Following its evaluation, ANSM will make one of the following decisions:

- to grant an ATU: this authorisation essentially contains the following information: name of the medicinal product, prescriber's contact details, patient's initials, duration of authorisation, contact details of the health establishment pharmacy.
  The ATU is faxed to the pharmacist who informs the prescriber accordingly. It may be accompanied by a letter to the prescriber and, if necessary, a copy of the Summary of Product Characteristics approved abroad or a Treatment Information Leaflet drawn up by ANSM.
- to refuse an ATU: the ATU may be refused, usually for the following reasons:
  - Existence of an appropriate alternative treatment that has already been granted a MA in France and is available on the market,
  - And/or lack of relevant, adequate information to assume the efficacy and safety of the medicinal product in the patient's clinical situation,
  - And/or use requested for investigational purposes,
  - And/or possible inclusion in an ongoing clinical trial.

The refusal is faxed to the pharmacist who informs the prescriber accordingly, and by registered letter with notification of receipt to the prescriber. A request for the decision to be reconsidered can be submitted to the Director General of the ANSM and/or an appeal may be lodged with the relevant administrative court within 2 months of receiving this decision.

The length of time taken by ANSM to respond to nominative ATU requests depends on the therapeutic emergency on the one hand and ANSM's level of knowledge about the medicinal product on the other hand. Thus:

- when the medicinal product has already been evaluated by ANSM, especially in the indication under consideration, the decision may be given relatively quickly (24 to 48 hours on average);
- When the medicinal product has never been evaluated before or has been evaluated for a different therapeutic purpose, the response time takes into account the length of time required to compile and assess the dossier.

5.3 Procedure for obtaining the medicinal product subject to nominative ATU and importing medicinal products

A nominative ATU serves as importation authorisation. If the product is not available in France, the health establishment pharmacist can import it himself or via a pharmaceutical establishment. The order must be accompanied by a copy of the nominative ATU issued by ANSM. The pharmacist in question is therefore responsible for importing, receiving and dispensing the medicinal product.

In order to optimise the dispensing schedule, medicinal products for which the importation or order delivery times can be lenghtly, can be stored and are available within health establishment pharmacies. Medicinal products stockpiling by these pharmacies can be authorised by ANSM in order to respond to severe emergency treatment situations or for other clinical situations that frequently arise within the same establishment.

Requests for stockpiling by hospital pharmacies, which must be duly justified, are written on hospital pharmacy headed paper and must stipulate the indication for which the product will be used. These are then faxed to ANSM on 01 55 87 36 12).
Even if the medicinal product is in stock, it cannot be dispensed by the pharmacy until ANSM issues the nominative ATU for the person in question, except in specific situations where the medicinal product is intended to be used in extreme clinical emergency situations.

5.4 Duration of a nominative ATU and treatment continuation

The duration of the nominative ATU is stipulated on the authorisation decision. It is equivalent to the treatment duration and cannot exceed one year.

If treatment has to be prolonged, the ANSM is asked to renew the ATU. This request is carried out under the same terms and conditions as the initial request, stipulating the nature of the request (renewal) and repeating the previous ATU number and any information relating to the safety and efficacy of the medicinal product warranting continuing treatment for the patient.

5.5 Patient information subject to a nominative ATU

The prescribing physician must be able to justify that, prior to the initiation of the treatment, the patient, his/her legal representative or person of trust has received suitable information relating to his/her situation, including confirmation that no other alternative treatment is available, the exceptional terms and conditions surrounding the authorisation of this medication, the risks incurred, constraints and the benefit the patient is likely to experience as a result of taking this medication. The relevant procedure used is described in the patient's medical record.
When a PTU is implemented for the medicinal product in question, a patient's information leaflet is issued by the prescriber accompanied by all of the verbal explanations required in order to promote understanding.

5.6 Role of the prescribing physician subject to a nominative ATU

The prescribing physician:

- informs his/her patients (see 5.5) and, if possible, their general practitioner and records the relevant information procedure used in the medical records of the patients concerned;
- strictly monitors the treated patients and, if necessary, collects and sends the information gathered in accordance with the terms and conditions stipulated in the PTU;
- complies with pharmacovigilance requirements (see chapter VII);
- keeps the pharmacist in his/her health establishment informed of the patient treatment procedure for the medicinal product in question;
- Answers to all requests for information from ANSM, to evaluate its request or as part of monitoring of the patient treated.

5.7 Information of prescribing physicians on medicinal products subject to nominative ATU

ANSM sends the following to the prescribing physician:

- A letter notifying the decision to grant an ATU and, in certain circumstances, contains information on warnings, precautions for use and/or adverse effects.
- a copy of the Summary of Product Characteristics (SPC) approved abroad, if available,
- Or, if necessary, if no SPC is available, a therapeutic information leaflet summarising the main characteristics of the medicinal product.

If the company distributing the medicinal product under ATU wishes to forward information about the said product to prescribers, the data must be validated in advance by ANSM (see chapter X).

5.8 Role of the health establishment pharmacist subject to nominative ATU

The pharmacist

- Sends the request for a nominative ATU to ANSM.
- Collects additional information requested by ANSM, if required.
- Receives the ATU, informs the prescriber accordingly and forwards a copy of any documents enclosed by ANSM, if required.
- Orders, imports, if required, receives and dispenses the medicinal product.

- Complies with pharmacovigilance requirements (see chapter VII).
- Where applicable, acknowledges and ensures compliance with PTU.
- Where applicable, receives an abridged version of the summary report approved by ANSM from the holder of the distributing rights.

5.9 Labelling of the medicinal product subject to nominative ATU

The label includes the name of the medicinal product at least, together with its code name, manufacturing batch number and expiry date, where applicable.

5.10 Protocol for therapeutic use and information collection (PUT)

Apart from exempt situations discussed in 1.1m the nominative ATUs are subject to a PUT between the company and the ANSM. This PUT essentially sets the terms and conditions for using the medicinal product and monitoring the patients (see 1.1, 6.2, 7.2 and template in annex E2).

5.11 Role of the company distributing the medicinal product subject to nominative ATU

The company distributing the medicinal product within the scope of a nominative ATU supplies the hospital pharmacy or the authorised person, in accordance with the ATU issued by ANSM.
It can only distribute to health professionals information relating to the medicinal product that has been previously validated by the ANSM (see X). When applicable, the company shall implement a PTU drawn up in conjunction with ANSM. In this case, it will draft a summary report of the data collected (see 6.9) and send it to ANSM within a set timeframe. Pharmacovigilance provisions shall be applied (see VII).

5.12 List of medicinal products subject to nominative ATU

The list of medicinal products for which nominative ATUs have been issued for a set period is available on the ANSM website: www.ansm.sante.fr.

VI. COHORT ATU

6.1 Cohort ATU application dossier

A cohort ATU application can be submitted by the holder of the medicinal product distributing rights:

- either at the same time as a MA application;
- Or prior to a MA application provided that a marketing authorisation request is subsequently filed within a set period.

The dossier shall include the information listed in Article R.5121-68 of the French code of Public Health and essentially:
a – the application for cohort ATU presented on the application form consistent with the template provided for in the decree dated 6 July 2007 (see Appendix D), which includes in particular:
- The reasons for the application, pursuant to Article L.5121-12 of the French code of Public Health,
- The commitment to file a MA application and the date scheduled for this submission.

b – An administrative dossier:
- A copy of the MA application, if relevant,
- The draft Summary of Product Characteristics (mSPC), Patient Information Leaflet and Label written in French,
- The draft protocol for therapeutic use and information collection, written in French (see template in Appendix E),
- the titles and objectives of the ongoing clinical trials, providing a progress report and details of research programmed for the same disease in France or abroad, the identity of the principal investigator(s) in France and the relevant study centre(s),

- if the medicinal product is authorised abroad: a copy of the authorisation issued by the competent authority concerned, a copy of the corresponding Summary of Product Characteristics, the last periodic safety update report (PSUR) or equivalent document,
- The European "orphan drug" designation, if relevant,
- Any information on an exceptional and early use of the medicinal product abroad ("compassionate use" or "expanded access programme", etc.) in the indication requested,
- A copy of the scientific advice(s) issued by the ANSM, the European Medicines Agency (EMA) or any competent authority, as relevant,
- The estimated number of patients in France affected by this request.

c – A dossier relating to the medicinal product:
The dossier contains all of the pharmaceutical and pharmacology-toxicology-clinical data available at the time of the request (even if the studies are ongoing).
The format of the dossier should resemble MA dossiers as closely as possible:

- dossier summary comprising expert reports, if available,
- chemical, biological and pharmaceutical data,
- pre-clinical and pharmacological data,
- clinical data,

If need be, the medicinal product dossier can be presented in the format of an updated investigational medicinal product dossier (see clinical trial authorisation procedure / IMPD – investigational medicinal product dossier).

The dossier, which can be written in French or English, must be submitted:

- in the form of a hard copy (5 copies) plus an electronic file (on CD Rom or USB key)

Or

- In a structured electronic format (E-CTD or NEES).

The dossier is to be submitted to the ANSM (DQFR – PGF, envelope code: 510) once the relevant Product Directorate and ATU Officer within the Evaluation Directorate have been informed by telephone, fax, mail or by mail or e-mail (atu@ansm.sante.fr).

The ANSM acknowledges receipt of the application to the applicant; it specifies the date on which the dossier was received and the number allocated to it. If the dossier is incomplete, the ANSM will send the applicant a list of missing documents. The procedure will only begin on receipt of a dossier eligible for assessment, i.e. complete.

6.2 Protocol for therapeutic use and information collection (PUT)

The protocol is prepared by the holder of the distributing rights for the medicinal product in close conjunction with the ANSM and must be approved by both parties.

The aims of the protocol are:

- to provide prescribers with all of the relevant information regarding the medicinal product and its use,
- to organise patient monitoring,
- to collect information relating to the real use of the medicinal product, the characteristics of patients treated with this product, the efficacy of the medicinal product and the adverse events resulting from its use with a view to drafting a periodic summary report and forwarding it to ANSM,

The contents of the protocol (see template in Appendix E) are described in detailed in Article L. 5121-70 of the French code of Public Health. It mainly comprises:

- a reminder of the general principles of ATU,
- the draft summary of product characteristics of the medicinal product with cohort ATU and the practical methods regarding the use, prescription and supplying of the medicinal product,
- patients information methods (patient information note),
- patients monitoring methods,
- methods to be used by the prescribers (including follow-up forms) then by the holder or the exploitant of the cohort ATU for the collection of information relating to patients follow-up

(especially the characteristics of the patients treated, the effective use of the medicinal product, the adverse events),
- pharmacovigilance obligations to be implemented,
- methods for the preparation of the periodical summary reports by the ATU holder,
- Methods for circulating the summary of these periodic summary reports to the partners concerned.

6.3 Assessment of cohort ATU applications

Each request is evaluated by the Product Directorate of the therapeutic area concerned (see organogram available online on the *ansm.sante.fr* website), by clicking the "ATU" link of the ANSM Evaluation Directorate.

The cohort ATU application is evaluated mainly with regards to the pharmaceutical quality, the safety and the efficacy of the medicinal product in the indication claimed, the draft protocol for therapeutic use and information collection, the draft summary of product characteristics, patient information leaflet and labelling, the conditions for prescription and supply, and the lack of therapeutic alternative on the French market.

The cohort ATU is granted for a precise indication, which must be respected. It is accompanied by the summary of product characteristics, the patient information leaflet, the labelling and the protocol for therapeutic use and information collection; all of these documents are published on the ANSM website. The ANSM sets the frequency for the periodic summary report (see 7.9). A regional pharmacovigilance centre (CRPV) can, if necessary, be appointed by the ANSM to ensure the national follow-up of the medicinal product-related adverse events within the scope of the cohort ATU.

6.4 Patient information subject to a cohort ATU

Prior to the introduction to treatment, each patient, his/her legal representative or appointed confidante must be informed of the following by the prescriber:
- no alternative treatment,
- the terms and conditions governing the exceptional availability of the medicinal product,
- the characteristics of the medicinal product (essentially the benefits, risks and constraints)
- the monitoring methods,
- The methods for reporting adverse events.

The patients are also informed that the prescriber will collect data relating to their treatment and that this data will be sent to the holder of the cohort ATU and to the ANSM, and could be processed electronically. In accordance with Law No. 78-17 of 6 January 1978, duly amended, i.e. the "French Data Protection Act", the patient can, at any time, exercise his/her rights to correct this information.

An information note, which is available in the protocol for therapeutic use and information collection, is given to the patient, his/her legal representative and the appointed confidante, accompanied by verbal explanations from the prescriber. A patient information leaflet is also enclosed with each box of medicinal product.

6.5 Role of the prescribing physician subject to a cohort ATU

The prescribing physician must:

- inform the patients and, if possible, their general practitioner (see 6.4) and record the information procedure followed in the medical dossier of the persons concerned;
- inform the health establishment pharmacist of the procedure for treating patients with the medicinal product within the scope of the cohort ATU;
- comply with all of the terms and conditions governing use described in the summary of product characteristics and the protocol for therapeutic use and information collection;
- guarantee the monitoring of the treated patients and the collection and transmission of the information collected to the holder of the cohort ATU in accordance with the terms and conditions described in the protocol for therapeutic use and information collection;

- report any discontinuation of treatment and the reasons for this interruption to the pharmacist of the health establishment concerned and to the holder of the cohort ATU;
- comply with Pharmacovigilance requirements (see VII);
- Comply with obligations described in the PUT.

6.6 Role of the health establishment pharmacist subject to a cohort ATU

The health establishment pharmacist:

- acknowledges and monitors compliance with the protocol for therapeutic use and information collection;
- ensures that he/she gets all of the information relating to the treatment of patients with the medicinal product under cohort ATU in his/her establishment;
- orders, receives and supplies the concerned medicinal product, and manages stocks;
- complies with pharmacovigilance requirements (see chapter VII);
- If relevant, receives the abridged version of the summary report approved by the ANSM from the holder of the distributing rights.

6.7 Procedures for initiating treatment and obtaining medicinal products subject to a cohort ATU

The prescribing physician and/or pharmacist initially contacts the holder of the cohort ATU in order to obtain the protocol for therapeutic use and information collection, or visits the ANSM website.
After having acknowledged this protocol, the prescriber sends, via his/her establishment pharmacist, a treatment access request form, in accordance with the terms and conditions described in the protocol for therapeutic use.
This request form is validated by the company, in accordance with the criteria covered in the ATU and the corresponding protocol for therapeutic use and information collection.
Once the request has been validated, the company managing the ATU supplies the medicinal products according to the pharmacist's order.
The cohort ATU medicinal products are supplied to patients by health establishment pharmacies in accordance with the conditions for prescription and supply set by the ATU.

6.8 Role of exploitant of the medicinal product covered by the cohort ATU

The exploitant of medicinal product under cohort ATU circulates the protocol for therapeutic use and information collection to the CRPV and Anti-Poison Centres as well as, upon request, to the concerned prescribers and pharmacists.
It guarantees the implementation, and controls for each patient the compliance with the inclusion criteria defined in the protocol for therapeutic use and information collection and in the summary of product characteristics.

It collects and subsequently analyses the data transmitted by prescribers and pharmacists.

It complies with the terms and conditions for reporting adverse events (see 7.2).

It draws up a periodic summary report for the ANSM comprising the analysis of all data collected within the scope of PUT (see 6.9) and all information that could impact upon the benefit-risk ratio assessment for the medicinal product in question.
It circulates a copy of this report, once validated by the ANSM, to prescribers, dispensing pharmacists and all of the CRPV and Anti-poison Centres. These summaries are also published on the ANSM website.

At the beginning of every month, it sends the ANSM the number of new patients included in the ATU cohort in the last month. This information is e-mailed to atu@ansm.sante.fr.

It keeps the ANSM constantly informed of any new information that could trigger a change in the evaluation of the medicinal product-related benefit/risk ratio (e.g. ban, restriction imposed by a foreign authority, study results, etc.).

6.9 Periodic summary reports subject to a cohort ATU

The periodic summary reports are sent to the ANSM (5 copies) and, if relevant, to the CRPV in charge of national follow-up, within a frequency set by the ANSM.

The reports contain a description of all the data collected during the ATU period (data collected since the previous report and cumulative data) as part of the protocol for therapeutic use and information collection as well as any new and relevant information on the medicinal product that comes to light since the cohort ATU was granted, especially in terms of the real conditions regarding use and safety. They also contain an analysis of the benefit/risk ratio associated with the medicinal product.

These reports essentially contain:

- updated information on the product status abroad: MA application, MA, "orphan drug" designation if applicable,
- a description of the real terms and conditions for using this medicinal product within the ATU framework (population, posology, criteria for use, concomitant medication, etc.), based on all information collected by prescribers in the designated forms,
- efficacy data collected,
- pharmacovigilance data (see 7.2.3).
- If relevant, updated data from clinical trial information (provide the last DSUR available).

A summary of these reports, once validated by the ANSM, is sent by the ATU holder to the prescribers, to the concerned pharmacists and to all CRPVs and anti-poison centres for information, according to the frequency set by the ANSM. This summary is also published on the ANSM website (www.ansm.sante.fr).

6.10 Importing of medicinal products subject to a cohort ATU

The cohort ATU authorises imports (see 1.2).

6.11 Labelling of the medicinal product subject to a cohort ATU

Labelling complies with Appendix IIIA of the cohort ATU decision and contains at least the following information written in French:

- the name of the medicinal product or, if applicable, its code name;
- the name or head office and address of the exploitant;
- the manufacturing batch number
- the route and, if applicable, the method of administration of the medicinal product;
- the active substance composition;
- the expiry date;
- the specific precautions for storage of the medicinal product;
- The conditions for prescription and supply.

6.12 List of medicinal products with a cohort ATU

The list of medicinal products available within the scope of a cohort ATU together with the SPC, the Patient Information Leaflet, and the protocol for therapeutic use and information collection as well as the abridged versions of the summary reports are available in the ANSM internet website at www.ansm.sante.fr.

6.13 Duration of cohort ATU and renewal

The cohort ATU is granted for a period of one year and may be renewed.

A renewal application is requested by post with acknowledgement slip, no later than 2 months before the ATU expires. The Product Directorate concerned and the Evaluation Directorate ATU Officer will be informed accordingly by telephone or e-mail (atu@ansm.sante.fr).

In accordance with Article R.5121-74 of the French code of Public Health, the renewal request dossier also contains the following updated information:

- a specific ATU renewal request form (see Appendix F), mainly referring to the justification of the continuation of ATU with regard to the criteria listed in Article L.5121-12 and, if relevant, a repeat of the holder's commitment to request a MA and the scheduled date for this submission,
- a copy of the MA request, if applicable,
- if the medicinal product was authorised abroad during the previous period:
  . A copy of this authorisation issued by the competent authority,
  . A copy of the corresponding summary of product characteristics or any equivalent document,
  . The last PSUR or equivalent document,
- the PUT provided for the next period, written in French and, if applicable, highlighting and justifying the modifications requested in the enclosed correspondence,
- if changes are required, the French drafts of:
  . The summary of product characteristics
  . The patient information leaflet
  . The labelling
  . And any information justifying the requested amendments.
- the biomedical studies carried out during the period preceding the renewal request:
  . The titles and objectives of ongoing and/or scheduled biomedical studies in France or abroad for the same condition,
  . As regards studies conducted in France: the identity of the principal investigator(s) in France, the name of the research centres concerned and a progress report on these trials.
- a copy of the "orphan drug" designation obtained during the previous period, if applicable,
- a copy of any new scientific advice sent to the applicant about the medicinal product during the previous period, by ANSM, EMA or any competent authority of a European Community Member State or within the European Economic Area, if applicable,
- any new information relating to an exceptional and early use of the medicinal product in another country,
- a dossier comprising any new information on the medicinal product obtained during the previous ATU period and the consequences on its use,
- The latest periodic summary report prepared during the previous ATU period and a concise analysis of all of the reports.

The ANSM shall confirm the date on which the dossier was received to the applicant. If the dossier is incomplete, the ANSM will provide the applicant with a list of missing items. The procedure will only begin on receipt of a dossier eligible for assessment, i.e. complete.

VII. PHARMACOVIGILANCE OF ATU MEDICINAL PRODUCTS

See paragraph 1.3 for the general principle.

The European Good pharmacovigilance practices cover the medicinal products, the status of which corresponds to ATUs issued in France, referring in particular to the treatment of adverse events (see GVP – Module VI – Management and reporting of adverse reactions to medicinal products).

7.1 Role of healthcare professionals

- **Who should report?**

Any physician, dental surgeon, midwife or pharmacist aware of an adverse reaction potentially due to the medicinal product with an ATU must report it immediately.
Any other healthcare professional can also report.

- **What should be reported?**

Any (serious or non-serious) adverse event including overdose, misuse, abuse, medication error and occupational exposure.

For some products, exposure during pregnancy or lactation should also be reported.

- **How to report?**

Cohort ATU and nominative ATU subject to PUT:
The declaration is made using an adverse event reporting form provided in the protocol for therapeutic use and information collection.

Nominative ATU without PUT:
The declaration must be submitted to the CRPV using the adverse event reporting form available on the ANSM webpage (www.ansm.sante.fr) or directly by contacting the CRPV, and specifying the name of the medicinal product with an ATU has been authorised and the number of the ATU allocated.

- **To whom report?**

Cohort ATU and nominative ATU subject to PUT:
The recipient of adverse event reports is listed in the PUT: it is generally the pharmacovigilance department of the exploitant of the medicinal product with an ATU.

Nominative ATU without PUT:
The declarations should be submitted to the Regional Pharmacovigilance Centre (CRPV) in the geographical area of the healthcare professional.

- **When to report?**

All adverse events must be reported as soon as the healthcare professional becomes aware of them.

7.2 Role of the exploitant of the medicinal product with an ATU

7.2.1 Pharmacovigilance manager for the medicinal product with an ATU

The exploitant of the medicinal product with an ATU shall send the name of the pharmacovigilance manager to the ANSM.

Nominative ATU:
If there is an exploitant in France for the medicinal product with ATU, this exploitant is responsible for ensuring pharmacovigilance.
Conversely, if there is no exploitant in France, the pharmacist of the health establishment importing the medicinal product with ATU is responsible; in this case, the holder of the distributing rights in the country of origin of the medicinal product with ATU will be the contact for pharmacovigilance.

Cohort ATU:
The holder of the cohort ATU is responsible for guaranteeing the pharmacovigilance of the medicinal product with ATU.

7.2.2 Notification of adverse events

7.2.2.1 Notification to the Eudravigilance database
In accordance with Article R. 5121-166 of the French Public Health Code, the exploitant of the medicinal product with ATU must:
- submit electronically to the EudraVigilance database:
  - any serious suspected adverse event which occurred in France of which the company is directly made aware , without delay and within 15 days of receipt of the information,
  - any serious suspected adverse event which occurred in a third country of which the company is made aware, immediately and within 15 days of receipt of the information,
- And ensure that the cases which occurred in a European Union Member State are available in EudraVigilance (according to current procedures in the country in which the event occurred)

[See EMA/321386/2012/ refer to the last published version: Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period).

(See "How to report? Information intended for pharmaceutical companies concerning the electronic transmission of individual pharmacovigilance cases (31/07/2012) (361 ko)* on the ANSM website: http://ansm.sante.fr/Declarer-un-effet-indesirable/Votre-declaration-concerne-un-medicament/Votre-declaration-concerne-unmedicament/
Votre-declaration-concerne-un-medicament-Vous-etes-un-laboratoire-pharmaceutique).

If a CRPV has been appointed for the national follow-up, the exploitant of the medicinal product with ATU sends the CRPV a copy of the serious adverse events reported to EudraVigilance. The practical methods for sharing the pharmacovigilance information between the company and the CRPV are defined when the ATU is implemented.

The reports must include in the narrative:
. reference to the product's status in France when the adverse event occurred ("nominative ATU" or "cohort ATU"),
. Whether or not the event was expected with regard to the SPC or any other equivalent document available and the causal relationship for serious adverse events occurring in France.
When sending electronically to EudraVigilance the adverse events taken from the medical and scientific literature, it is recommended to send the corresponding article to the ANSM (*DM SURV-SIGNAL Envelope Code 213),* referring in the accompanying letter to the case number for facilitating its identification in the EudraVigilance database and to the concerned medicinal product if several medicinal products are quoted in the publication).

7.2.2.2: Other mandatory information
In the case of a serious event (regardless of the country in which it occurred and the frame of its use) or any new information likely to impact upon the benefit/risk ratio of the medicinal product and warranting the swift transmission of information to users of the medicinal product with ATU (physicians, pharmacists, patients), the exploitant or the company holding the distributing rights shall contact the ANSM immediately and forward all relevant documentation. Thus the exploitant or the company holding the distributing rights will inform the ANSM of any circulation or change in the information, of which the company is aware, performed in the scope of the use of the medicinal product in clinical trials to investigators, in order to guarantee the same level of information to ATU prescribers.

7.2.3 Transmission of periodic safety update reports (PSURs)
a) General information:
In accordance with Article R. 5121-168 of the Public Health Code, the PV Manager must send the following in the form of a periodic safety update report (PSUR) to the General Director of ANSM and the designated CRPV, if applicable:
1) All of the information relating to the benefits and risks associated with this medicinal product including the results of studies likely to impact upon the authorisation;
2) A scientific evaluation of the benefit/risk ratio associated with the medicinal product and carried out on the basis of all the information available;
3) All information relating to sales, prescriptions and the population exposed to the medicinal product.

b) Specific features for medicinal products with *cohort ATU and nominative ATU subject to a protocol for therapeutic use and information collection (PUT):*
The periodic pharmacovigilance update report relating to data collected within the scope of the ATU is included in the periodic summary report of the ATU, for which the compilation methods and submission deadlines are set in the protocol for therapeutic use and information collection (see 5.11, 6.2 and 6.9).
Furthermore, when the medicinal product is authorised abroad, the last available international PSUR is also sent to the ANSM during the period of availability of the medicinal product in the scope of the ATU.

c) Specific features for medicinal products *with nominative ATU without any protocol for therapeutic use and information collection (PUT):*
An annual report of pharmacovigilance observations having occurred in France is sent to the ANSM in accordance with the procedures and the template set by decision of the General Director of ANSM.

Furthermore, the international PSUR available, if applicable, during the period of availability of the medicinal product in nominative ATU is also sent to the ANSM.

7.2.4 Specific case: medicinal product with ATU and parallel application for marketing authorisation

During the period between the submission of a MA application dossier (regardless of the registration procedure) and the issuing of a MA for the medicinal product previously available through ATU, the MA applicant must ensure that all of the information made available in the context of the ATU and impacting upon the benefit/risk ratio of the medicinal product has also been reported to the ANSM, but also:
- To the competent authorities currently assessing the MA application for this medicinal product (reference Member State and concerned Member States), when it is a mutual recognition or a decentralised procedure;
- To the EMA, to the rapporteur and co-rapporteur when it is a European centralised registration procedure
(see GVP volume VI paragraph VI.C.2.2.7. Period between the submission of the marketing authorisation application and the granting of the marketing authorisation).

7.3 Role of the ANSM

The ANSM conducts the assessment of the information it receives, namely:
- The reports of adverse events submitted:
    - By the CRPV to the National Pharmacovigilance Database (managed by ANSM)
    - By the company to EudraVigilance.
- The periodic summary reports and, if applicable, the periodic safety update reports,
- The information sent by the CRPVs,
- Any new information forwarded by the company and impacting upon the benefit/risk ratio.

The ANSM shall send electronically to EudraVigilance, and by mail to the exploitant of the medicinal product, any serious adverse event which occurred in its territory and was reported to the CRPVs. This information must be sent within fifteen days of the report date.
The company must not resend EudraVigilance the cases received from the ANSM, in order to avoid any duplication.

The ANSM can request the opening of an official pharmacovigilance enquiry or a pharmacovigilance follow-up in order to assess the safety of the medicinal product.

The ANSM can inform the healthcare professionals concerned for any safety issue via mail and/or by circulating information on the ANSM website.

The ANSM publishes the abridged versions of summary reports on its website.

7.4 Role of the Regional Pharmacovigilance Centres (CRPV)

Nominative ATU without PUT:
The CRPVs are essentially responsible for:
- collecting and evaluating the information relating to the adverse events of the medicinal products with nominative ATU, communicated by healthcare professionals, amongst others,
- sending the ANSM (via the National Pharmacovigilance Database – BNPV) the previously mentioned information, immediately in case of serious adverse events,
- completing an expertise assignment by carrying out studies and investigations at the request of the ANSM.

Cohort ATU and nominative ATU subject to PUT:
If necessary (Article R.5121-155), a CRPV may be appointed by the ANSM to be responsible for the national pharmacovigilance follow-up of a medicinal product with ATU, in close collaboration with the exploitant of this medicinal product. It is the recipient (*via* the exploitant of the medicinal product) of a copy of the serious adverse events reported to EudraVigilance and of the periodic summary reports, for being analysed.

VIII. WITHDRAWAL AND SUSPENSION OF AN ATU

The ATU can be amended, suspended or withdrawn at any time by the General Director of ANSM for public health reasons or if the conditions of Articles L.5121-12 and R.5121-68 et seq. in the Public Health Code are no longer met.

Except in an emergency situation, the ATU can only be suspended or withdrawn after the holder has been asked to provide comments.

Decisions to suspend or withdraw the ATU must be justified and the remedies and periods allowed for appeals must be specified.

The ATU cannot be suspended for more than three months.

IX. SWITCHING FROM ATU TO MA

According to Article R.5121-76 of the Public Health Code, when a medicinal product with ATU is granted a MA, the General Director of ANSM shall set the date on which the cohort ATU becomes invalid or the date on which the grant of nominative ATUs shall stop, depending on the MA notification date or the length of time needed to make the medicinal product available in accordance with its MA.

This date basically depends on the length of time required in order to ensure the compliance of the patient information leaflet and label with the MA and, if applicable, to implement the risk management plan and risk minimisation plan. It does not, under any circumstances whatsoever, take into account the timescales needed to publish the decree for the hospitals and institutions use covered by the MA, or to include the medicinal product in the list of refundable drugs.

This delay will not be less than one months as from the notification of the MA decision and should be limited to three months, apart from in exceptional circumstances.

The date of the end of the ATU is set in conjunction with the MA holder and must be notified by the ANSM to the MA holder, with communication to the ministers responsible for health and social security, respectively. Circular DGS/DSS/DGOS/PP2/1C/PF2/PF4/2014/144 of 8 July 2014 sets the conditions under which medicinal products with ATU must be supplied and managed.

X. ADVERSTISING AND ATU

A medicinal product with ATU cannot be advertised, in accordance with Article L.5122-3 of the Public Health Code. Nevertheless given the specific characteristics of medicinal products with ATU, information for healthcare professionals, drafted in conjunction with ANSM, may be required. In this case, the information is sent in advance for validation by the ANSM prior to circulation.

XI. INFORMATION AVAILABLE ON THE ANSM WEBSITE

Apart from the present information for applicants and the legislative and regulatory provisions relating to ATU, the following information is available on the ANSM website (www.ansm.sante.fr, ATU section):

- list of proprietary products with current cohort ATU, with the corresponding summary of product characteristics (SPC) and the patient information leaflet,
- list of proprietary products with cohort ATU since 1994,
- list of proprietary products for which cohort ATU has been refused, since January 2001,
- list of proprietary products with nominative ATU, over a given period,
- list of hospital preparations that may be replaced by proprietary products available within the scope of a MA or ATU,
- application form for nominative ATU for a medicinal product,
- Cerfa form for reporting an adverse event potentially associated with a medicinal product or device listed in Article R.5121-150,
- cohort ATU application form,
- cohort ATU renewal application form,
- Abridged versions of the periodic safety reports.

APPENDICES

APPENDIX A

- **“ application form requesting nominative ATU status for a medicinal product”**

http://ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/Faire-une-demande-d-autorisation-temporaire-d-utilisation/(offset)/1

This form can be completed directly online

APPENDIX B

"Cerfa form for reporting an adverse even likely to be related to a medicinal product or device mentioned in Article R.5121-150"

https://www.formulaires.modernisation.gouv.fr/gf/cerfa_10011.do

APPENDIX C
"Role of various key players"

	Nominative ATU	Cohort ATUY
Prescriber	The prescriber is responsible for the application. He/she must submit a detailed request for a ATU to ANSM, on a form and justifying the application. The request must be submitted by a healthcare establishment pharmacist to ANSM. The medicinal product cannot be used until ANSM has granted the ATU. The prescriber informs the patient and, if possible, his/her general practitioner of the status of the medicinal product and gives them all of the information available on the said product. He/she reports serious or unexpected adverse events to the regional pharmacovigilance centre covering the geographical region in which he/she works. He/she must keep ANSM informed of the efficacy/safety in use of the medicinal product in terms of treatment if the ATU is to be renewed. If applicable, he/she complies with the protocol governing the therapeutic use and collection of information: prescription criteria, patient's information and monitoring condition; data collection and pharmacovigilance requirements	He/she acknowledges and complies with the protocol governing the therapeutic use and collection of information: prescription criteria, patient's information and monitoring condition; data collection and pharmacovigilance requirements. He/she informs the patient and, if possible, his/her general practitioner of the medicinal product status and gives them all the information available on this medicinal product. He/she guarantees the monitoring of the treated patients, collects and sends information to the holder of the cohort ATU in accordance with the terms and conditions described in the protocol governing the therapeutic use and collection of information.
Pharmacist in healthcare establishment	- He/she co-signs the ATU request and sends it to ANSM - He/she receives the ATU and informs the prescriber - He/she orders, imports, if applicable, receives and dispenses the medicinal product after having obtained the ATU. - He/she manages supplies. - He/she reports adverse events to the regional pharmacovigilance centre in the geographical area in which he/she works or in accordance with the terms/conditions specified in the PUT.	- He/she is aware of and complies with the protocol governing the therapeutic use and collection of information and the pharmacovigilance conditions. - He/she ensures that the information relating to the treatment of patients in his/her establishment is maintained. - He/she orders, receives and dispenses the medicinal product and manages supplies. - He/she complies with pharmaco-vigilance requirements.
"exploitant" of ATU	In accordance with the ATU granted by ANSM, the holder distributes the medicinal product to a healthcare establishment pharmacy or authorised organisation. The holder forwards a periodical pharmaco-vigilance updated report to ANSM. If a protocol governing the therapeutic use and collection of information is in place, the holder sends periodical summary reports to ANSM and the CRPV responsible, if applicable. The holder submits all information relating to the medicinal product to ANSM, for proof-reading, prior to circulation. The holder informs CEPS of the price of the medicinal product with ATU status.	The holder circulates the protocol governing the therapeutic use and collection of information. The holder distributes the medicinal product to a healthcrae establishment pharmacy or authorised structure. The holder ensures users observe the protocol The holder collects and analyses the information forwarded by the prescribers, especially adverse events. The holder complies with the terms and conditions for reporting pharmacovigilance issues. The holder sends periodical summary reports to ANSM and the responsible CRPV, if applicable. The holder informs ANSM of the number of new patients treated each

		month, on a monthly basis. The holder forwards a summary of these reports to the pharmacists concerned, the CRPVs an anti-poison centres once the reports have been validated by ANSM. Any information relating to the medicinal product must be submitted to ANSM for proof-reading, prior to circulation. The holder informs CEPS of the price of the medicinal product with ATU status.

APPENDIX D
Application form for Cohort ATU

MEDICINAL PRODUCT
. Name of medicinal product:
- Dosage:
- Pharmaceutical form([a]):
- Active substance(s):

. Indication claimed:
- ATC (Anatomical Therapeutic Chemical Classification System) code

APPLICANT

- Company distributing the medicinal product "exploitant" (name, address)

- contact person: (name, address, telephone, fax, electronic address)

_____
Signature

_____
At Date

1. The medicinal product with respect to the scope of application for the centralised marketing authorisation (MA) procedure set up by (EC) regulation No. 726/2004 of 31 March 2004

1.1 Is obtained from one of the biotechnological processes listed in 1 of the Appendix to (EC) regulation No. 726/2004: yes no

1.2 Contains a new active substance indicated in the treatment of:
- AIDS yes no
- Cancer yes no
- A neurodegenerative disease yes no
- Diabetes yes no

1.3 Is designed as an orphan medicinal product in accordance with the (EC) regulation No, 141/2000 of the European Parliament and Council dated 16 December 1999:
Yes Date of designation:
Indication:
No A designation request is under consideration
yes no

1.4 Contains a new active substance not authorised in the European Community as at 20 November 2005 (optional centralised procedure)
yes no

1.5 Constitutess a significant innovation on a therapeutic, scientific or technical level or the granting of

a Marketing Authorisation (MA) according to the centralised procedure presents an interest at community level for patients (optional centralised procedure)

yes no

Justification:

2. (ATU delivery criteria

In accordance with the provisions of Article L.5121-12 1° of the French Public Health Code, an authorisation can be granted for the exceptional use of medicinal products intended to treat serious or rare diseases provided that the following conditions are met: there is no appropriate treatment, the efficacy and safety of these medicinal products are strongly presumed, based on the results of clinical trials carried out with a view to applying for a MA and this request has been submitted or the applicant is in the process of submitting the request within a specified timeframe. This ATU must be requested within the scope of a protocol for the therapeutic use and collection of information.

2.1It is a medicinal product intended for:

a) the treatment yes no
prevention yes no
diagnosis yes no
b) of a serious disease yes no
of a rare disease yes no

2.2 No appropriate treatment is available: yes no

Justification:

2.3 The efficacy and safety of this product are strongly presumed yes no

Justification:

3. Administrative information:

3.1 The medicinal product is the subject of an application for a MA:

Yes

Date of submission to ANSM[b] *or* to the European Medicines Agency[b]:

Name of the medicinal product:

No

The holder is in the process of submitting an application for a MA[c]: yes no

If the holder is in the process of submitting an application for a MA:

I, the undersigned, …….. responsible pharmacist (*name of the company*) will be submitting a MA application dossier for (*name of the medicinal product*), on (*scheduled submission date*) to ANSM[b] or the European Medicines Agency[b]

Signature: …….

3.2 The medicinal product is the subject of biomedical research in France or abroad:

Yes

(Provide the list of biomedical research)

No

3.3 The medicinal product has been granted a MA abroad:

Yes

(Indicate the country and the names of the corresponding medicinal products as well as the date on which the authorisation was granted)

Country	Name of the medicinal products	Date of the MA

Scheduled date for the submission of the next periodical safety update reports (PSUR) or equivalent

document: ……..
No

[b] Tick as appropriate

[c] Article L.5121-12 a) of the French Public Health Code specifies that a cohort ATU can only be granted if a MA application has been submitted or the applicant is submitting an application within a set timeframe. In the absence of this undertaking, the application for a cohort ATU is not admissible for evaluation.

3.4 An early, exceptional use exists abroad (pre-MA): Yes Country: ….. Indication: ……. Status for use: …….. No 3.5 Role of the medicinal product compared to the therapeutic arsenal available in France: …….. 3.6 Number of patients likely to be treated each year in France with this product with ATU status: …….

4. List of documents / information to enclose	Yes	No
4.1 Copy of the MA application, if applicable		
4.2 When the medicinal product is authorised abroad:		
4.2.1. Copy of the authorisation(s) granted by the competent authority		
4.2.2. Copy of the summary of characteristics of the corresponding product		
4.2.3 Last PSUR or equivalent document		
4.3 Draft protocol governing the therapeutic use and collection of information, written in French		
4.4 Drafts, written in French		
4.4.1. of the summary of product characteristics		
4.4.2. of the patient information leaflet		
4.4.3. of the label		
4.5 Biomedical research:		
4.5.1. Titles and objectives of current and/or scheduled research in France or abroad for the same disorder, and identity of the main investigator(s)		
4.5.2. Regarding research conducted in France: identity of all the investigators and names of the test centres and research progress report		
4.6 Copy of the designation of the orphan drug, if applicable		
4.7 Copy of any scientific opinion relating to the medicinal product, sent to the applicant by ANSM, the European Medicines Agency or any competent authority in another European Economic Area Member State, if applicable		
4.8 Any information relating toan early, exceptional use (pre-MA) in another country		
4.9 Dossier relating to the medicinal product a) MA application dossier or b) Updated investigational medicinal product dossier in 5 copies on paper format and in electronic format		

<table>
<tr><td colspan="3">INITIAL APPLICATION FOR A COHORT ATU
ACKNOWLEDGEMENT OF ADMISSIBILITY</td></tr>
<tr><td colspan="3">I. SECTION TO BE COMPLETED BY THE APPLICANT</td></tr>
<tr><td colspan="3">. <u>Name of the medicinal product:</u>
- Dosage:
- Pharmaceutical form:
<u>Applicant:</u>
- Company distributing the medicinal product:”exploitant”
(name, address)

- Contact person:
(name, address, tel. No., fax No., electronic
Address)</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td colspan="3">II. SECTION TO BE COMPLETED BY ANSM</td></tr>
<tr><td colspan="3">Date on which application was received:</td></tr>
<tr><td colspan="3">Date of receipt of the requested additional documents</td></tr>
<tr><td colspan="3">Person in charge of the dossier at ANSM</td></tr>
<tr><td>Name:</td><td></td><td rowspan="4">French National Agency for Medicines and Health Products Safety (ANSM).
ATU
Product Directorate: ……..
143/147, Boulevard Anatole France
93285 Saint-Denis Cedex
France</td></tr>
<tr><td>Electronic address:</td><td></td></tr>
<tr><td>Tel. No.:</td><td></td></tr>
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<tr><td colspan="3">□ ADMISSIBLE</td></tr>
<tr><td colspan="3">□ NOT ADMISSIBLE</td></tr>
<tr><td colspan="3">Points to be noted by the applicant</td></tr>
<tr><td colspan="3">□ MISSING documents[1]</td></tr>
<tr><td colspan="3">□ ANSM’S COMMENTS [1]</td></tr>
<tr><td colspan="3">No. allocated to the dossier:</td></tr>
<tr><td colspan="3">Produced on: XII. <u>Signature:</u></td></tr>
</table>

[1] See subsequent page(s)

III. MISSING documents
□ 1. Cohort ATU application form
□ 2. Copy of MA application
3. When the medicinal product is authorised abroad:
□ 3.1 Copy of the authorisation(s) delivered by the competent authority
□ 3.2 Copy of the summary of product characteristics for the product in question
□ 3.3 The last PSUR or equivalent document
□ 4. The draft protocol governing the therapeutic use and collection of information, written in French
5. Drafts, written in French for the ATU of:
□ 5.1 Summary of product characteristics
□ 5.2 Patient information leaflet
□ 5.3 Labelling
□ 6. Biomedical research
□ 6.2 Regarding research carried out in France: the identity of the principal investigator(s) in France, the name of the test centre(s) concerned and the trial progress report
□ 7. Copy of the "orphan drug" designation
□ 8. Copy of any scientific opinion relating to the medicinal product, sent by ANSM, EMA or any competent authority in another European Economic Area Member State
□ 9. Any information relating to early or exceptional use (pre-MA) in another country
□ 10. The dossier relating to the medicinal product
□ 10.1 MA dossier
□ or 10.2 Updated investigational medicinal product dossier
□ 10.3 Number of additional paper copies to be submitted:
□ 10.4 Number of additional CD Rom copies to be submitted:
□ 11. Other items (see below)
IV. ANSM'S COMMENTS, IF APPLICABLE

APPENDIX E

Template of the protocol for therapeutic use and information collection

APPENDIX E1: Cohort ATU - PTU template
APPENDIX E2: Nominative ATU- PTU template

APPENDIX E1: Cohort ATU - PTU Template

COHORT
TEMPORARY AUTHORISATION FOR USE

PROTOCOL FOR THERAPEUTIC USE
AND THE INFORMATION COLLECTION

NAME, dosage, pharmaceutical form
(International non-proprietary name)

Date

French National Agency for Medicines and Health Products Safety (ANSM) **ATU** **143-147 Bd Anatole France** **93285 Saint Denis Cedex** **Tel.: 33 (0)1 55 87 36 11** **Fax: 33 (0)1 55 87 35 12** **Mail: atu@ansm.sante.fr**	**Holder of the Cohort Temporary Authorisation for Use** **Pharmaceutical company distributing YYY**

INTRODUCTION
The Medicinal Product

On xx/xx/xxxx, the French National Agency for Medicines and Health Products Safety (ANSM) granted a "cohort" Temporary Authorisation for Use (ATU) [Article L.5131-12 1 – 1° of the French Code of Public Health] to *"YYY"* for XXX [*name (INN), dosage, pharmaceutical form*] in the indication:

"……"
A Marketing Authorisation (MA) application has been submitted…… / will be submitted on…./will soon be submitted to: .....

Temporary authorisation for use

General information
This is an exceptional authorisation procedure.
The "cohort" ATU allows a medicinal product with no marketing authorisation (MA) to be available early provided that it satisfies the criteria of Article L.5121-12.1-1° of the French Code of Public Health (PHC) i.e. when the following conditions are met:
. It is intended for the treatment, prevention or diagnosis of serious or rare diseases,
. No appropriate treatment is available on the market,
. Its efficacy and safety in use are strongly presumed based on the results of clinical trials carried out with a view to submitting a MA application. This request has been submitted or the applicant is in the process of submitting it within a specified timeframe.
. The medicinal product is likely to offer a real clinical benefit and the introduction of treatment cannot be deferred.

Unlike a clinical trial, the purpose of the ATU is not to establish the efficacy of the medicinal product.
The ATU can be amended, suspended or withdrawn by ANSM for public health reasons or if the afore-mentioned conditions are no longer satisfied.

The protocol for therapeutic use and the collection of information (PTU)

Since this medicinal product has not been granted a marketing authorisation in France, its use is subject to a strict monitoring procedure by ANSM, especially in terms of pharmacovigilance. Consequently, this ATU is accompanied by a protocol for the therapeutic use and collection of information, established by ANSM in cooperation with the pharmaceutical company *YYY*. The protocol allows:

1. The follow-up and monitoring of patients treated: all patients receiving the treatment within the scope of this ATU are followed up and monitored according to the methods described in the protocol. All of the monitoring data collected by the prescribers are gathered and analysed by the pharmaceutical company *"YYY"* and sent to ANSM within a timescale set by the latter.

Pharmaceutical company *"YYY"* has the obligation to send ANSM a summary report on this ATU every …. months. This report must contain all of the data collected and especially:
. The characteristics of the treated patients,
. Description of the actual conditions of use of the medicinal product,
. Efficacy and pharmacovigilance data including a summary of all the adverse events and all useful information relating to the safety of the medicinal product collected in France and abroad during this period, including data from literature.

A summary of this report, duly validated by ANSM, is sent by the pharmaceutical company to prescribers and healthcare establishment pharmacists supplying the medicinal product and to the Regional Pharmacovigilance Centres (CRPV) and Anti-Poison Centres (APCs) for information. It is also published on the ANSM website (www.ansm.sante.fr).

2. Relevant information relating to the use of this medicinal product in order to ensure it is used properly, especially the summary of product characteristics (SPC) setting the criteria for using the medicinal product, ways of informing patients about the medicinal product and the ATU.

3. A definition of the criteria for use and dispensing of the medicinal product and methods for monitoring treated patients.

4. The role of all the key players.

A copy of this protocol is given by the company to every prescribing physician and healthcare establishment pharmacist who requests a copy as well as to the CRPV and APCs. It is also available on the ANSM website (www.ansm.sante.fr – ATU header).

Patient information

Before treatment is started, every patient, his/her legal representative or the person of trust must be informed by the prescriber about the medicinal product, the procedure for the exceptional use of this medication and the reporting of adverse events. A patient information note (Appendix B) is given to the patient by the prescribing physician with relevant explanations to ensure understanding. The patient (his/her legal representative or person of trust) must read this information note and show it to any doctor consulted. Furthermore, every pack of medication is accompanied by a patient information leaflet.

PRACTICAL CONDITIONSFOR THE PRESCRIPTION AND DISPENSING OF THE MEDICINAL PRODUCT AND PATIEN FOLLOW-UP

The Temporary Authorisation for Use implies strict compliance with the instructions given in the summary of product characteristics (Appendix A), with particular reference to the indications and contraindications as well as the information and prospective follow-up of treated patients.

Indication: ……..
The contraindications, warnings and special precautions for use are given in detail in the SPC (Appendix A).

Within the scope of the ATU, *XXX is subject to hospital prescription / reserved for hospital use.*
The prescription is reserved for specialists in….

Only prescribers and pharmacists practising in a public or private health establishment can prescribe and dispense, respectively.

Role of the prescribing hospital physician

Formalities prior to treatment

> When the prescriber wishes to introduce a treatment for a given patient, he/she must:
. Consult the PTU,
. Check the indication of the cohort ATU,
. Check the absence of any contraindication,
. Fill in the treatment access form and send it to the pharmacist in his/her establishment who will then validate the request and forward it to *"YYY"*.

> Having acknowledged the request, I"YYY" shall send a treatment access agreement to the prescribing physician and pharmacist for each patient. This agreement shall include the patient's initials and the number allocated to him/her in the cohort ATU or, if applicable, will explain why the patient cannot be included in the cohort (non-compliance with ATU criteria).

Medical follow-up of patients

The schedule of patient follow-up visits is drawn up as follows:

Visits and examinations	Visit D0 start of treatment	Follow-up visit	Follow-up visit	Follow-up visit	Treatment discontinuation

. **Visit D0 – start of treatment**

After having obtained treatment access approval from *"YYY"*, the prescribing hospital physician will plan a treatment initiation visit at the date on which the medicinal product will be available in the hospital pharmacy.

During this visit, the doctor shall:
. Confirm the absence of any contraindication to the treatment since the request for treatment access,
. give the patient and/or his/her legal representative and/or designated person of trust the patient information note accompanied by the form used to report any adverse events likely to be associated with a medicinal product (see Appendix B) and the patient information leaflet, also supplied with each pack of medication,
. Explain the treatment to the patient (or his/her legal representative or person of trust), its adverse events and shall ensure that this information has been understood properly. The doctor shall also record the information procedure in the patient's record,
. Write a prescription for *XXX*,
. Inform the patient's treating physician, if possible,
. Complete the treatment initiation form (see APPENDIX D) and send it to the health establishment pharmacist who will then forward it to *"YYY"*.

. **Follow-up visits**

During each of the follow-up visits, the prescriber shall:
. Look for any contraindication to the continuation of treatment,
. Look for the onset of adverse events, complete an adverse event reporting form (APPENDIX D), if applicable,
. Complete the pregnancy reporting form (APPENDIX D, if applicable,
. Write a prescription for *XXX*,
. Fill in the corresponding follow-up visit form (APPENDIX D),
. Fill in the treatment discontinuation form (APPENDIX D), if applicable.

A copy of each form is routinely sent immediately to the health establishment pharmacist who then forwards it to *"YYY"*.

Discontinuation of treatment

If treatment is to be discontinued, this must be reported using the treatment discontinuation form (see APPENDIX D). The reason for withdrawing medication must be mentioned.
If treatment withdrawal is linked to the onset of an adverse event or pregnancy, the relevant form must also be completed.
These forms must be sent immediately to *"YYY"*.

Role of the health establishment pharmacist

When a hospital physician asks *"YYY"* for a PTU for *"XXX"*, the pharmacist in his/her establishment will automatically receive a copy.

The pharmacist routinely sends the treatment access request form and the follow-up forms completed by the prescriber at each patient visit to the following address:

"YYY" contact details *Tel. No.* *Fax No.* *E-mail*

The pharmacist can dispense the prescribed medication after having received *"YYY"*'s approval to start treatment stipulating the patient's initials and the ATU number allocated to the patient.

The pharmacist dispenses *XXX* on a monthly basis, as prescribed by the doctor. The PTU adverse event reporting forms can be used by the pharmacist to inform the pharmaceutical company of any adverse event reported to the pharmacist.

The health establishment pharmacist is responsible for ordering and managing supplies.

Role of pharmaceutical company YYY

"YYY":
- provides a copy of this PTU on request for doctors practising in a public or private establishment and to the pharmacists concerned as well as the CRPVs and APCs for information as soon as the protocol is implemented.
- receives all treatment access request forms for XXX within the scope of the cohort ATU.
- checks that the patients satisfy the cohort ATU criteria (with particular reference to the indications and contraindications).
- sends the treatment access agreement, duly signed, to the prescribing physician and establishment physician, by fax or mail. This document shall identify the patient by the first three letters of his/her name and the first two letters of the first name, the date of birth and ATU number allocated to the patient. The doctor and pharmacist must also be sent this information if treatment access is refused. A Nominative ATU application can be sent to ANSM for this patient if necessary (see Chapter 4).
- responds on receipt to orders issued by the hospital pharmacist for patients to be included in the cohort ATU.
- collects all of the information gathered within the scope of the PTU, especially pharmacovigilance information.
- complies with and applies legislative obligations regarding pharmacovigilance, as described in chapter 3.3.
- Shares pharmacovigilance information with the CRPV …. responsible for national follow-up.
- analyses all of the information collected and sends a summary report every ….. months to ANSM and the CRPV responsible for national follow-up.
- compiles a summary of these reports every …. months and circulates it, after validation by ANSM, to prescribers and health establishment pharmacists as well as CRPVs and APCs for information.

PHARMACOVIGILANCE

Role of health professionals

Who should report?

Any physician, dentist, midwife or pharmacist aware of an adverse reaction likely to be attributed to the medicinal product for which an ATU has been granted, must report it immediately.
Any other health professional can also take part in the reporting procedure.

What should be reported?

All serious or non-serious adverse events including overdose, misuse, abuse, prescribing error and occupational exposure.

Exposure during pregnancy or lactation should also be reported.

When to report?

All adverse events must be reported as soon as the health professional becomes aware of them.

How to report?

The report must be submitted using an adverse event reporting form (see APPENDIX D).
If treatment is discontinued, the treatment discontinuation form should also be completed (see APPENDIX D).
In the event of pregnancy, the pregnancy reporting form should also be completed (see APPENDIX D).

To whom should it be reported?

Report to:

"YYY"

Role of patients and/or patient associations

The patient or his/her legal representative or person of trust or registered associations likely to contact patients can report:

- Adverse events suspected by the patient or his/her friends/family to be associated with the use of one or more medicinal products including those occurring during pregnancy or lactation.
- Cases of abuse, misuse, drug dependence, prescribing errors and overdose.

How to report?

As soon as possible after occurrence of the adverse event(s):
- The patient should complete the form* for reporting adverse event(s) associated with medicinal products or health products
- And send it by e-mail or post to the Regional Pharmacovigilance Centre (CRPV) in his/her geographical* region (see Appendix B).

Role of the pharmaceutical company *YYY*

"YYY" collects the pharmacovigilance information gathered by health professionals and complies with regulatory requirements governing pharmacovigilance:

Immediate notification to ANSM of serious adverse events known to *"YYY"*

"YYY" must notify the ANSM (directly by e-mail r via the EudraVigilance module – EVPM) all serious adverse events brought to its attention and occurring:

- in France
- in a country outside the European Union

* These documents are available on the ANSM website: www/ansm.sante.fr

> and for cases occurring in other European Union Member States, *"YYY"* shall ensure that the information is sent to EudraVigilance in accordance with procedures in force in the country of origin.

The pharmaceutical company and the CRPV responsible for national follow-up shall work together to define the practical methods for forwarding these cases.
These methods do not concern the transmission of suspected unexpected serious adverse reactions observations (SUSARs) occurring in interventional clinical trials.

If a serious adverse event occurs (regardless of the country of origin and application status), or if new information likely to impact upon the benefit/risk ratio of the medicinal product comes to light, information has to be sent quickly to users of the medicinal product with ATU status (doctors, pharmacists and patients), *"YYY"* shall contact ANSM immediately and forward any relevant documentation.

Transmission of periodic summary safety reports to ANSM

Every …. months, *"YYY"* drafts a summary report containing details of how XXX is used, efficacy and safety information including all (serious and non-serious) adverse events and any information that may be useful in evaluating the benefit/risk ratio associated with the use of the medicinal product.
Every … months, this summary report accompanied by a draft abridged version is sent by *"YYY"* to ANSM by post and e-mail (atu@ansm.sante.fr) and to the CRPV responsible for national follow-up.

Following validation by ANSM, *"YYY"* sends the abridged version of this report every …. months to doctors, relevant pharmacists and to all CRPVs and APCs.
This abridged version is also published on the ANSM website.

Role of ANSM

ANSM:
- acknowledges the information received from *"YYY"* and the CRPV responsible for national follow-up and takes all of the measures needed to ensure patient safety and the proper use of the medicinal product.
- informs *"YYY"* of any serious adverse event reported directly to ANSM.
- validates the abridged version of the periodical summary reports drafted by *"YYY"* prior to circulation by the latter.
- publishes the SPC, patient information leaflet and abridged versions of the summary reports on its website (www.ansm.sante.fr).

Role of the CRPV appointed to carry out the national follow-up

The …. CRPV is responsible for the national monitoring of adverse events reported with XXX.

The CRPV receives (via *"YYY"*) details of the serious adverse events reported to ANSM, periodic safety updated reports and abridged versions, and expertly analyses these documents.
The CPRV can ask *"YYY"* to submit any additional information required for evaluation purposes.

Nominative ATUs
If a patient cannot be treated within the scope of a cohort ATU, the prescribing hospital physician can request a Nominative ATU from ANSM via the health establishment pharmacist.

To do this, the hospital physician must complete the form "requesting a nominative temporary authorisation for use for a given medicinal product", justifying the request and stipulating the patient's history and treatments previously administered. This request is accompanied by a form requesting initial access to *XXX* treatment within the scope of the cohort ATU and the corresponding refusal.
The pharmacist completes the relevant section on the form and faxes it to:

ANSM ATU 143-147 bd Anatole France 93285 Saint Denis Cedex

Tel.: 33(0) 1 55 87 36 11 / Fax: 33(0) 1 55 87 36 12

Within the scope of these Nominative ATUs, patient follow-up and the reporting of adverse events must comply with the procedures described in this Protocol for Therapeutic Use and the Collection of Information.

APPENDICES

APPENDIX A: Summary of product characteristics subject to of the cohort ATU

APPENDIX B: Patient information note

APPENDIX C: Request form for the protocol for therapeutic use and the collection of information.

APPENDIX D: Medical follow-up forms:
. Treatment access request form
. D0 start of treatment form
. Follow-up forms
. Treatment discontinuation form
. Adverse event and/or pregnancy reporting form

APPENDIX A: Summary of product characteristics (SPC)

APPENDIX B: Patient information note

Patient information note

where patients are unable to read and clearly understand this information, it is given to their legal representative or, if applicable, to the person of trust they have designated

To be given to the patient prior to any prescription

COHORT TEMPORARY AUTHORISATION FOR USE
XXX

Your doctor has recommended XXX treatment for you.
The purpose of this note is to provide you with information in order to allow you to accept and understand the treatment proposed. It comprises:

1) general information on Temporary Authorisations for Use (ATUs)
2) information on XXX (patient information leaflet)
3) Ways in which patients can report adverse events.

1) General information on Temporary Authorisations for Use (ATUs)

XXX is available within the scope of a cohort Temporary Authorisation for use (ATU) granted by the French National Agency for Medicines and Health Products Safety (ANSM) on ../../…. This is a procedure that allows a medicinal product without a marketing authorisation (MA) to be available at an early date in France. The safety and efficacy of XXX are already strongly presumed in relation to the condition from which you are suffering.

Since no MA has been granted for this medicinal product in France to date, the medication is subject to a strict monitoring procedure by ANSM, focusing primarily on potential adverse events. This medicinal product is used and all treated patients are monitored in accordance with the Protocol governing Therapeutic Use (PTU) validated by ANSM. Data concerning all treated patients will be collected and sent to ANSM every …. months. A summary of these reports is also published by ANSM on its website (www.ansm.sante.fr).

Confidentiality
Your doctor must complete documents allowing him/her to collect information relating primarily to the safety of use of XXX during your treatment. All of this confidential information will be sent to *"YYY"* and may be processed electronically. In any correspondence concerning you, you will be identified only by the first three letters of your surname and the first two letters of your first name as well as your date of birth. The information will be forwarded to ANSM on a regular basis. ANSM will ensure that the use of XXX is monitored nationally in conjunction with the Regional Pharmacovigilance Centre (CRPV) …… responsible for national follow-up.

Application of law No. 78-17 dated 6 January 1978, duly amended, namely the French Data Protection Act, enables you to access and correct your personal computerised data at any time via your physician. Obviously, your decision to accept XXX treatment is entirely voluntarily and you can refuse the treatment if you so wish.

2) Information on XXX (patient information leaflet)

A patient information leaflet is supplied on the next page. This is also enclosed with each box of medication. This leaflet contains important information for your treatment and you should show it to all physicians you consult.

Patient information leaflet

XXX

Since no marketing authorisation (MA) has been granted for this medicinal product to date, its use is subject to a Temporary Authorisation for Use (ATU) and a strict monitoring procedure by the French National Agency for Medicines and health Products Safety (ANSM), focusing primarily on potential adverse events.
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
Keep this leaflet. You may need to read it again.
If you have any questions or doubts, ask your physician or pharmacist for further information.
This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
If you get any side effects, talk to your physician or pharmacist. This includes any possible side effects not listed in this leaflet.
You can also report this adverse event yourself using the patient form for reporting side effects likely to be associated with a medicinal product.

What is in this leaflet?

1. What XXX is and what it is used for

2. What you need to know before taking XXX

Never take XXX
Warnings and precautions

Other medicines and XXX

Pregnancy and breast-feeding

Driving and using machines

3. How to take XXX

If you take more XXX than you should:

If you forget to take XXX

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

If you feel that any of the effects mentioned are serious, or if you have any adverse reactions not mentioned in this leaflet, please inform your physician or pharmacist.

You can also report:
- side effects that you or your friends/family suspect to be related to the use of one or more medicinal products including any side effects experienced during pregnancy or breast-feeding.
- Cases of abuse, misuse, drug dependency, prescribing errors and overdose.

How to report?

As soon as possible after the occurence of the side effect(s):
- You should complete the form* for reporting side effect(s) associated with medicinal products or health products
- And send it by e-mail or post to the Regional Pharmacovigilance Centre (CRPV) in your geographical* region (see Appendix B).

5. How to store XXX

6. Contents of the pack and other information

What XXX contains

What XXX looks like and contents of the pack

Holder of the cohort ATU:

Manufacturer:

This leaflet was last revised in …

Detailed information on this medicine are available on the ANSM website

* These documents are available on the ANSM website: www.ansm.sante.fr

3) Patients adverse reaction notification procedures

The patient or his/her appointed representative (parent of a child, approved patient associations) can report side effects which are suspected by the patient or his/her friends and family to be related to the use of one or more medicinal products including side effects occurring during pregnancy or breast-feeding.

Cases of abuse, misuse, drug-dependency, prescribing errors and overdoses can also be reported.

The report must be submitted as soon as possible after the occurrencet of the event.

Below you will find a form devised by ANSM and also available on the ANSM website (ansm@santefr), which you can complete to ensure that you report this side effect and provide all of the information needed for its evaluation.
Once you have completed the form, send it by e-mail or post to the Regional Pharmacovigilance Centre (CRPV) in your geographical area. The contact details are enclosed.
The ANSM and the CRPV network must have access to all of your medical data in order to assess any correlation between the medicine and the side effect that you have experienced. It is also important that you enclose all of the documentation required in order to complete your report with this form (hospital reports, additional examinations/tests, etc.), noting that the information shall remain confidential.
However, what you consider to be a side effect may, in fact, be a new symptom of your condition, likely to alter the diagnosis or require a change in your treatment. In any case, we would encourage you to consult your physician who will then examine you and report the side effect himself/herself, if required. You can also contact your pharmacist and ask him/her to report the side effect or help you to complete this form.

PATIENT'S REPORT
OF SIDE EFFECT(S) RELATED TO
MEDICINAL PRODUCTS OR HEALTH PRODUCTS

In accordance with medical confidentiality, the information collected will be processed electronically and sent to the Regional Pharmacovigilance Centre (CRPV) and the French National Agency for Medicines and Health Products Safety (ANSM). In accordance with Articles 34 and 38 to 43 of Law No. 78-17 relating to the Data Protection Act, the ***CRPV shall maintain the confidentiality of the data mentioned in this report by not disclosing the patient's identity****. Furthermore, the patient is entitled to access all of this information via the CRPV*	Send the report to the Regional Pharmacovigilance Centre in your geographical area. Enter the department No. (e.g.: 01)

Person presenting with the side effect	**Person reporting the side effect (if different from the person experiencing the side effect)**	**Doctor treating the patient or another health professional, preferably the person who noticed the side effect**
Name First name E-mail Tel. No. Address Postal code Town/City Gender F M Weight Height Date of birth Or age when the side effect was experienced **Patient's medical history**	Name First name E-mail Tel. No. Address Postal code Town/City ***If the report concerns a new-born baby, how was the medicinal product taken?*** Directly by the new-born infant By the mother whilst breast-feeding By the mother during pregnancy during…… trimester *If possible, specify the date of last period* By the father	Name First name E-mail Tel. No. Address Postal code Town/City Qualification

Medicinal product	**Batch No.**	**Method of administration (oral, cutaneous, nasal, etc.)**	**Daily dose**	**Treatment start date**	**Treatment completion date**	**Reason for using the medicinal product**
1						
2						
3						
4						
5						
6						

If you use other medication, continue the list on a separate sheet

Side effect Date of onset *Day Month Year* Duration of effect Type and description of side effect *Use the box below*	**Clinical course** **Cure** Without sequelae With sequelae – please specify On-going **Patient still suffering from side effect** **Impact on daily life** (sick leave, unable to go out, etc.) NO YES Specify:
Description of the side effect and its clinical course *Clearly describe the side effect, the conditions of onset (gradually, during the day, the next day, after food, etc.). Describe the clinical course by listing the events. Also specify if:*	

- following the onset of the side effect, one (or more) medicinal treatments were stopped (please specify)
- the side effect disappeared after discontinuing treatment or reducing the dose of the medicinal product(s) (please specify)
- one or more medicinal products were reinstated (please specify), describing the clinical course of the side effect after reintroducing treatment
- other medicinal products, products (food supplements, physiotherapy, etc.) are still being used or were used recently
Enclose a copy of medical documents available (results of pharmaceutical company tests and hospital reports, etc.)

. In order for your report to be taken into consideration, you must at least specify the name of the suspect medicinal product, the type of side effect and the age gender and post code of the person who experienced the side effect.
. You can complete this form personally or via a patient association, and send it to the Regional Pharmacovigilance Centre in your geographical region.

N.B.: The report you are submitting on this form is not, in any way, a substitute for a medical consultation. If you have any doubts about the symptoms experienced, their clinical course or simply to find out more information, speak to your doctor. The purpose of the reporting procedure is not to gain any compensation for the consequences of the side effect but to help monitor risks associated with medicinal products. Visit the www.ansm.sante.fr website to find out more about the national pharmaco-vigilance system.

Contact Details for the Regional Pharmacovigilance Centres

Regional Pharmacovigilance Centre	**Department**	**Address**	**Telephone No. / E-mail address**

[Insert list from source PDF]

APPENDIX C: Form to request protocol for therapeutic use and information collection

APPENDIX D: Medical follow-up forms

- Treatment access request form
- D0 start of treatment form (if required)
- Treatment follow-up forms
- Treatment discontinuation form
- Adverse event and/or pregnancy reporting form

APPENDIX E2: ATU Nominative - PTU Template

ATU NOMINATIVE

PROTOCOL FOR THERAPEUTIC USE
AND THE INFORMATION COLLECTION

NAME, dosage, pharmaceutical form
(International non-proprietary name)

XXX

Date - Version

French National Agency for Medicines and Health Products Safety (ANSM) **ATU** **143-147 Bd Anatole France** **93285 Saint Denis Cedex** **Tel.: 33 (0)1 55 87 36 11** **Fax: 33 (0)1 55 87 35 12** **Mail: atu@ansm.sante.fr**	**Holder of the Cohort Temporary Authorisation for Use** **Pharmaceutical company distributing YYY**

1. INTRODUCTION

1.1 The Medicinal Product

……

1.2 Temporary authorisation for use

1.2.1 General information

A nominative ATU allows certain medicinal products to be available under exceptional circumstances, prior to obtaining a marketing authorisation (MA) provided that the criteria defined in 2° of Article L.5121-12 of the French Public Health Code (PHC) are satisfied, i.e. when the following conditions are met:

- the medicinal products are intended to treat named patients who cannot take part in biomedical research,
- they are intended to treat serious or rare disorders,
- no appropriate treatment is available on the market,
- the efficacy and safety of the medicinal product in question are strongly presumed based on scientific knowledge,
- the medicinal product is likely to offer a real benefit,
- The introduction of treatment cannot be deferred.

The Nominative ATU is authorised by ANSM, for a limited period at the request of a prescribing physician and is subject to the implementation of a protocol governing therapeutic use and the collection of information.

Unlike a clinical trial, the purpose of the ATU is not to establish the efficacy of a medicinal product but to treat patients.

The ATU can be suspended or withdrawn by ANSM for public health reasons or if the afore-mentioned conditions are no longer satisfied.

1.2.2 The protocol governing therapeutic use and the collection of information (PTU)

Since this medicinal product has not been granted a marketing authorisation in France, its use is subject to a strict monitoring procedure on the part of ANSM, especially in terms of pharmacovigilance. Consequently, this Nominative ATU is accompanied by a protocol governing the therapeutic use and collection of information, drafted by ANSM in conjunction with pharmaceutical company *YYY*. The protocol describes:

1. The follow-up and monitoring of patients being treated: all of the patients receiving the treatment within the scope of this ATU are followed up and monitored according to the terms and conditions described in the protocol. All of the monitoring data collected by the prescribers are collated and analysed by pharmaceutical company *"YYY"* and sent to ANSM within a timescale set by the latter.

"YYY" is obliged to send ANSM a summary report on this ATU every …. months. This report must contain all the data collected and especially:

- the characteristics of the treated patients,
- the effective methods for using the medicinal product,
- Efficacy and pharmacovigilance data including a summary of all the adverse events and all useful information relating to the safety of the medicinal product collected in France and abroad during this period, including published data.

A summary of this report, duly validated by ANSM, is sent by the pharmaceutical company to prescribers and health establishment pharmacists who dispensed the medicinal product as well as to the Regional Pharmacovigilance Centres (CRPV) and Anti-Poison Centres (APCs) for information. It is also published on the ANSM website (www.ansm.sante.fr).

2. Relevant information relating to the use of this medicinal product in order to ensure correct usage, especially the information note intended for prescribers and ways of informing patients about the medicinal product and the ATU.

3. Methods for dispensing the medicinal product and monitoring treated patients.

4. The role of all the key players.

A copy of this protocol is given by the company to every prescribing physician and health establishment pharmacist who requests a copy as well as to the CRPV and APCs. It is also available on the ANSM website (www.ansm.sante.fr – ATU header).

1.3 Patient information

Prior to the introduction of treatment, every patient, his/her legal representative or person of trust must be informed by the prescriber about the medicinal product, the procedure governing the exceptional use of this medication and the reporting of adverse events. A patient information note (Appendix B) is given to the patient by the prescribing physician with relevant explanations to ensure understanding. The patient (his/her legal representative or appointed confidante) must read this information note and show it to any doctor consulted.

2. PRACTICAL TERMS AND CONDITIONS GOVERNING THE PRESCRIPTION AND DISPENSING OF THE MEDICINAL PRODUCT AND PATIENT FOLLOW-UP

Within the scope of the ATU, XXX is subject to hospital prescription / reserved for hospital use.

Only prescribers and pharmacists practising in a public or private health establishment can prescribe and dispense, respectively.

2.1 Role of the prescribing hospital physician

2.1.1 Formalities for obtaining a Nominative ATU

1. Any hospital physician wishing to prescribe XXX within the scope of a ATU must submit a prior request for this PTU from YYY.

YYY sends the relevant document by return to the prescriber and pharmacist in the establishment in question.

2. In order to initiate the request for a nominative authorisation, the doctor sends the following items, duly completed, to the health establishment pharmacist:
> Form for the Nominative ATU request (see Appendix C);
> Treatment access request form (see APPENDIX D).

3. These forms are sent to ANSM by the health establishment pharmacist:

French National Agency for Medicines and Health Products Safety (ANSM)
ATU
143-147 bd Anatole France, 93285 Saint Denis Cedex
Tel.: 33(0) 1 55 87 36 11 / Fax: 33(0) 1 55 87 36 12
E-mail: atu@ansm.sante.fr

4. Having acknowledged the request and following evaluation, ANSM will send the prescriber and pharmacist confirmation of approval specifying the patient's initials and the Nominative ATU authorisation number, for a defined treatment period. If the request is refused, an explanation must be given.

2.1.2 Medical follow-up of patients

2.1.2.1 Treatment initiation visit

After having obtained approval from ANSM, the prescribing hospital physician will plan a treatment initiation visit on the date when the medicinal product will be available in the hospital pharmacy.

During this treatment initiation visit, the doctor shall:
. Confirm the absence of any contraindication to the treatment,
. give the patient and/or his/her legal representative and/or designated person of trust the patient information note accompanied by the form for reporting any adverse events likely to be associated with a medicinal product (see Appendix B),
. Explain the treatment to the patient (or his/her legal representative or person of trust), its adverse events and shall ensure that this information has been understood properly,
. Write a prescription for *XXX* and inform the patient's treating physician, if possible,
. Complete *the treatment initiation form (see APPENDIX D), if necessary.*

This form is sent to the health establishment pharmacist who will then fax it to:

YYY

2.1.2.2 Follow-up visits

On expiry of the Nominative ATU, the prescribing physician must complete the following if he/she wishes to continue treatment:
- A medical follow-up form (see APPENDIX D),
- Form for requesting a Nominative ATU (see Appendix C).

These forms must be sent to ANSM by the health establishment pharmacist:

French National Agency for Medicines and Health Products Safety (ANSM) ATU 143-147 bd Anatole France, 93285 Saint Denis Cedex Tel.: 33(0) 1 55 87 36 11 / Fax: 33(0) 1 55 87 36 12 E-mail: atu@ansm.sante.fr

Having acknowledged the request and as with the initial request, ANSM will send the prescriber and pharmacist confirmation of approval specifying the patient's initials and a new Nominative ATU authorisation number. If the request is refused, an explanation must be given.

2.1.3 Discontinuation of treatment

If treatment is to be discontinued, this must be reported to YYY using the treatment discontinuation form (see APPENDIX D). The reason for withdrawing medication must be stipulated.
If treatment withdrawal is linked to the occurrence of an adverse event or pregnancy, the relevant form must also be completed.
These forms must be sent immediately to?

2.2 Role of the health establishment pharmacist

When a hospital physician requests a copy of the XXX PTU. The pharmacist in his/her establishment will automatically receive a copy. The adverse event reporting forms can be used by the pharmacist to inform the pharmaceutical company of any adverse event reported to the pharmacist whilst dispensing the medication.

The pharmacist must ensure that he has a Nominative ATU validated by the ANSM for every patient whilst dispensing XXX.

The health establishment pharmacist is responsible for ordering and managing supplies.

When initially ordering treatment, the health establishment pharmacist must send the order for the medicinal product to YYY accompanied by copies of the ATU and the initial treatment request form (see APPENDIX D).

For any renewal, the hospital pharmacist must send copies of the ATU (renewal) and the follow-up form (see APPENDIX D).

XXX **will be dispatched by** YYY **on receipt of these documents.**

All orders must be sent to:

YYY

2.3 Role of the French National Agency for Medicines and Health Products Safety (ANSM)

ANSM has implemented this protocol governing therapeutic use and the collection of information in conjunction with YYY.

ANSM's role is to evaluate and then grant or refuse Nominative ATUs for XXX. This applies to both initial requests and renewals.

ANSM evaluates the ATU summary report drafted by YYY every n months. Following validation by ANSM, a summary of these reports will be sent every n months by YYY to prescribers and health establishment pharmacists who dispensed the medicinal product as well as to CRPV and APCs for information. This summary will also be circulated on the ANSM website (www.ansm.sante.fr).

2.4 Role of pharmaceutical company YYY

YYY sends a copy of this protocol for therapeutic use and the collection of information on request to doctors and pharmacists practising in a public or private establishment as well as to CRPVs and APCs for information.

YYY honours orders for XXX from pharmacists under the following conditions:

1. For the first order for any new patient, the order is honoured when the following documents are received:
a. The order form,
b. A copy of the ATU granted,
c. A copy of the initial treatment request form, duly completed (see APPENDIX D).

2. For any interim orders in cases where the first order was completed for one month's treatment but the ATU is granted for a longer period, the order is honoured on receipt of the following documents.
a. The order form,
b. A copy of the ATU granted.

3. For a ATU renewed by ANSM, the order is honoured on receipt of the following documents:
a. The order form
b. A copy of the renewed ATU
c. A copy of the last medical follow-up form, duly completed (see APPENDIX D).

YYY:

- collects all of the information gathered within the scope of the PTU, especially pharmacovigilance information and complies with legislative obligations regarding pharmacovigilance.

- Shares pharmacovigilance information with the CRPV responsible for the national follow-up of XXX.

- analyses all of the information collected and sends a summary report every n months to ANSM and the CRPV responsible for national follow-up.

- circulates, every n months, a summary of these reports, following validation by ANSM, to prescribers and health establishment pharmacists as well as CRPV and APCs for information purposes.

3. PHARMACOVIGILANCE

3.1 Role of health professionals

3.1.1 Who is responsible for reporting?

Any doctor, dental surgeon, midwife or pharmacist aware of an adverse reaction likely to be attributed to the medicinal product for which an ATU has been granted, must report it.
Any other health professional can also take part in the reporting procedure.

3.1.2 What should be reported?

All adverse events including overdose, misuse, abuse, prescribing error and occupational exposure.
Exposure during pregnancy or lactation should also be reported.

3.1.3 When to report?

All adverse events must be reported as soon as the health professional becomes aware of them.

3.1.4 How to report?

The report must be submitted using an adverse event reporting form (see APPENDIX D).
In the event of pregnancy, the pregnancy reporting form should also be completed (see APPENDIX D).
If treatment is discontinued, the treatment discontinuation form should also be completed (see APPENDIX D).

3.1.5 To whom should reports be submitted?

Report to:

YYY

3.2 Role of patients and/or patient associations

The patient or his/her legal representative or person of trust or approved associations linked with the patient can report:

- Adverse events suspected by the patient or his/her friends/family to be associated with the use of one or more medicinal products including those occurring during pregnancy or lactation.
- Cases of abuse, misuse, drug dependency, prescribing errors and overdose.

How should reports be submitted?

As soon as possible after the occurrence of the adverse event(s):
- The patient should complete the form* for reporting adverse event(s) associated with medicinal products or health products
- And send it by e-mail or post to the Regional Pharmacovigilance Centre (CRPV) in your geographical* region (see Appendix B).

3.3 Role of pharmaceutical company YYY

YYY collects the pharmacovigilance information gathered by health professionals and complies with regulatory obligations governing pharmacovigilance:

3.3.1 Immediate transmission to ANSM of serious adverse events known to YYY

YYY is obliged to inform ANSM (directly by e-mail or via the EudraVigilance module – EVPM) of all serious adverse events brought to its attention and occurring:

- in France
- in a country outside the European Union
- And for cases occurring in other European Union Member States, YYY shall ensure that the information is sent to EudraVigilance in accordance with procedures in force in the country of origin.

The practical methods for forwarding these cases to the CRPV responsible for national follow-up are defined by the CRPV and sent to *"YYY"*.

These methods do not concern the transmission of suspect, unexpected and serious adverse reactions (SUSARs) occurring within the scope of interventional clinical trials.

If a serious adverse event occurs (regardless of the country of origin and application status), or if new information likely to impact upon the benefit/risk ratio of the medicinal product comes to light and information has to be sent quickly to users of the medicinal product with ATU status (doctors, pharmacists and patients), YYY shall contact ANSM immediately and forward any relevant documentation.

3.3.2 Transmission of periodical summary reports

Every n months, YYY drafts a summary report containing details of how XXX is used. One section of this report refers to pharmacovigilance and includes all adverse events and any information that may be useful in evaluating the benefit/risk ratio associated with the use of the medicinal product.
Every n months, this periodical summary report accompanied by a draft abridged version is sent by YYY to ANSM by post and e-mail (atu@ansm.sante.fr) and to the CRPV responsible for national follow-up.
Following validation by ANSM, YYY sends the abridged version of this report every n months to doctors, relevant pharmacists and to all CRPVs and APCs.
This abridged version will also be circulated on the ANSM website.

3.4 Role of ANSM

ANSM:

* These documents are available on the ANSM website: www/amsm.sante.fr

- acknowledges the information received from YYY and the CRPV responsible for national follow-up and takes all of the measures needed to ensure patient safety and the correct use of the medicinal product.
- informs YYY of any serious adverse event reported directly to ANSM.
- validates the abridged version of the periodical summary reports drafted by YYY prior to circulation by the latter.
- circulates the PTU and abridged versions of the summary reports on its website (www.ansm.sante.fr).

3.5 Role of the CRPV appointed to carry out the national follow-up

The …. CRPV is responsible for the national monitoring of adverse events reported with XXX.

The CRPV receives (via YYY) details of the serious adverse events reported to ANSM, periodical summary reports and abridged versions, and expertly analyses these documents.
The CPRV can ask YYY to submit any additional information required for evaluation purposes.

APPENDICES

APPENDIX A: Treatment information note intended for prescribers

APPENDIX B: Patient information note

APPENDIX C: Request form for a Nominative ATU

APPENDIX D: Medical follow-up forms:
D1: Treatment access request form
D2: Treatment initiation form (*if required*)
D3: Follow-up form
D4: Serious or unexpected adverse event reporting form
D5: Pregnancy reporting form
D6: Treatment discontinuation form

APPENDIX A: Information note intended for prescribers

APPENDIX B: Patient information note

Appendix B - Patient information note

Where patients are unable to read and clearly understand this information, it is given to their legal representative, or where applicable, to the person of trust they have designed.

To be given to the patient prior to any prescription

TEMPORARY AUTHORISATION FOR USE
XXX

Your doctor has recommended XXX treatment for you.
The purpose of his note is to provide you with information in order to allow you to accept and understand the treatment being made available to you. It comprises:

4) general information on Temporary Authorisations for Use (ATUs)
5) information on XXX (patient information leaflet)
6) Ways in which patients can report adverse events.

3) General information on Temporary Authorisations for Use (ATUs)

XXX is available within the scope of a cohort Temporary Authorisation for use (ATU) granted by ANSM.
This is a procedure that allows a medicinal product without a marketing authorisation (MA) to be available under exceptional circumstances in France. The safety and efficacy of this medicinal product are already strongly presumed in relation to the condition from which you are suffering.

Since no MA has been granted for this medicinal product in France to date, the medication is subject to a strict monitoring procedure by ANSM, focusing primarily on potential adverse events. This medicinal product is used and all treated patients are monitored in accordance with the Protocol governing Therapeutic Use (PTU) validated by ANSM. Data concerning all treated patients will be collected and sent to ANSM every n months. A summary of these reports is also published regularly by ANSM on its website (www.ansm.sante.fr).

Confidentiality
Your doctor must complete documents allowing him/her to collect information relating primarily to the safety in use of XXX during your treatment. All of this confidential information will be sent to YYY and may be processed electronically. In any correspondence concerning you, you will be identified only by the first three letters of your surname and the first two letters of your first name as well as your date of birth. The information will be forwarded to ANSM on a regular basis. ANSM will ensure that the use of XXX is monitored nationally in conjunction with the ____Regional Pharmacovigilance Centre (CRPV) responsible for national follow-up.

Application of law No. 78-17 dated 6 January 1978, duly amended, namely the French Data Protection Act, enables you to access and correct your personal computerised data at any time via your doctor. Obviously, your decision to accept XXX treatment is entirely voluntarily and you can refuse the treatment if you so wish.

4) Information on XXX (patient information leaflet)

A patient information leaflet is supplied on the next page. This contains important information for your treatment. You should show it to all doctors you consult.

Patient information leaflet

XXX

- Since no marketing authorisation (MA) has been granted for this medicinal product to date, its use is subject to a Temporary Authorisation for Use (ATU) and a strict monitoring procedure by the French National Agency for Medicines and health Products Safety (ANSM), focusing primarily on potential adverse events.
- Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- If you have any questions or doubts, ask your doctor or the hospital pharmacist who dispensed XXX for further information.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
-Keep this leaflet. You may need to read it again.

What is in this leaflet?

1. WHAT XXX IS AND WHAT IT IS USED FOR

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE XXX

Always take the medicine exactly as your doctor has told you. This may differ from the general information contained in this leaflet. Take the doses prescribed by your doctor.

Never take XXX

Warnings and precautions

Other medicines and XXX

Pregnancy and breast-feeding

Driving and using machines

Athletes:

3. HOW TO TAKE XXX

If you take more XXX than you should:

If you forget to take XXX

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects although not everybody gets them.

…….

If you feel that any of the effects mentioned are serious, or if you have any adverse reactions not mentioned in this leaflet, please inform your doctor or pharmacist.

You can also report:
- side effects that you or your friends/family suspect to be related to the use of one or more medicinal products including any side effects experienced during pregnancy or breast-feeding.
- Cases of abuse, misuse, drug dependency, prescribing errors and overdose.

How should reports be submitted?

As soon as possible after the onset of the side effect(s):
- You should complete the form* for reporting side effect(s) associated with medicinal products or health products
- And send it by e-mail or post to the Regional Pharmacovigilance Centre (CRPV) in your geographical* region.

5. HOW TO STORE XXX

Keep this medicine out of the sight and reach of children.

Expiry date

Storage conditions

6. ADDITIONAL INFORMATION

Full list of active substances and excipients

Pharmaceutical form and contents of the pack

Manufacturer:

This leaflet was last revised in …

Detailed information on this medicine are available on the ANSM website

* These documents are available on the ANSM website: www.ansm.sante.fr

3) Patient adverse reaction notification procedures

The patient or his/her appointed representative (parent of a child, approved patient associations) can report side effects which are suspected by the patient or his/her friends and family to be related to the use of one or more medicinal products including side effects occurring during pregnancy or breast-feeding.

Cases of abuse, misuse, drug-dependency, prescribing errors and overdoses can also be reported.

The report must be submitted as soon as possible after the onset of the event.

Below you will find a form devised by ANSM and also available on the ANSM website (ansm@sante.fr), which you can complete to ensure that you report this side effect and provide all of the information needed for its evaluation.
Once you have completed the form, send it by e-mail or post to the Regional Pharmacovigilance Centre (CRPV) in your geographical area. The contact details are enclosed.
The ANSM and the CRPV network must have access to all of your medical data in order to assess any correlation between the medicine and the side effect that you have experienced. It is also important that you enclose all of the documentation required in order to complete your report with this form (hospital reports, additional examinations/tests, etc.), noting that the information shall remain confidential.
However, what you consider to be a side effect may, in fact, be a new symptom of your condition, likely to alter the diagnosis or warrant a change in your treatment. In any case, we would encourage you to consult your doctor who will then examine you and report the side effect himself/herself, if required. You can also contact your pharmacist and ask him/her to report the side effect or help you to complete this form.

PATIENT'S REPORT
OF SIDE EFFECT(S) RELATED TO
MEDICINAL PRODUCTS OR HEALTH PRODUCTS

In accordance with medical confidentiality, the information collected will be processed electronically and sent to the Regional Pharmacovigilance Centre (CRPV) and the French National Agency for Medicines and Health Products Safety (ANSM). In accordance with Articles 34 and 38 to 43 of Law No. 78-17 relating to the Data Protection Act, the ***CRPV shall maintain the confidentiality of the data mentioned in this report by not disclosing the patient's identity****. Furthermore, the patient is entitled to access all of this information via the CRPV*	Send the report to the Regional Pharmacovigilance Centre in your geographical area. Enter the department No. (e.g.: 01)

Person presenting with the side effect	**Person reporting the side effect (if different from the person experiencing the side effect)**	**Doctor treating the patient or another health professional, preferably the person who noticed the side effect**
Name First name E-mail Tel. No. Address Postal code Town/City Gender F M Weight Height Date of birth Or age when the side effect was experienced **Patient's medical history**	Name First name E-mail Tel. No. Address Postal code Town/City ***If the report concerns a newborn baby, how was the medicinal product taken?*** Directly by the newborn infant By the mother whilst breast-feeding By the mother during pregnancy during…… trimester *If possible, specify the date of last period* By the father	Name First name E-mail Tel. No. Address Postal code Town/City Qualification

Medicinal product	**Batch No.**	**Method of administration (oral, cutaneous, nasal, etc.)**	**Daily dose**	**Treatment start date**	**Treatment completion date**	**Reason for using the medicinal product**
1						
2						
3						
4						
5						
6						

If you use other medication, continue the list on a separate sheet

Side effect Date of onset *Day Month Year* Duration of effect Type and description of side effect *Use the box below*	**Clinical course** **Cure** Without sequelae With sequelae – please specify On-going **Patient still suffering from side effect** **Impact on daily life** (sick leave, unable to go out, etc.) NO YES Specify:
Description of the side effect and its clinical course *Clearly describe the side effect, the conditions of onset (gradually, during the day, the next day, after food, etc.). Describe the*	

clinical course by listing the events. Also specify if:
- following the onset of the side effect, one (or more) medicinal treatments were stopped (please specify)
- the side effect disappeared after discontinuing treatment or reducing the dose of the medicinal product(s) (please specify)
- one or more medicinal products were reinstated (please specify), describing the clinical course of the side effect after reintroducing treatment
- other medicinal products, products (food supplements, physiotherapy, etc.) are still being used or were used recently
Enclose a copy of medical documents available (results of pharmaceutical company tests and hospital reports, etc.)

. In order for your report to be taken into consideration, you must at least specify the name of the suspect medicinal product, the type of side effect and the age gender and post code of the person who experienced the side effect.
. You can complete this form personally or via a patient association, and send it to the Regional Pharmacovigilance Centre in your geographical region.

N.B.: The report you are submitting on this form is not, in any way, a substitute for a medical consultation. If you have any doubts about the symptoms experienced, their clinical course or simply to find out more information, speak to your doctor. The purpose of the reporting procedure is not to gain any compensation for the consequences of the side effect but to help monitor risks associated with medicinal products. Visit the www.ansm.sante.fr website to find out more about the national pharmaco-vigilance system.

Contact Details for the Regional Pharmacovigilance Centres

Regional Pharmacovigilance Centre	**Department**	**Address**	**Telephone No. / E-mail address**

[Insert list from source PDF]

APPENDIX C: Request form for a Nominative ATU:
Available on the ANSM website: www.ansm.sante.fr

This form can be completed directly online

REQUEST FOR A NOMINATIVE TEMPORARY AUTHORISATION FOR USE RELATING TO MEDICINAL PRODUCT

Public Health Code Article L.5121-121-2° - Articles R.5121-73 and R.5121-74

<table>
<tr><td colspan="6">To be completed by the Health Establishment Pharmacist</td></tr>
<tr><td colspan="2">Date of request
DD MM YYYY</td><td colspan="2">ATU renewal? No
Yes: previous ATU No. _____</td><td colspan="2" rowspan="2">

Stamp of the Establishment Pharmacy</td></tr>
<tr><td colspan="2">FAX DOCUMENT TO THE ATU UNIT:
FAX: 01 44 87 36 12
TEL.: 01 55 87 36 11/36 13
atu@ansm.sante.fr</td><td colspan="2">Pharmacist’s name:
E-mail:
Tel.:
Fax:</td></tr>
<tr><td colspan="6">To be completed by the Senior Prescribing Physician</td></tr>
<tr><td colspan="3">Medicinal product concerned</td><td>Patient</td><td colspan="2">Gender F M</td></tr>
<tr><td colspan="2">Name of the pharmaceutical speciality or International Non-proprietary Name or code (in capitals):</td><td>Pharmaceutical form:</td><td>Name:
(1st^t3 letters)</td><td colspan="2">Age:</td></tr>
<tr><td>Dosage:</td><td>Posology:</td><td>Duration of treatment:</td><td>First name
(1st 2 letters)</td><td colspan="2">Weight:</td></tr>
<tr><td colspan="6">Reasons for request (in particular: patient’s clinical history and previous treatments):</td></tr>
<tr><td colspan="6">In the case of a ATU renewal (Article R.5121-74 of the French PHC):
- data relating to the efficacy of the treatment introduced:

- data relating to the safety of the treatment introduced:</td></tr>
<tr><td colspan="2">I hereby undertake to inform the afore-mentioned patient about the medicinal product and the exact scope of the authorisation. I hereby undertake to provide ANSM with all of the information relating to the safety and efficacy of the medicinal product for this patient

Date:
DD MM YYYY</td><td colspan="2">Name of the prescribing physician:

Department:

Tel.:

E-mail: @

Signature:</td><td colspan="2">

Doctor’s stamp</td></tr>
</table>

> Any items enclosed can only be identified with the first three letters of the patient’s name and the first two letters of the first name.

In accordance with Articles 34 and 38 to 43 of Law No. 78-17 dated 6 January 1978, relating to the Data Protection Act, the French National Agency for Medicines and Health Products Safety ***shall maintain the confidentiality of the data mentioned in this declaration. Furthermore, any person concerned by this declaration is entitled to access all of the personal data collected and to correct any inaccurate, incomplete or ambiguous data.***

APPENDIX D

D1: Treatment access request form
D2: Treatment initiation form (if required)
D3: Treatment follow-up form
D4: Serious or unexpected adverse event reporting form
D5: Pregnancy reporting form
D6: Treatment discontinuation form

XXX Nominative Temporary Authorisation for Use	
TREATMENT ACCESS REQUEST FORM	Page 1/N

Patient

Patient's name (first 3 letters): -- -- -- First name (first 2 letters): -- --

Date of birth: -- -- ---- Weight (kg): ---- Gender: Male Female

Name of prescribing physician: Doctor's stamp and signature:
Hospital:
Department:
Tel.: Fax:
E-mail address:
Date: --/--/----

Please send this form together with the Nominative ATU request form to the establishment pharmacist who should preferably fax this document to:	**French National Agency for Medicines and Health Products Safety** ATU 143-147 boulevard Anatole France 93285 Saint Denis Cedex Fax: 01 55 87 36 12 Tel.: 01 55 87 36 11
To initially order this product, a copy of this form should be sent to YYY with a copy of the ANSM nominative authorisation: fax: 02 31 47 92 75	

XXX Nominative Temporary Authorisation for Use	
TREATMENT INITIATION FORM *If required*	Page 1/N

Patient

Patient's name (first 3 letters): -- -- -- First name (first 2 letters): -- --

Date of birth: -- -- ---- Weight (kg): ---- Gender: Male Female

Name of prescribing physician: Doctor's stamp and signature:
Hospital:
Department:
Tel.: Fax:
E-mail address:
Date: --/--/----

Please send this form together with the Nominative ATU request form to the establishment pharmacist who should preferably fax this document to:	**French National Agency for Medicines and Health Products Safety** ATU 143-147 boulevard Anatole France 93285 Saint Denis Cedex Fax: 01 55 87 36 12 Tel.: 01 55 87 36 11
To initially order this product, a copy of this form should be sent to YYY with a copy of the ANSM nominative authorisation: fax: 02 31 47 92 75	

XXX Nominative Temporary Authorisation for Use	
TREATMENT FOLLOW-UP FORM	Page 1/N

Patient

Patient's name (first 3 letters): -- -- -- First name (first 2 letters): -- --

Date of birth: -- -- ---- Weight (kg): ---- Gender: Male Female

Name of prescribing physician: Doctor's stamp and signature:
Hospital:
Department:
Tel.: Fax:
E-mail address:
Date: --/--/----

Please send this form together with the Nominative ATU request form to the establishment pharmacist who should preferably fax this document to:	**French National Agency for Medicines and Health Products Safety** ATU 143-147 boulevard Anatole France 93285 Saint Denis Cedex Fax: 01 55 87 36 12 Tel.: 01 55 87 36 11
To initially order this product, a copy of this form should be sent to YYY with a copy of the ANSM nominative authorisation: fax: 02 31 47 92 75	

D3: Adverse Event Reporting Form

Form to be sent to Pharmacovigilance by YYY: Contact details

D4: **Pregnancy Reporting Form**

D5: Treatment Discontinuation Form

XXX Nominative Temporary Authorisation for Use	
TREATMENT DISCONTINUATION FORM	Page 1/N

Patient

Patient's name (first 3 letters): -- -- -- First name (first 2 letters): -- --

Date of birth: -- -- ---- Weight (kg): ---- Gender: Male Female

Please send this form, preferably by fax, to ANSM and YYY at the end of treatment

APPENDIX F: Cohort ATU RENEWAL REQUEST FORM

. Name of medicinal product:
- Dosage:
- Pharmaceutical form([a]):
- Active substance(s):

. Cohort ATU number
- Date on which the cohort ATU was granted

. Applicant

- Distributing company (name, address)"exploitant":

- contact person:
(name, address, telephone, fax, electronic address)

_____
Signature

_____
At Date

1. Administrative information:

1.1 The medicinal product is already the subject of a marketing authorisation (MA) application:
Yes
Date of submission to ANSM[b] or to the EMA[b:]
Name of the medicinal product: ------

No
The holder shall undertake to submit a MA application dossier[c]:

yes no

If the holder undertakes to submit a MA application:

I, the undersigned, …….. responsible pharmacist *pharmaceutical company* of the company hereby confirm my undertaking to submit a MA application dossier for (*name of the medicinal product)* on (*scheduled submission date*) to ANSM[b] or to European Medicines Agency[b]
Signature: ……

1.2 The medicinal product is subject to biomedical research in France or abroad:
Yes
(Provide a list of biomedical research)
No

[a]: use the standard terms given in the European Pharmacopoeia
[b]: tick as appropriate
[c]: Article L.5121-12a) of the French Public Health Code states that a cohort ATU can only be granted if a MA application has been submitted or the applicant undertakes to submit an application within a set timescale. If this undertaking is not given, the cohort ATU request is not admissible for evaluation.

1.3 The medicinal product was authorised abroad (MA) during the previous ATU period:
Yes
(Specify the countries and names of the relevant medicinal products and the date on which the authorisation was granted)

Country	Name of the medicinal products	MA date

Scheduled date for the submission of the next periodical safety update reports (PSUR) or equivalent document: ……

No

1.4 An exceptional, early use has been granted abroad (pre-MA):
Yes
Country: ……..
Indication: ----------
Status regarding use: -------

No

1.5 Was the medicinal product referred to as an "orphan drug" during the previous ATU period, in accordance with European regulation (EC) No. 141/2000?
Yes
Date of designation: ……
Indication …….

No
Was a designation request considered?
Yes No
If yes, please specify date: …….

II. COHORT ATU

2.1 Current indication of cohort ATU

2.2 Number of persons treated with the medicinal product subject to the ATU:
- since the initial ATU was granted:
- since the last ATU renewal, if applicable:

2.3 Quantities of medicinal products dispensed during the previous authorisation period:

III. RENEWAL REQUEST

3.1 Justification for continuation of ATU:

3.2 Does the renewal request cover the same use for the medicinal product as the one described in the initial cohort ATU decision?

Yes No

If not, describe and justify the differences [d]

[d] provide all of the information needed to justify the required amendments.

4. List of documents / information to enclose 4.1 Copy of the MA application request, if required 4.2 If the medicinal product was authorised abroad during the previous period: 4.2.1. Copy of the authorisation(s) issued by the competent authority 4.2.2. Copy of the summary of characteristics of the corresponding product 4.2.3 Last PSUR or equivalent document 4.3 The protocol governing the therapeutic use and collection of information covering the next period, written in French and highlighting the changes requested if any, with a justification in the cover letter 4.4 In case of requested amendments, drafts, written in French, of 4.4.1. the summary of product characteristics 4.4.2. the patient information leaflet 4.4.3. the labelling 4.4.4 and any information warranting the amendments requested for the ATU 4.5 Biomedical research: 4.5.1. Titles and objectives of current and/or scheduled research in France or abroad for the same disease 4.5.2. Regarding research conducted in France: identity of all the principal investigators in France, names of the test centres concerned and a research progress report 4.6 Copy of the "orphan drug" designation, obtained during the previous period, if applicable 4.7 Copy of any scientific opinion relating to the medicinal product, sent to the applicant by ANSM, the European Medicines Agency or any competent authority in another European Economic Area Member State, if applicable 4.8 Any new information relating to an early, exceptional use in another country 4.9 Dossier including any new information about the medicinal product obtained during the previous ATU period and consequences on its use 4.10 Last periodic summary report written during the previous ATU period and a concise analysis of all of the periodic summary reports. 4.11 A copy of the periodic summary reports sent by the ATU holder to concerned persons, together with submission dates.	Yes	No

COHORT ATU RENEWAL APPLICATION ACKNOWLEDGEMENT OF ADMISSIBILITY		
I. SECTION TO BE COMPLETED BY THE APPLICANT		
. Name of the medicinal product: - Dosage: - Pharmaceutical form: Applicant: - Company distributing the medicinal product "exploitant": (name, address) - contact person: (name, address, tel. No., fax No., electronic Address)		
II. SECTION TO BE COMPLETED BY ANSM		
Date on which application was received:		
Date of receipt of the requested additional documents		
Person in charge of the dossier at ANSM		
Name:		French National Agency for Medicines and Health Products Safety (ANSM). ATU Product Directorate: …….. 143/147, Boulevard Anatole France 93285 Saint-Denis Cedex France
Electronic address:		
Tel. No.:		
Fax No.:		
Admissibility		
□ ADMISSIBLE		
□ NOT ADMISSIBLE		
Points to be noted by the applicant		
□ MISSING DOCUMENTS[1]		
□ ANSM'S COMMENTS [1]		
No. allocated to the dossier:		
Produced on: XII. Signature:		

[1] See subsequent page(s)

III. MISSING DOCUMENTS
□ 1. Cohort ATU renewal application form
□ 2. Copy of MA application
□ 3. If the medicinal product was authorised abroad during the previous period:
3.1 Copy of the authorisation issued by the competent authority
3.2 Copy of the summary of product characteristics for the product in question
3.3 The last PSUR or equivalent document
□ 4. The protocol for the therapeutic use and collection of information, covering the next period, written in French and, if needed , highlighting the amendments requested, if any, with justification in the cover letter
□ 5. If amendments are required, drafts highlighting these amendments and written in French of
5.1 Summary of product characteristics
5.2 Patient information leaflet
5.3 Labelling
5.4 and any information supporting the amendments requested for the ATU
□ 6. Biomedical research
6.1 The titles and objectives of current and/or scheduled biomedical research in France or abroad for the same disorder.
6.2 Regarding research carried out in France: the identity of the investigator(s) in France, the name of the test centre(s) concerned and a trial progress report
□ 7. Copy of the “orphan drug” designation obtained during the previous period
□ 8. Copy of any scientific opinion relating to the medicinal product, sent to the applicant by ANSM, EMA or any competent authority in another European Economic Area Member State o the European Economic Area
□ 9. Any new information relating to early or exceptional use in another country
□ 10 Dossier including any new information obtained during the previous ATU period and relating to the medicinal product and consequences for its use
□ 11 The last periodic updated report written during the previous ATU period and a concise analysis of all periodic summary reports
□ 12 An example of the abridged versions of the periodical summary reports sent by the ATU holder to the persons concerned, with transmission dates
□ 11. Other items :
IV. ANSM’S COMMENTS, if applicable