



Agence française de sécurité sanitaire
des produits de santé

**DIRECTION FOR THE EVALUATION OF MEDICINAL PRODUCTS AND
BIOLOGICAL PRODUCTS**

*Department of the Evaluation of Medicinal Products
with Special Status and Clinical Trials*

**Notice to applicants
for Temporary Authorisation for Use (ATU)**

November 2007

**Contact: Afssaps/Unité ATU
Tel: 33 (0) 1 55 87 36 11
Fax: 33 (0) 1 55 87 36 12
E-mail: atu@afssaps.sante.fr**

SUMMARY

I. ATU : GENERAL PRINCIPLES	5
II. REGULATION	5
2.1 Legislative relating to ATU	5
2.2 Provisions relating to ATU	6
2.3 Provisions relative to the import of medicinal products which are the object of ATU	6
2.4 Provisions concerning pharmacovigilance	6
2.5 Regulatory provisions relating to the conditions of prescription, supply and retrocession	6
2.6 Provisions relative to the cost of ATU.....	7
2.7 Supply and responsibility for medicinal products.....	7
2.8 European provisions	7
III. MEDICINAL PRODUCTS CONCERNED BY ATU AND CONDITIONS OF PRESCRIPTION, SUPPLY AND RETROCESSION	8
3.1 Medicinal products concerned.....	8
3.2 Conditions of prescription, supply and retrocession.....	8
IV. IDENTITY OF THE APPLICANT FOR ATU.....	8
V. WHERE SHOULD APPLICATIONS FOR ATU BE ADDRESSED?	9
VI. NOMINATIVE ATU	9
6.1 Application file for nominative ATU.....	9
6.2 Evaluation of applications for nominative ATU and Afssaps decision	9
6.3 Procedure for obtaining nominative ATU medicinal product and importing the medicinal products	10
6.4 Duration of the nominative ATU and continuations of treatment	10
6.5 Information for patients in the case of nominative ATU.....	10
6.6 Role of the prescribing physician in the case of nominative ATU	10
6.7 Information for prescribing physicians concerning nominative ATU medicinal products	11
6.8 Role of the hospital pharmacist in the case of nominative ATU	11
6.9 Labelling of the medicinal product for nominative ATU.....	11
6.10 Protocol for therapeutic use and information collection	11
6.11 Role of the exploitant of the medicinal product in nominative ATU	11
6.12 List of nominative ATU medicinal products	11

VII. COHORT ATU	11
7.1 Application file for cohort ATU	11
7.2. Protocol for therapeutic use and information collection.....	12
7.3. Assessment of cohort ATU applications.....	13
7.4. Patient information in the context of a cohort ATU.....	13
7.5. Role of the prescribing physician in the context of a cohort ATU	13
7.6. Role of the hospital pharmacist in the context of a cohort ATU.....	13
7.7. Procedure to obtain a medicinal product in the context of a cohort ATU and treatment initiation procedure.....	14
7.8. Role of the exploitant of the medicinal product with a cohort ATU	14
7.9. Periodic ATU reports in the context of a cohort ATU	14
7.10. Importing medicinal products in the context of a cohort ATU	14
7.11. Labelling of a medicinal product in the context of a cohort ATU.....	15
7.12. List of medicinal products with a cohort ATU.....	15
7.13 Duration of cohort ATU and renewal	15
VIII. PHARMACOVIGILANCE AND ATU	16
8.1 Role of healthcare professionals	16
8.2 Role of the exploitant of the medicinal product with an ATU	17
8.3. Role of Afssaps.....	18
8.4 Role of Regional Pharmacovigilance Centres (CRPV)	18
IX. WITHDRAWAL AND SUSPENSION OF ATU.....	19
X. APPROVAL OF ATU MEDICINAL PRODUCTS FOR HOSPITAL USE.....	19
XI. CHANGING FROM ATU TO MA.....	19
XII. ADVERTISING.....	20
XIII. INFORMATION AVAILABLE ON AFSSAPS' INTERNET SITE	20
XIV. FINANCING OF ATU MEDICINAL PRODUCTS	20
ANNEXS.....	21
ANNEX A.....	22
Nominative ATU Cerfa application form.....	22
http://www.sante.gouv.fr/cerfa/autotemp/atu.pdf.....	22

ANNEX B	23
Cerfa form for the notification of an adverse reaction likely to be due to a medicinal product or a product mentioned in Article R.5121-150	23
ANNEX C	24
“Roles of the various parties”	24
ANNEX D	25
Application form for cohort ATU	25
ANNEX E	30
Template – Protocol for therapeutic use and information collection	30
ANNEX F	46
Template for drafting of Periodic ATU Report	46
ANNEX G	50
Application form for renewal of cohort ATU	50

I. ATU : GENERAL PRINCIPLES

The use of medicinal products not benefiting from Marketing Authorisation (MA) in France and not used in clinical trials is conditioned by first obtaining a Temporary Authorisation for Use (ATU) by the French Health Products Safety Agency (Afssaps).

ATU are granted on a purely derogatory, exceptional and temporary basis, when the following conditions are met :

- treating, preventing or diagnosing serious or rare pathologies,
- in the absence of a suitable therapeutic alternative (medicinal product or other) available in France,
- when the benefit /risk ratio of the medicinal product is supposed positive.

This concerns medicinal products authorised abroad or under development.

In practice, there are two types of ATU :

- ATU known as nominative, delivered for only one named patient not taking part in biomedical research, at the application and under the responsibility of the prescribing physician, since the medicinal product is likely to present a benefit for this patient.

These are medicinal products whose efficacies /safety ratio is supposed favourable considering the available data or, exceptionally, medicinal products prescribed because a fatal outcome in the short run for the patient is unavoidable, in the current state of available therapies.

- cohort ATU, concerns a group or sub-group of patients, treated and supervised according to perfectly defined criteria in a protocol for therapeutic use and information collection.

A cohort ATU is issued at the request of the holder of distribution rights (the so called "exploitant"), who must undertake to submit a MA application within a stated time.

This relates to medicinal products which are strongly supposed to be effective and to have an acceptable safety profile, having reached an advanced stage of their development, for example with a MA file in the course of being drafted or registered.

The use of medicinal products subject to ATU cannot replace a clinical trial and the aim is not one of investigation. The decision for ATU must not slow down the implementation or the continuation of clinical trials, alone intended to determine precise and essential elements concerning the benefit/risk ratio of a medicinal product. Indeed, only clinical trials make it possible to collect reliable data, in particular in terms of efficacy, safety of use, medicinal product interactions and therapeutic strategies, while authorizing the access to medicinal products without MA.

Making medicinal products available according to the ATU procedure or for clinical trials depends in particular on the level on information available on the medicinal product in question. Generally, in the early stages of the development of the medicinal product, clinical trials must be favoured.

ATU does not represent either a means of continuing the treatment of a patient initiated within the framework of a clinical trial. To do this, it is advisable to prolong the clinical trial concerned by amending the protocol.

II. REGULATION

The following provisions apply :

2.1 Legislative relating to ATU

Notwithstanding the marketing authorisation of medicinal products for human use, article L.5121-12 of the French public health code fixes the rules of use for therapeutic ends and, exceptionally, of medicinal products without MA in France, intended to treat, prevent or diagnose serious or rare diseases when no suitable treatment exists provided that :

- a) For cohort ATU, the efficacy and the safety of use of these medicinal products are strongly supposed, taking into account the clinical trial results performed with the object of MA application, and that this application has been filed or that the applicant commits himself to filing it within a given time ;

b) or for nominative ATU, that these medicinal products, imported if necessary, are prescribed under the responsibility of a physician, for a named patient who cannot be included in a clinical trial, since they are likely to present a benefit for him and that :

- either their efficacy and their safety are supposed in the state of the scientific knowledge available,
- or a fatal outcome for the patient in the short run is unavoidable, given the therapies currently available.

The requesting physician must justify that the patient, his legal representative or the trusted person who is designated, has received the appropriate information on the absence of therapeutic alternative, the risks incurred, the constraints and the advantages of using the medicinal product. The procedure followed is registered in the patient's medical file.

The use of these medicinal products is authorised by Afssaps, for a limited time, at the request of the exploitant in the case of cohort ATU, or at the request of the prescribing physician in the case of nominative ATU.

Cohort ATU is subordinated to the implementation of a protocol for therapeutic use and information collection, established by Afssaps in collaboration with the exploitant. Afssaps may consider necessary that such a protocol is also set up for certain medicinal products made available within the framework of nominative ATU.

ATU can be modified, suspended or withdrawn for reasons of public health or if the conditions which led to granting it are no longer met.

2.2 Provisions relating to ATU

Articles R.5121-68 to R.5121-76 of the French public health code specify in particular:

- the conditions of granting ATU,
- the contents of the ATU application file,
- the methods of file assessment,
- the duration of ATU,
- the methods of follow-up of patients within the protocol for therapeutic use and information collection if necessary, and the conditions of transmission to Afssaps of information thus collected,
- the conditions of supplying of the medicinal product,
- the conditions of renewal, withdrawal, suspension and ending of ATU.

2.3 Provisions relative to the import of medicinal products which are the object of ATU

The methods of import of medicinal products being the object of nominative ATU or cohort ATU are specified in articles L.5124-13 and R.5121-108 to R.5121-114 of the French public health code.

Nominative ATU and cohort ATU constitute an authorisation for import.

The importing of a nominative ATU medicinal product in order to stock up on the medicinal product by a pharmaceutical company or the hospital pharmacy requires obtaining a prior authorisation delivered by the Director general of Afssaps ("ATU Unit").

2.4 Provisions concerning pharmacovigilance

Articles R.5121-150 to R.5121-201 of the French public health code apply to ATU medicinal products (cf. article R.5121-152). The decree of April 28th, 2005 published in the Journal Officiel on May 26th, 2005 and available on the Afssaps' Internet site, defines the good practices for pharmacovigilance.

2.5 Regulatory provisions relating to the conditions of prescription, supply and retrocession

Decree n°2004-546 of June 15th, 2004 relating to the categories of restrictively prescribed medicinal products and to the sale of these medicinal products to the public by certain hospital pharmacy modifying the public health code and the code of social security applies to medicinal products which are the object of ATU (cf. articles R.5121-77 to R.5121-95 and R.5126-102 to R.5126-115 of the French public health code).

2.6 Provisions relative to the cost of ATU

Article L.162-16-5-1 of the French code of social security lays down the methods for declaration to the "Comite Economique des Produits de Sante "(CEPS) by the exploitant of the ATU medicinal product, of the amount of allowance claimed from hospital pharmacies (PUI) as well as in the absence of exploitant in France, the methods of declaration by the PUI of the amount of the allowance which is claimed from them.

2.7 Supply and responsibility for medicinal products

Circular NDGS/SD3A /DSS/FSS/DHOS/E2 n°2007-143 of April 11th, 2007 fixes the conditions under which medicinal products which are or have been the object of ATU can be provided and reimbursed. This circular repeals that of November 21st, 1996.

2.8 European provisions

Article 83 of Regulation EC/726/2004 of March 31st, 2004 lays down the possibility, for the Member States, to make available "for compassionate use" any medicinal product to be authorised by the Community (on an obligatory basis or on an optional basis) provided this medicinal product is the object either of a an application for centralised MA, or clinical trials. This concerns the following medicinal products:

- Obligatory basis :
 - o medicinal products developed by means of 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 ; hybridoma and monoclonal antibody methods ;
 - o medicinal products containing a new active substance which, on November 20th, 2005, was not authorised in the Community, for which the therapeutic indication is the treatment of any of the following diseases : AIDS, cancer, neurodegenerative disorder, diabetes, and starting from May 20th, 2008, auto-immune diseases and other immune dysfunctions, and viral diseases.
 - o medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) N°141/2000.
- Optional basis :
 - o medicinal product containing a new active substance which, on November 20th, 2005, was not authorised in the Community ;
 - o medicinal product for which the applicant shows that it constitutes a significant therapeutic, scientific or technical innovation, or that the granting of authorisation in accordance with the regulation (EC) 726/2004 is in the interest of patients at Community level.

"Compassionate use" shall mean making a medicinal product available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactorily by an authorised medicinal product. Thus, for France, these are ATU known as cohort ATU.

The compassionate use for named patients (in France, the nominative ATU) is not concerned with this Regulation.

This Regulation provides in particular that :

- Member States (MS) notify the European Medicines Agency (EMA) of their project to set up a program of compassionate use,
- the Committee of Medicinal products for Human Use (CHMP) of the EMA may adopt an opinion on the distribution and the conditions of use of the medicinal product concerned, and also on the target population.

For the implementation of the procedure set up by this article, a guideline (guideline on compassionate use of medicinal products, pursuant to article 83 of Regulation (EC) N°726/2004/July 2007) has been developed by the CHMP and is available on the Internet site of the EMA (www.emea.europa.eu).

This guideline specifies in particular :

- the field of application of the procedure (see above),
- the initialisation of an opinion from the CHMP and the scope of this opinion,
- measures of transparency implemented by EMA.

In addition, it is pointed out that :

- the implementation of a program of compassionate use remains the responsibility of the Member States (MS),
- the inclusion of patients in clinical trials must be favoured before considering them for compassionate use medicinal products,
- the opinion of the CHMP is given either when a MS asks for it, or when two MS give notification of a program of compassionate use for the same medicinal product, even if these MS do not specifically require the opinion of the CHMP.

III. MEDICINAL PRODUCTS CONCERNED BY ATU AND CONDITIONS OF PRESCRIPTION, SUPPLY AND RETROCESSION

3.1 Medicinal products concerned

ATU allows the use, outside of the framework of clinical trials, of medicinal products without MA in France, whether they benefit or not from a MA abroad.

ATU does not apply to the following :

- the continuation of treatment at the end of a clinical trial which must in this case contain an amendment to the initial protocol,
- the use of a medicinal product having a MA in France for an indication other than that envisaged in its MA: this off label use is the unique responsibility of the prescriber,
- the use of a medicinal product having a MA in France but not marketed in France (in this case : authorisation for import),
- the use of a hospital or extemporaneous preparation specially made up by a pharmacist for a particular patient with deconditioning of a medicinal product with no MA in France,
- medicinal products subjected to authorisation for import.

3.2 Conditions of prescription, supply and retrocession

Medicinal products benefiting from ATU can only be supplied by hospital pharmacies belonging to public or private health care institutions (cf. articles R.5121-72 and R.5121-73 of the French public health code).

The classification of a medicinal product benefiting from a ATU in the category of the medicinal products “reserved for hospital use” implies, in accordance with article R.5121-83 of the French public health code, that its prescription, its supply and its administration are carried out within a health care institution.

In certain cases, its prescription can be restricted to certain categories of prescribers and be subordinated to performing periodic patient examinations.

When the medicinal product benefiting from a ATU is “not reserved for hospital use” :

- . in the case of nominative ATU, deemed to be retroceded by the hospital pharmacy,
- . in the event of cohort ATU, registered on the list of medicinal products which can be retroceded mentioned in article L.5126-4 of the French public health code.

In practice, it can be sold to patients by pharmacies of health care institutions authorised for retrocession.

IV. IDENTITY OF THE APPLICANT FOR ATU

Applications for nominative ATU are initiated by the prescribing physician and are transmitted by fax to Afssaps by the pharmacist of the health care institution. This physician is the holder of the nominative ATU.

The applications for cohort ATU are carried out at Afssaps by the exploitant of the medicinal product being the subject of cohort ATU or by his representative.

V. WHERE SHOULD APPLICATIONS FOR ATU BE ADDRESSED?

The applications for ATU are to be addressed to:

Afssaps
Unité Autorisations Temporaires d'Utilisation
143-147, boulevard Anatole France
93285 SAINT-DENIS Cedex
FRANCE
Fax: (33) 1.55.87.36 .12
Tel: (33) 1. 55.87.36 .11

The applications for nominative ATU are addressed by fax by the hospital pharmacist.

VI. NOMINATIVE ATU

6.1 Application file for nominative ATU

The application for nominative ATU is carried out using the Cerfa form n° 10058 01 (appendix A) available on Afssaps' Internet site: www.afssaps.sante.fr.

It should contain in particular information concerning the envisaged treatment (name of the medicinal product, posology, length of treatment), the patient (initials of first name and surname, sex, age), the exact indication and justification for the application.

This form must be filled in, dated and signed by the prescribing physician and completed by the pharmacist of the health care institution. Their respective contact details must be precisely indicated.

If all the relevant information necessary to examine the application cannot be set down on the Cerfa form, separate documents should be enclosed, by indicating the references of the application on them (name of the prescriber, patient initials, name of the medicinal product).

When additional details are required by Afssaps, these should be addressed as soon as possible, enclosing a copy of the initial Cerfa application form.

6.2 Evaluation of applications for nominative ATU and Afssaps decision

The assessment concerns the medicinal product, its quality, safety and its efficacy for the indication specified in the application for ATU, and also the absence of therapeutic alternative. Each application for nominative ATU is examined by Afssaps, assisted by experts.

To this end, Afssaps refers to the file requested from the company in charge of the medicinal product for which a ATU is required, which comprises in particular :

- a copy of the summary of product characteristics (SPC) authorised abroad, if applicable ;
- any available information relating to the quality, efficacy and safety (litterature, investigator's brochure, investigational medicinal product dossier and PSUR (Periodic Safety Update Report) if applicable) ;
- the list of clinical trials in progress and planned in France and abroad.

The prescribing physician requesting an ATU may also be asked by Afssaps to provide scientific information justifying his application for ATU.

The decisions of Afssaps are the following :

- ATU granted : a granted ATU mentions in particular the following information: name of the medicinal product, contact details of the prescriber, patient initials, duration of the treatment, contact details of the health care institution pharmacy.

The ATU is addressed by fax to the pharmacist who in turn informs the prescriber. It is accompanied, if necessary, by a copy of the SPC approved abroad or a therapeutic information notice written by Afssaps. The prescriber is informed by letter of the granting of ATU;

- ATU refused : ATU is not granted and for the following reasons in particular :
 - . existence of alternative therapy having a MA in France and available on the market,
 - . and/or absence of convincing elements suggesting benefit to the patient,
 - . and/or the object of the application is for an investigation,
 - . and/or possible inclusion of the patient in a clinical trial in progress.

The refusal is addressed by fax to the pharmacist who in turn informs the prescriber and by registered letter with acknowledgement of receipt to the prescriber. This decision may be appealed to the Director general of Afssaps and/or by litigation before a qualified administrative court, within 2 months from the date of notification.

The deadline for Afssaps reply to applications for ATU depends on the one hand on therapeutic urgency and on the other the amount of information that Afssaps has on the medicinal product. Thus :

- when the medicinal product has already been evaluated by Afssaps, the decision is fast, generally about 24 to 48 hours.
- when the medicinal product has never been evaluated, the deadline for replying takes into account the delay in setting up the file and its evaluation.

6.3 Procedure for obtaining nominative ATU medicinal product and importing the medicinal products

A nominative ATU qualifies as authorisation to import. When the product is not available in France, the hospital pharmacist imports it himself or via a pharmaceutical company. He then carries out the order on a purchase order accompanied by the ATU delivered by Afssaps. He then takes delivery of the medicinal product and supplies it.

In order to optimize medicinal product delivery time, it is recommended that products for which import or orderring delays can be long, be physically available in hospital pharmacies by setting up of medicinal product stocks. The constitution of stocks by hospital pharmacist may be authorised by Afssaps in cases of extreme therapeutic urgencies or in other clinical situations occurring frequently within the same hospital.

The applications for stock setting up, addressed to the ATU unit by the pharmacist, are duly justified and should mention in particular the indication for which the product will be used.

Then, the medicinal product may be supplied by the pharmacy only after having obtained a nominative ATU from Afssaps for each patient, except in particular cases where the medicinal product is intended to be used in situations of extreme clinical emergency.

6.4 Duration of the nominative ATU and continuations of treatment

The duration of the nominative ATU is specified on the authorisation. It corresponds to the duration of the treatment and cannot exceed one year.

In the event of the need to prolong the treatment, a renewal of ATU is applied for to Afssaps. This application is carried out according to same procedure as the initial application, mentioning the nature of the application (renewal) and the reference number of the preceding ATU as well as any information relative to efficacy and tolerance of the treatment which justifies its continuation.

6.5 Information for patients in the case of nominative ATU

The prescribing physician must be able to justify that before starting treatment, the patient, his legal representative or a trusted person receive information relative to the absence of therapeutic alternative, the risks incurred, the constraints and the benefits likely to be obtained from using the medicinal product. The procedure followed is registered in the patient's medical file.

6.6 Role of the prescribing physician in the case of nominative ATU

The prescribing physician is responsible for:

- informing the patients (cf. 6.5) and if possible their general practitioner,
- ensuring the monitoring of the patients treated,
- respecting the pharmacovigilance requirements (cf. VIII),
- keeping the pharmacist of the health care institution informed,
- answering any request for information coming from Afssaps.

6.7 Information for prescribing physicians concerning nominative ATU medicinal products

Afssaps addresses to the prescribing physician :

- a letter informing him of the decision to grant ATU which can, if necessary, contain special warning statements, precautions for use and/or adverse reactions,
- a copy of the summary of product characteristics of (SPC) approved abroad if appropriate,
- or if necessary, in the absence of SPC, a therapeutic information note summarizing the main characteristics of the medicinal product.

When the exploitant of the ATU medicinal product wishes to address information medicinal product prescribers, this are re-read in practice beforehand by Afssaps. It can be for instance the last version of investigator brochure.

6.8 Role of the hospital pharmacist in the case of nominative ATU

The pharmacist addresses the application for nominative ATU to the ATU unit at Afssaps. If necessary, he collects further information requested by Afssaps.

He receives the ATU, informs the prescriber and transmits, if necessary, a copy of the letters sent by Afssaps.

He orders, imports if necessary, delivers and supplies the medicinal product and respects the pharmacovigilance requirements (cf. VIII).

6.9 Labelling of the medicinal product for nominative ATU

Labelling comprises at least the name of the medicinal product or if appropriate its code name, the batch number and the expiry date.

6.10 Protocol for therapeutic use and information collection

In certain situations, Afssaps can require that the use of the nominative ATU medicinal product and the monitoring of the patients be, as for a cohort ATU medicinal product, fixed by a protocol for therapeutic use and information collection (cf. 7.2).

6.11 Role of the exploitant of the medicinal product in nominative ATU

The exploitant of the medicinal product in nominative ATU distributes the medicinal product to the PUI or to an authorised structure, after checking the ATU delivered by Afssaps.

It only distributes information concerning the medicinal product only after validation by Afssaps. If necessary, it sets up a protocol for therapeutic use and information collection established in collaboration with Afssaps; in this case, it draws up a summary report of the data collected and transmits it to Afssaps within the stated time. It applies the provisions of pharmacovigilance (cf. VIII).

6.12 List of nominative ATU medicinal products

The list of medicinal products for which nominative ATU have been delivered over a given period is available on the Afssaps' Internet site at: www.afssaps.sante.fr.

VII. COHORT ATU

7.1 Application file for cohort ATU

An application for cohort ATU can be submitted :

- at the same time as an application for MA ;
- before filing an application for MA, subject to a commitment to apply for MA later on.

The application file includes :

1. the application for cohort ATU filled in on the application form in conformity with the format laid down by decree of July 6th, 2007 (cf. ANNEX D), which includes in particular :
 - the reasons for the application with respect to article L.5121-12 of the French public health code,
 - a commitment to file an application for MA and the expected date.

2. an administrative dossier including :

- if relevant, a copy of the application for MA,
- project of ATU summary of product characteristics (SPC), patient information leaflet and labelling in French language,
- project of protocol for therapeutic use and information collection in French language (cf. model in appendix E),
- the titles and objectives of the ongoing clinical trials with their progress reports and the trials planned for the same disease in France or abroad, the identity of the principal investigator(s) in France and the name of the research centre(s) concerned in France,
- when the medicinal product is authorised abroad: the copy of the authorisation delivered by the competent authority, the copy of the summary of product characteristics, the latest periodic safety updated report (PSUR) or equivalent document and the date envisaged for submitting the following PSURs,
- if relevant, the European "orphan medicinal product" designation,
- any information concerning exceptional and early use of the MP abroad ("compassionate use" or "expanded access program", ...),
- a copy of the scientific advice(s) delivered by Afssaps, the European Medicines Agency (EMA) or any competent authority of a Member State of the European Community or European Economic Area, if relevant,
- the estimated number of patients in France concerned by the ATU application.

3. a medicinal product dossier :

The file contains all the pharmaceutical and pharmaco-toxico-clinical data available at the moment of the application (even if the studies are ongoing).

The format of the file must be the nearest possible to that necessary for the MA files:

- summary of the file including reports by experts if available,
- chemical, biological and pharmaceutical data,
- preclinical and pharmacological data,
- clinical data.

If necessary, the medicinal product file can be presented in the format of the updated investigational medicinal product dossier (IMPD) (cf. procedure of clinical trial authorisation).

The file, in French or in English language, must be presented in the form of a paper document (5 copies) and in electronic format (CD ROM 5 copies or protected email).

The file, addressed to the ATU unit, must be deposited at the office of the reception of the application for MA of Afssaps after the ATU unit has been informed by telephone, fax or by ordinary or electronic mail (atu@afssaps.sante.fr).

Afssaps notifies the applicant of the reception date of the dossier and the registered number which is allotted to it. If the dossier is not complete the list of missing parts is notified. The examination of the dossier only begins when the file is considered complete.

7.2. Protocol for therapeutic use and information collection

This protocol (PTU) is drawn up by the exploitant of the medicinal product concerned in close collaboration with the ATU unit at Afssaps.

The aim of this protocol is :

- to provide prescribing physicians with any relevant information about the medicinal product and its use,
- to organise patients monitoring,
- and to collect information relative to the actual use of the medicinal product during the ATU and pharmacovigilance with the view of drawing up a periodic ATU report which is intended to be regularly transmitted to Afssaps.

In particular, this protocol (cf. ANNEX E) includes :

- a review of the general principles concerning ATU,
- the summary of product characteristics for the medicinal product with the cohort ATU,
- a description of the practical conditions for use of the medicinal product, prescribing and supplying conditions.
- a description of the conditions relative to patient information (patient information note),
- a description of the patient monitoring conditions,

- a description of the conditions relative to the data collection by prescribing physicians (including follow-up forms) and by the holder or the exploitant of cohort ATU ; information from the follow-up of patients (namely characteristics of the patients treated, actual use of the medicinal product, serious or unexpected adverse reactions),
- a description of the pharmacovigilance measures/provisions to apply,
- a description of the conditions relative to periodic update reporting by the exploitant,
- a description of the conditions relative to the diffusion of these periodic ATU reports to concerned partners.

7.3. Assessment of cohort ATU applications

Each cohort ATU application is assessed by the Marketing Authorisation Committee of Afssaps. In particular, assessment deals with the pharmaceutical quality, safety and efficacy of the medicinal product for the indication claimed, the draft protocol for therapeutic use and information collection, the draft summary of product characteristics, the draft patient information leaflet and labelling, the prescribing and supplying conditions as well as the absence of therapeutic alternative available on the French market.

A cohort ATU is granted for a fixed indication which must be respected. To the authorisation are attached the summary of product characteristics, the patient information leaflet, the labelling as well as the protocol for therapeutic use and information collection. Afssaps also notifies the frequency of periodic ATU (cf. 7.9). A regional pharmacovigilance centre (CRPV), designated by Afssaps, may be appointed to be in charge of the national monitoring of adverse reactions associated with the medicinal product.

7.4. Patient information in the context of a cohort ATU

Prior to treatment initiation, each patient, his legal representative or the trusted person must be informed by the prescribing physician of the following :

- the conditions relative to the exceptional use of the medicinal product ;
- the medicinal product characteristics (in particular expected benefits, risks and constraints) ;
- the conditions relative to patient monitoring.

Patients are also informed that the prescribing physician will collect data regarding their treatment and that this data will be transmitted to the cohort ATU holder and Afssaps and could be subject to computerised processing. Pursuant to French Law N°78-17 of 6th January 1978, amended, the so-called data protection law, the patient may exercise his right to correct this information at any time.

An information note, which is available in the protocol for therapeutic use and information collection, is given by the prescribing physician, to the patient, his legal representative or the trusted person, together with oral explanations. A patient information leaflet is also available in each box of medicinal product.

7.5. Role of the prescribing physician in the context of a cohort ATU

The prescribing physician must :

- inform his patients and, if possible, their general practitioner (cf. 7.4) ;
- inform the hospital pharmacist concerned about the details of patients treatment with the medicinal product in the context of a cohort ATU ;
- respect the conditions for use described in the ATU summary of product characteristics and the protocol for therapeutic use and information collection ;
- ensure monitoring of treated patients, information collection and transmission of the information collected to the cohort ATU holder according to the conditions described in the protocol for therapeutic use and information collection ;
- notify any treatment discontinuation and the reasons for it to the concerned hospital pharmacist and the cohort ATU holder ;
- respect the pharmacovigilance reporting requirements (cf. VIII).

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

The hospital pharmacist :

- reads and ensures compliance with the protocol for therapeutic use and information collection ;
- ensures he gets all the necessary information relative to patient treatment with the medicinal product with a cohort ATU in his hospital ;
- orders, receives and supplies the concerned medicinal product and manages stocks.

7.7. Procedure to obtain a medicinal product in the context of a cohort ATU and treatment initiation procedure

Medicinal products with a cohort ATU are supplied to patients by hospital pharmacies in accordance with the prescribing and supplying conditions as set out in the ATU.

The conditions for obtaining the medicinal product are described in the protocol for therapeutic use and information collection. In general, the physician and/or the pharmacist first contact the cohort ATU holder in order to obtain the protocol for therapeutic use and information collection.

After reading this protocol, the prescribing physician sends a treatment initiation form to the cohort ATU holder through the hospital pharmacist concerned.

The treatment initiation form is validated by the cohort ATU holder in accordance with the specific criteria set out in the ATU and the corresponding protocol for therapeutic use and information collection.

Once the application is validated, the exploitant supplies the medicinal product concerned ordered by the hospital pharmacist.

7.8. Role of the exploitant of the medicinal product with a cohort ATU

The exploitant of the medicinal product with a cohort ATU circulates the protocol for therapeutic use and information collection to prescribing physicians and hospital pharmacists concerned, CRPVs, and Poison Control centres.

It makes sure the protocol is implemented and checks that the inclusion criteria defined in the protocol for therapeutic use and information collection and the summary of product characteristics are met for each patient.

It gathers and analyses the data transmitted by the prescribing physicians and hospital pharmacists.

It acts in compliance with the pharmacovigilance reporting conditions (cf. VIII).

It produces a periodic ATU report for Afssaps including an analysis of all the data collected in the context of the protocol for therapeutic use and information collection (cf. 7.9) and sends a summary of these reports to the prescribing physicians, hospital pharmacists and all CRPVs and Poison Control centres once it has been validated by Afssaps.

7.9. Periodic ATU reports in the context of a cohort ATU

Periodic ATU reports (cf. template in ANNEX F) are sent to Afssaps (3 copies to the ATU unit (Unité ATU) and 2 copies to the pharmacovigilance unit) and, if applicable, to the CRPV in charge of the national monitoring, according to a periodicity set by Afssaps.

They include a descriptive analysis of all the data collected during the ATU validity period (data collected since the previous report and cumulated data) in the context of the protocol for therapeutic use and information collection, as well as any new relevant information on the medicinal product since the cohort ATU was granted, particularly as regards actual conditions of use and safety.

In particular, these reports include :

- updated data concerning the status of the medicinal product abroad: marketing authorisation application, marketing authorisation, "orphan medicinal product" designation if applicable,
- a description of the actual conditions for use of the medicinal product within the context of the ATU (population, posologies, criteria for use, associations with other medicinal products, etc.) on the basis of the information collected by prescribing physicians using the forms provided for this purpose,
- a section relative to pharmacovigilance (cf.. 8.2.2),
- if applicable, updated data relative to clinical trials.

Once it has been validated by Afssaps, a summary of each report is sent by the cohort ATU holder to prescribing physicians and hospital pharmacists concerned as well as CRPVs and Poison Control centres for information, according to a periodicity laid down by Afssaps.

7.10. Importing medicinal products in the context of a cohort ATU

A cohort ATU accords automatic importation rights (cf 2.3).

7.11. Labelling of a medicinal product in the context of a cohort ATU

Labelling complies with ANNEX IIIA of the cohort ATU notification and includes at least the following information written in French :

- the name of the medicinal product or, if applicable, its code name ;
- the name and address of the exploitant ;
- the manufacturing batch number ;
- the route of administration and, if applicable, the method of administration of the medicinal product ;
- the active substance(s) ;
- the expiry date ;
- the special precautions for storage of the medicinal product ;
- conditions of prescribing and supply.

7.12. List of medicinal products with a cohort ATU

The list of medicinal products available in the context of a cohort ATU as well as SPCs and patient information leaflets are available on Afssaps' website: www.afssaps.sante.fr.

7.13 Duration of cohort ATU and renewal

Cohort ATU is granted for a duration of one year and can possibly be renewed.

The application for renewal formulated, preferably 2 months before the expiry of ATU, is the subject of an opinion of the MA Committee. The application file comprises :

- the application form for renewal formulated of ATU (cf. ANNEX G) mentioning in particular the justification of the continuation of ATU taking into consideration the criteria mentioned in article L.5121-12 of French public health code and if necessary, a renewal of the commitment of the holder to apply for a MA and the date envisaged for this submission,
- a copy of the application for MA, if relevant,
- when the medicinal product has been authorised abroad within the previous period :
 - . the copy of this authorisation delivered by the competent authority,
 - . the copy of the corresponding summary of product characteristics,
 - . the last PSUR or equivalent document,
- protocol for therapeutic use and information collection envisaged for the period to come, in French language and, if necessary, revealing the modifications requested and their justification on an enclosed cover letter,
- in case of modifications, projects in French language of :
 - . summary of the product characteristics,
 - . the patient information leaflet,
 - . labelling,
 - . and any information justifying the modifications requested,
- clinical trials :
 - . titles and objectives of the clinical trials in progress and/or planned in France or abroad for the same indication,
 - . concerning clinical trials undertaken in France: identity of the principal investigator(s) in France, the details of the research centre(s) concerned in France and the progress status of the trials,
- the designation "orphan medicinal product", obtained for the previous period, if applicable,
- any scientific advice on the medicinal product given for the previous period, by Afssaps, the EMEA or any competent authority of a Member State of the European Community or European Economic Area, if applicable,
- all new information relative to early and exceptional use of the MP in another country,
- a any new information obtained during the preceding period of ATU on the medicinal product and the consequences of its use,
- latest periodic ATU report for the preceding period of ATU and a concise analysis of all previous reports,
- a copy of the summaries of the periodic ATU reports transmitted by the holder of ATU to the persons concerned, with the dates of transmission.

Afssaps notifies the applicant of the date of reception of the file and the number which is allotted to it. If the file is not complete, it notifies the list of the missing documents. The assessment of the dossier only begins when the file is considered complete.

VIII. PHARMACOVIGILANCE AND ATU

8.1 Role of healthcare professionals

- **Who should report ?**

Any physician, pharmacist, dentist or midwife observing a serious or unexpected adverse reaction that could be due to the medicinal product with an ATU, whether they prescribed it or not, and any pharmacist knowing of any serious or unexpected adverse reaction which could be due to the medicinal product with an ATU which he delivered, should report it immediately. Any healthcare professional making the same observation may also report.

- **What should be reported ?**

Serious adverse reactions (expected or unexpected)
Unexpected adverse reactions (serious or not)

In addition, it is strongly recommended to report :

- any case of overdose ;
- any case of exposure during pregnancy or lactation ;
- any other effect or situation with a potential or known harmful consequence for health ;
- any observed efficacy loss (especially with vaccines, contraceptives or medicinal products intended for treatment of life threatening disease),
- any reaction judged as relevant for reporting.

Targeted monitoring of some adverse reactions may also be set up for some medicinal products.

Pursuant to Article R.5121-153 of the French Public Health Code, the various definitions are as follows :

ADVERSE REACTION :

A response to a medicinal product or product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

SERIOUS ADVERSE REACTION :

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

UNEXPECTED ADVERSE REACTION¹:

An adverse reaction, the nature, severity or outcome of which is not consistent with the Summary of Product Characteristics (SPC)

MISUSE :

Use which is not compliant with the recommendations of the SPC

ABUSE :

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects

- **How to report ?**

In the context of a nominative ATU :

Notification should be done using Cerfa form N° 10011*01 (Annex B), indicating in particular the name of the medicinal product with a nominative ATU as well as the ATU number allocated to the patient. This form is also available on Afssaps' website (www.afssaps.sante.fr (heading ATU)) or from CRPVs. A similar form may also be included in the protocol for therapeutic use and information collection, if applicable.

¹ To determine the expected/unexpected nature of an adverse reaction, the following is used as a reference:

- For a medicinal product with a nominative ATU:

. the SPC approved abroad, if the medicinal product is authorised abroad,

. in the absence of an SPC approved abroad: the investigator's brochure or the therapeutic information note, if applicable (cf. 6.7)

- For a medicinal product with a cohort ATU : the ATU SPC.

In the context of a cohort ATU :

Notification should preferably be done using the adverse reaction notification form provided in the protocol for therapeutic use and information collection, or using Cerfa form N° 10011*01 (Annex B), indicating the name of the medicinal product with a cohort ATU as well as the number allocated to the patient in the cohort ATU.

- To whom ?

In the context of a nominative ATU :

Notification should be made to the regional pharmacovigilance centre (CRPV) of which the reporter is geographically linked with.

In the context of a cohort ATU or a nominative ATU subject to a protocol for therapeutic use and information collection :

Serious or unexpected adverse reactions should be notified to the addressee indicated in the protocol for therapeutic use and information collection. Most often, this is the pharmacovigilance department of the exploitant of the medicinal product with an ATU.

- When to report ?

In the context of a nominative ATU :

Immediately in case of serious or unexpected adverse reactions

In the context of a cohort ATU or a nominative ATU subject to a protocol for therapeutic use and information collection :

Immediately in case of serious or unexpected adverse reactions

At each visit scheduled in the protocol in any other situation.

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

8.2.1 Who is in charge of pharmacovigilance of the medicinal product with an ATU ?

In the context of a nominative ATU :

If a pharmaceutical company in France imports the medicinal product : this pharmaceutical company is in charge of pharmacovigilance of the said medicinal product with an ATU.

If no pharmaceutical company exists in France importing the medicinal product with an ATU but the hospital pharmacist imports it, then the exploitant of the ATU medicinal product in the original country is in charge of pharmacovigilance.

In the context of a cohort ATU :

The cohort ATU holder is necessarily in charge of pharmacovigilance of the medicinal product.

8.2.2 Immediate notification of serious adverse reactions to Afssaps

The exploitant of the medicinal product with an ATU must notify the following to Afssaps as early as possible, within 15 days following reception at the latest :

- any serious adverse reaction which occurred in France and likely to be due to the medicinal product, which was reported by a healthcare professional to the company,
- any other serious adverse reaction which occurred in France and likely to be due to the medicinal product, which the company may be informed about via existing publications mentioning it or accessible databases including it, or which was reported in accordance with the criteria as laid down in good pharmacovigilance practices (decree of 28th April 2005, published in the Official Bulletin of 26th May 2005),
- any serious and unexpected adverse reaction which occurred in a third country and likely to be due to the medicinal product, which the company was informed about.

Adverse reactions are notified by fax to the Pharmacovigilance unit of Afssaps, preferably using the CIOMS - I A form ("Suspect adverse reaction report") and also to the CRPV in charge of the national pharmacovigilance monitoring of the medicinal product with an ATU, if one has been appointed.

Notification forms (either in French or in English language) must include the following information :

- . the mention of the MP status in France ("nominative ATU" or "cohort ATU") at the time of the reaction whatever the country in which the reaction occurred,
- . the unexpected nature of the adverse reaction as well as its imputability for serious adverse reactions occurring in France.

8.2.3. Transmission of periodic safety update reports (PSUR)

The exploitant of the medicinal product with an ATU must transmit, to the Director General of Afssaps and the CRPV appointed, if applicable, in the form of a periodic safety update report (PSUR), the information relative to the adverse reactions possibly due to the medicinal product with an ATU which it notified or was notified as well as all the information useful for the evaluation of the risks and benefits related to the use of this medicinal product.

a) *In the context of a cohort ATU or a nominative ATU subject to a protocol for therapeutic use and information collection :*

The periodic safety update report related to data collected within ATU is included in the periodic ATU report which periodicity is laid down in the protocol for therapeutic use and information collection (cf. 7.2, 7.9 and template in ANNEX F).

In addition, when the medicinal product is authorised abroad, the international PSUR is also transmitted to Afssaps during the period of availability of the medicinal product within the context of the ATU.

b) *In the context of a nominative ATU :*

A summary report of the pharmacovigilance observations having occurred in France (cf. template in ANNEX F) is required annually as well as the international PSUR, if available, during the period of availability of the medicinal product with a nominative ATU.

8.2.4 Particular case: simultaneous application for a marketing authorisation of ATU medicinal product

For the period between the submission of an MA application (whatever the procedure) and the granting of the marketing authorisation for a medicinal product available previously within ATU, the MA applicant must make sure that any information made available within the framework of ATU and having an impact on the benefit /risk ratio of the medicinal product is declared to Afssaps as well as :

- to the competent authorities for whom an application for MA for the medicinal product is under assessment (reference Member State and Member States concerned), when a mutual or decentralised recognition procedure is used ;
- to the EMEA, the rapporteur and the co- rapporteur, for a European centralised procedure.
(cf. *Regulation for the medicinal products in the European Community, 9-A-pharmacovigilance part I-5.2*).

8.3. Role of Afssaps

Afssaps

- receives pharmacovigilance notifications and periodic ATU reports,
- informs the exploitant of the medicinal product with an ATU about any serious adverse reaction that could be due to this medicinal product which it was reported or notified.

Afssaps may request the opening of an official pharmacovigilance investigation or a pharmacovigilance follow-up in order to assess the medicinal product safety.

8.4 Role of Regional Pharmacovigilance Centres (CRPV)

In the context of a nominative ATU :

CRPVs are in particular, in charge of :

- gathering and assessing the information relative to the adverse reactions or other reactions related to medicinal products with a nominative ATU, especially transmitted by healthcare professionals,
- transmitting the above mentioned information to Afssaps, without delay when these informations concern serious adverse reactions,
- an expertise mission by conducting studies and investigations at the request of Afssaps.

In the context of a cohort ATU or a nominative ATU subject to a protocol for therapeutic use and information collection:

If necessary (Article R.5121-155), a CRPV may be appointed by Afssaps to be in charge of the national pharmacovigilance monitoring of a medicinal product with an ATU in close collaboration with the exploitant. It receives (via the company) copies of all serious adverse reaction notification forms sent to Afssaps and periodic ATU reports which it analyses.

IX. WITHDRAWAL AND SUSPENSION OF ATU

The ATU may be suspended or withdrawn by the Director General of Afssaps for public health reasons or if the conditions in Article L.5121-12 of the French Public Health Code which led to its granting are no longer met. The suspension decision is justified and suspension can not be decided upon for a period longer than 3 months.

The withdrawal decision is also justified and may be decided upon only after the ATU holder has been invited to provide its observations and, for cohort ATU, after the marketing authorisation committee has issued an opinion.

X. APPROVAL OF ATU MEDICINAL PRODUCTS FOR HOSPITAL USE

Circular NDGS/SD3A/DSS/DHOS/E2 n°2007-143 of April 11th, 2007 lays down the conditions under which medicinal products being the object or having been the object of ATU can be provided and financed.

Medicinal products available within a cohort ATU are approved for hospital use by inter-ministerial “arrêté”, a favorable opinion for granting an ATU by the MA committee constituting a proposal for inscription on the list of MP approved for hospital use. By way of derogation, the Transparency Committee of the French National Authority for Health is not consulted on this inscription. The medicinal products subjected to nominative ATU are considered approved for hospital use as from the date of granting of the ATU.

In the transitory period between the granting of a cohort ATU and the publication of the approval for hospital use under the ATU conditions, hospital pharmacies are authorised to purchase the medicinal product concerned as soon as the ATU is granted by Afssaps. Hospital pharmacies are authorised to purchase medicinal products with a nominative ATU throughout the ATU validity period.

For medicinal products with a cohort ATU or a nominative ATU, the approval for hospital use granted on the basis of the ATU remains valid until an approval for hospital use on the basis of the marketing authorisation (if any) is decided upon. The request for this approval of hospital use should be submitted within 30 days following the notification of the marketing authorisation to the holder.

XI. CHANGING FROM ATU TO MA

Article R.5121-76 of the French public health code provides that when a medicinal product with ATU obtains a MA, the Director general of Afssaps fixes the date on which cohort ATU ceases or the date on which the granting of nominative ATU ceases, according to the date of notification of MA and the delay necessary to make the medicinal product available in accordance with its MA conditions.

This date depends only on the time necessary for the patient information leaflet and labelling to comply with the MA.

This date is fixed in consultation with the MA holder and is the subject of a notification by Afssaps to the MA holder and transmitted to the ministers in charge respectively for health and social security.

In any way, this does not take into account of the time necessary for the publication of the decree of approval for hospital use issued on the basis of the MA or the registering of the medicinal product on the list of reimbursable medicinal products.

This time should be the shortest possible and should not exceed three months. Thus, it is appropriate that the ATU holder contacts the ATU Unit and the Regulatory Affairs unit at Afssaps as early as possible, i.e. as soon as a favourable opinion for MA has been confirmed by the committee of the medicinal products for human use (CHMP) or by the French MA committee, without waiting for the MA notification.

During this period :

- the indications of cohort ATU remain applicable. For nominative ATU, the ATU granted before the date on which the granting of ATU ceases, are valid until their term,
- cohort ATU as well as approval for hospital use granted on the basis of cohort ATU remain in force,
- ongoing nominative ATU remain valid as well as the approval for hospital use. Afssaps can continue granting nominative ATU for new patients.

XII. ADVERTISING

A medicinal product subjected to ATU cannot be the subject of publicity, in accordance with article L.5122-3 of the French public health code. Nevertheless, taking into account the specificity of ATU medicinal products, information for users drafted in connection with Afssaps may be necessary. In this case, this is first addressed to Afssaps (ATU Unit) for second reading before circulation.

XIII. INFORMATION AVAILABLE ON AFSSAPS' INTERNET SITE

In addition to the present notice to applicants and the special regulations for ATU, the following information is also available on the Internet site of Afssaps (www.afssaps.sante.fr, heading ATU) :

- list of medicinal products which are currently the subject of a cohort ATU with summaries of product characteristics (SPC) and patient information leaflets,
- list of the medicinal products having been the subject of a cohort ATU since 1994,
- monthly and annual lists of the medicinal products having been the subject of nominative ATU,
- list of the hospital preparations which can be replaced by medicinal products available in the context of a MA or ATU,
- Cerfa application form for nominative ATU of a medicinal product,
- Cerfa declaration form for an adverse reaction likely to be due to a medicinal product or product mentioned in article R.5121-150,
- application form for cohort ATU,
- application form for renewal of cohort ATU.

XIV. FINANCING OF ATU MEDICINAL PRODUCTS

Article L.162-16-5-1 of the French code of social security specifies that :

- The exploitant of ATU medicinal product declares to the economic committee of health products (CEPS, French ministry of Health) the amount of the maximum allowance which he claims for the ATU medicinal product from hospitals. In the absence of exploitant, any hospital pharmacy interested in the purchase of this medicinal product declares to the CEPS the amount of the allowance which is claimed from him to acquire the product, if this allowance has not already been the subject of a declaration to the committee. The committee makes these declarations public.
- The exploitant of the ATU medicinal product or hospital pharmacies which have obtained this product, inform the CEPS annually of the turnover corresponding to these medicinal products as well as the number of units provided or received.
- There are provisions covering the case where the price fixed for the MA is different from the ATU's one.

ANNEXS

ANNEX A

Nominative ATU Cerfa application form

<http://www.sante.gouv.fr/cerfa/autotemp/atu.pdf>

ANNEX B

Cerfa form for the notification of an adverse reaction likely to be due to a medicinal product or a product mentioned in Article R.5121-150

<http://www.sante.gouv.fr/cerfa/efindes/abvitot.pdf>

ANNEX C
“Roles of the various parties”

	Nominative ATU	cohort ATU
Prescribing physician	<p>He is responsible for the nominative ATU application. He provides Afssaps with a detailed, ATU application, preferably using the Cerfa form.</p> <p>He transmits the application to the hospital pharmacist who then sends it to Afssaps. The medicinal product may be used only after being granted the ATU by Afssaps. He informs the patient and, if possible, the patient's attending physician of the status of the medicinal product and gives them any available information about this medicinal product. He notifies serious or unexpected adverse reactions to the regional pharmacovigilance centre which he is geographically linked with.</p> <p>He must keep Afssaps informed about the efficacy and safety of the medicinal product at the end of treatment if he applies for ATU renewal.</p> <p>If applicable, he acts in compliance with the protocol for therapeutic use and information collection : prescription criteria, patient information and monitoring conditions ; information collection and pharmacovigilance requirements.</p>	<p>He acts in compliance with the protocol for therapeutic use and information collection : prescription criteria, patient information and monitoring conditions; information collection and pharmacovigilance requirements.</p>
Hospital pharmacist	<p>He co-signs the nominative ATU application and sends it to Afssaps.</p> <p>He receives the ATU and informs the prescribing physician.</p> <p>He orders, imports if applicable, receives and supplies the medicinal product after the ATU is granted.</p> <p>He manages stocks.</p> <p>He notifies serious or unexpected adverse reactions to the regional pharmacovigilance centre which he is geographically linked with.</p>	<p>He reads and complies with the protocol for therapeutic use and information collection and pharmacovigilance requirements.</p> <p>He ensures that he has all the information relative to the treatment of patients in his hospital.</p> <p>He orders, receives and supplies the medicinal product and manages stocks.</p>
Exploitant of ATU medicinal product	<p>In accordance with the ATU granted by Afssaps, it delivers the ATU medicinal product to the hospital pharmacy department or authorised structure.</p> <p>He transmits an updated periodic pharmacovigilance report to Afssaps. When a protocol for use and information collection is set up, he transmits the periodic ATU reports to Afssaps and the CRPV in charge (if applicable).</p> <p>He submits any information relative to the ATU medicinal product to Afssaps for validation prior to circulation.</p> <p>He declares the cost of the ATU medicinal product to the CEPS.</p>	<p>He transmits the protocol for therapeutic use and information collection.</p> <p>He supplies the medicinal product to the hospital pharmacy department or authorised structure.</p> <p>He checks the compliance of users with the protocol.</p> <p>He gathers and analyses the information transmitted by prescribing physicians, especially adverse reactions.</p> <p>He complies with the pharmacovigilance reporting conditions.</p> <p>He sends periodic ATU reports to Afssaps and the CRPV in charge of national monitoring, if applicable.</p> <p>He transmits summaries of periodic ATU reports to the prescribing physicians ATU and hospital pharmacists concerned, as well as CRPVs and Poison Control centres once they have been validated by Afssaps.</p> <p>He must submit any information relative to the ATU medicinal product to Afssaps for validation prior to circulation.</p> <p>He declares the cost of the ATU medicinal product to the CEPS.</p>

ANNEX D

Application form for cohort ATU

MEDICINAL PRODUCT

• **Name of medicinal product :**

- **Dosage:**

- **Pharmaceutical form (°):**

- **Active substance(s):**

• **Indication claimed:**

- **ATC Code (Anatomical Therapeutic Chemical Classification System)**

APPLICANT

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

- **Contact person :**
(name, address, telephone N°, fax, email address)

Signature

At

Date

1. The medicinal product within the scope of the centralised authorisation procedure for MA established by Regulation (EC) n° 726/2004 of 31 March 2004 :

1.1 Is a product derived from biotechnological processes mentioned in annex 1 of Regulation (EC) n° 726/2004 :

yes no

1.2 Contains a new active substance indicated for the treatment of:

- AIDS yes no
- Cancer yes no
- Neurodegenerative disease yes no
- Diabetes yes no

1.3 Is designated as an "orphan medicinal product" in accordance with Parliament and Council Regulation (EC) n° 141/2000 of 16 December 1999 :

yes Date of designation:

Indication :

no, an application for "orphan medicinal product" designation is being considered :

yes no

1.4 Contains a new active substance which had not been authorised in the European community on 20th November, 2005 (optional centralised procedure)

yes no

1.5 Constitutes a significant innovation on the therapeutic, scientific or technical level, or the granting of an MA according to centralised procedure presents a benefit for patients within the EC? (optional centralised procedure)

yes no

Justification :

2. ATU delivery criteria

Pursuant to Article L.5121-12 a) of the French Public Health Code, temporary authorisations for use may be granted for the exceptional use of medicinal products intended for the treatment of serious or rare diseases when there is no appropriate treatment available, the efficacy and safety of these medicinal products are strongly presumed following clinical trials undertaken with a view to apply for MA and that this application has been submitted or a the applicant undertakes to submit it in a limited period .

2.1 This medicinal product is intended for :

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

2.2 There is no existing appropriate treatment: yes no

Justification :

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

Justification:

3. Administrative information

The medicinal product is the subject of an going marketing authorisation (MA) application :

- yes
Date of submission to Afssaps^b or the European Medicines Agency^b :
Name of the medicinal product :
- no
The holder undertakes to submit a MA application dossier^c: yes no

If the holder undertakes to submit a MA application dossier :

I, the undersigned....., responsible pharmacist for (*name of company*) undertake to submit a MA application dossier for (*name of medicinal product*), on (*date envisaged for submission*), to Afssaps^b or the European Medicines Agency^b

Signature :

3.2 The medicinal product is the subject of clinical trials in France or abroad :

- yes
(supply list of clinical trials)
 no

3.3 The medicinal product is already authorised abroad (MA) :

- yes
Please specify the countries and corresponding medicinal products as well as the date of authorisation:

Country	Name of medicinal product	Date of MA

Scheduled date of submission of the next Periodic Summary Update Report (PSUR) or equivalent document :

- no

^b Fill in the appropriate box

^c article L. 5121-12 a) of the French public health code stipulates that a cohort ATU can only be granted if an application for MA has been submitted or if the applicant commits to submitting one within a given time. Without this commitment, the application for cohort ATU is not admissible.

3.4 Existence of an early, exceptional use abroad (pre-MA):

yes

Country :

Indication :

Status of use :

no

3.5 What is the position of the ATU medicinal product in comparison with the therapeutic choice available on the French market?

3.6 Estimated number of patients to be treated in France in the context of the ATU :

4. List of documents / information to be enclosed	Yes	No
4.1 A copy of the marketing authorisation application, if applicable,	<input type="radio"/>	<input type="radio"/>
4.2 If the medicinal product is authorised abroad :	<input type="radio"/>	<input type="radio"/>
4.2.1 a copy of the authorisation(s) issued by the competent authority,	<input type="radio"/>	<input type="radio"/>
4.2.2a copy of the corresponding summary of product characteristics,	<input type="radio"/>	<input type="radio"/>
4.2.3 the latest PSUR or equivalent document,	<input type="radio"/>	<input type="radio"/>
4.3 Draft protocol for therapeutic use and information collection in French language,	<input type="radio"/>	<input type="radio"/>
4.4 Draft in French language of :	<input type="radio"/>	<input type="radio"/>
4.4.1 summary of product characteristics,	<input type="radio"/>	<input type="radio"/>
4.4.2 patient information leaflet,	<input type="radio"/>	<input type="radio"/>
4.4.3 labelling.	<input type="radio"/>	<input type="radio"/>
4.5 Clinical trials :	<input type="radio"/>	<input type="radio"/>
4.5.1. Titles and objectives of clinical trials in progress and/or planned in France or abroad for the same disease,	<input type="radio"/>	<input type="radio"/>
4.5.2. For clinical trials performed in France, the identity of the investigator(s), the designation of the study centre(s) concerned and the progress reports of these trials	<input type="radio"/>	<input type="radio"/>
4.6 "Orphan medicinal product" designation, if applicable,	<input type="radio"/>	<input type="radio"/>
4.7 A copy of any scientific advice concerning the medicinal product, addressed to the applicant by Afssaps, the European Medicines Agency or any competent authority of another Member State of the agreement within the EEC, if applicable	<input type="radio"/>	<input type="radio"/>
4.8 Any information relative to an exceptional and early use (pre-MA) in another country	<input type="radio"/>	<input type="radio"/>
4.9 Dossier relative to medicinal product :	<input type="radio"/>	<input type="radio"/>
(a) MA file	<input type="radio"/>	<input type="radio"/>
or	<input type="radio"/>	<input type="radio"/>
(b) updated investigational medicinal product dossier (IMPD).	<input type="radio"/>	<input type="radio"/>
In 5 copies on paper format	<input type="radio"/>	<input type="radio"/>
and in electronic form	<input type="radio"/>	<input type="radio"/>

INITIAL REQUEST FOR COHORT ATU NOTICE OF ADMISSIBILITY

I. SECTION TO BE FILLED IN BY THE APPLICANT

MEDICINAL PRODUCT	
• Name of medicinal product :	<input style="width: 100%;" type="text"/>
- Dosage:	<input style="width: 100%;" type="text"/>
- Pharmaceutical form (a):	<input style="width: 100%;" type="text"/>
- Active substance(s):	<input style="width: 100%;" type="text"/>
• Applicant :	
Company distributing the medicinal product	
("exploitant") :	
(Name, address, telephone N°, fax, email)	
<input style="width: 100%;" type="text"/>	
Contact person :	
(Name, address, telephone N°, fax, email adress)	
<input style="width: 100%;" type="text"/>	

II. SECTION TO BE FILLED IN BY AFSSAPS

Date of reception of application	<input style="width: 100%;" type="text"/>
Date of reception of requested complementary elements	<input style="width: 100%;" type="text"/>

Person in charge of the dossier at Afssaps

Name :	<input style="width: 100%;" type="text"/>	Agence française de sécurité sanitaire des produits de santé Direction de l'évaluation des médicaments et des produits biologiques Département de l'Evaluation des médicaments à Statut Particulier et des Essais Cliniques Unité ATU 143 / 147, Boulevard Anatole France 93285 Saint-Denis Cedex France
Email address :	<input style="width: 100%;" type="text"/>	
Telephone number :	<input style="width: 100%;" type="text"/>	
Fax:	<input style="width: 100%;" type="text"/>	

Admissibility

<input type="checkbox"/> ADMISSIBLE
<input type="checkbox"/> NOT ADMISSIBLE

Elements to be taken into account by the applicant

<input type="checkbox"/> MISSING ITEMS ^[1]	<input style="width: 100%;" type="text"/>
<input type="checkbox"/> AFSSAPS' COMMENTS ^[1]	<input style="width: 100%;" type="text"/>

Number allotted to the file:	
On this day:	Signature:
<input style="width: 100%;" type="text"/>	<input style="width: 100%;" type="text"/>

[1] Cf. following page (s)

III. MISSING ITEMS

<input type="checkbox"/>	1. Application form for cohort ATU
<input type="checkbox"/>	2. Copy of application for MA
	3. If the medicinal product is authorised abroad:
<input type="checkbox"/>	3.1. a copy of the authorisation or authorisations delivered by the competent authority
<input type="checkbox"/>	3.2. a copy of the corresponding summary of product characteristics
<input type="checkbox"/>	3.3. latest PSUR or equivalent document
<input type="checkbox"/>	4. The draft protocol for therapeutic use and information collection in French language
	5. Drafts, for the ATU, in French language, of :
<input type="checkbox"/>	5.1. summary of product characteristics
<input type="checkbox"/>	5.2. patient information leaflet
<input type="checkbox"/>	5.3. labelling
	6. Clinical trials
<input type="checkbox"/>	6.1. Titles and objectives of the trials in progress and/or planned in France or abroad for the same disease
<input type="checkbox"/>	6.2. Concerning the trial performed in France: identity of the principal investigator(s) in France, designation of the research centre(s) concerned and clinical trial progress reports
<input type="checkbox"/>	7. A copy of the "orphan medicinal product" designation
<input type="checkbox"/>	8. A copy of any scientific advice relating to the medicinal product addressed by Afssaps, the EMEA or any competent authority of another State which is part of the Agreement within the European economic Area
<input type="checkbox"/>	9. Any information relating to use in exceptional and early (pre-MA) circumstances in another country
<input type="checkbox"/>	10. The file relating to the medicinal product
<input type="checkbox"/>	10.1. MA file
<input type="checkbox"/>	or 10.2. Updated investigational medicinal product dossier (IMPD)
<input type="checkbox"/>	10.3. Number of additional paper copies to be submitted:
<input type="checkbox"/>	10.4. Number of additional CD ROM copies to be submitted:
<input type="checkbox"/>	11. Other items (see below)

XV. AFSSAPS' COMMENTS

--	--

ANNEX E

Template – Protocol for therapeutic use and information collection

Name, dosage, pharmaceutical form (International Non-proprietary Name)

COHORT TEMPORARY AUTHORISATION FOR USE

March 2008

<p>Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) Direction de l'Évaluation des Médicaments et des Produits Biologiques Département de l'Évaluation des Médicaments à Statut Particulier et des Essais Cliniques</p> <p>Unité ATU 143-147 Bd Anatole France 93285 Saint Denis Cedex</p> <p>tel : 33 (0)1 55 87 36 11 fax: 33 (0)1 55 87 36 12 mail : atu@afssaps.sante.fr</p>	<p>Contact details of exploitant</p>
--	---

1. INTRODUCTION

1.1 The medicinal product

Following the opinion of the Marketing Authorisation Committee, the French Health Product Safety Agency (Afssaps) grants on xx/xx/xxxx a so-called "cohort" Temporary Authorisation for Use (ATU) [Article L.5121-12 a) of the French Public Health Code] to *the company distributing the medicinal product (so called "exploitant")* for *medicinal product (name, INN, dosage, pharmaceutical form)*. A marketing authorisation (MA) application has been submitted on / will be submitted to..... on

1.1.1 General principles

This is an exceptional authorisation procedure.

The so-called "cohort" ATU is aimed at making a medicinal product available for a patient before it is actually granted MA, 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 are strongly presumed considering the results of clinical trials performed within the MA application. This application has been submitted or the applicant undertakes to submit it within a determined period of time.

Unlike a clinical trial, the ATU is not aimed at determining the efficacy profile of the medicinal product.

The ATU may be modified, suspended or withdrawn for public health reasons or if the above mentioned conditions are no longer met.

1.1.2 Protocol for therapeutic use and information collection

Since *medicinal product* does not have a MA in France, its use is subjected to a strict monitoring procedure by Afssaps, especially in terms of pharmacovigilance. This is the reason why the ATU of *medicinal product* is associated with a protocol for therapeutic use and information collection, established by Afssaps in collaboration with the ATU holder.

This protocol includes any relevant information about the use of *medicinal product* in order to ensure its appropriate use: it describes the criteria for use and supplying of the medicinal product as well as the patient monitoring conditions.

In addition, it allows for the collection, by *exploitant*, of information provided by physicians and pharmacists concerning the actual conditions for use of the medicinal product, this information being regularly transmitted to Afssaps.

Indeed, each, *exploitant* has to provide Afssaps with a periodic ATU report including all the data collected in the context of the ATU, especially :

- a description of the actual conditions for use of the ATU medicinal product (geographical distribution of applications, characteristics of the treated patients, posologies, associations with other medicinal products, etc.)
- a pharmacovigilance section including a summary of all undesirable effects as well as any information useful for assessing safety data related to the medicinal product, collected and accumulated during the ATU period.

A summary of this report, once validated by Afssaps, is sent by *exploitant* to every physician every... and hospital pharmacists supplying the medicinal product and to regional pharmacovigilance centres (CRPV) and Poison Control centres.

Therefore, the present protocol for therapeutic use and information collection includes:

- a description of the conditions relative to patient information about the medicinal product and the ATU (cf. chapter 2) ;
- the ATU summary of product characteristics (SPC) (cf. chapter 3) determining the criteria for use of the medicinal product (cf. chapter 3) ;
- a description of the practical conditions for use of the medicinal product, prescribing and supplying conditions and patient monitoring (cf. chapter 4) ;
- a description of the conditions relative to information collection (cf. chapters 4 and 5) ;
- a description of the conditions/requirements relative to pharmacovigilance (cf. chapter 5) ;
- a description of the conditions relative to the production and circulation of periodic ATU reports ;
- a description of the conditions of diffusion of the summary of these reports.

A copy of this protocol is transmitted to each of the prescribing physicians who ask for it, to the hospital pharmacists supplying the medicinal product as well as to the regional pharmacovigilance centres (CRPV) and to the Poison Control centres.

2. REGULATORY ASPECTS

2.1 Patient information

Prior to treatment initiation with *medicinal product*, each patient or his legal representative or the trusted person, must be informed by the prescribing physician about the medicinal product and the exceptional dispensation procedure. A patient information note (Appendix B) will be given to him by the prescribing physician along with any necessary explanation for it to be clearly understood.

The patient (or his legal representative) will have to read this patient information note and show it to any physician he will consult. In addition, each medicinal product packaging includes a patient information leaflet.

2.2 Information to prescribing physicians and hospital pharmacists

Copies of the protocol for therapeutic use and information collection are sent by *exploitant* to the physicians prescribing the medicinal product and hospital pharmacists concerned.

2.3 Information to Regional Pharmacovigilance Centres (CRPV) and Poison Control centres

Prior to treatment initiation in the context of the ATU, copies of the protocol for therapeutic use and information collection are sent by *exploitant* to every CRPV and Poison Control centres.

3. SUMMARY OF PRODUCT CHARACTERISTICS

The summary of product characteristics (SPC) for *medicinal product* in the context of the cohort ATU is joint on Appendix A. It lays down the conditions for use of the medicinal product.

The SPC and patient information leaflet are also available on Afssaps' website: www.afssaps.sante.fr.

4. PRACTICAL CONDITIONS FOR USE, PRESCRIBING AND SUPPLYING OF THE MEDICINAL PRODUCT AND PATIENT FOLLOW-UP

The ATU implies strict compliance with the information defined in the summary of product characteristics, especially indications and contra-indications, as well as the information and prospective follow-up of treated patients.

4.1 Indication / contra-indications / prescribing and supplying conditions

Indication : (please specify)

Contra-indications, special warnings and special precautions for use are detailed in the SPC (Appendix A).

Medicinal product is classified in the category of medicinal products subject to *hospital prescription /for hospital use*. Therefore, only prescribing physicians and pharmacists working in public or private hospitals may respectively prescribe and supply it.

4.2 Role of the prescribing physician

4.2.1 Formalities prior to treatment

Any prescribing physician working in a public or private hospital wishing to prescribe *medicinal product* in the context of this ATU must apply for a Protocol for Therapeutic Use and information collection in writing, using the corresponding application form (cf. Appendix C), and send it to :

contact details of exploitant

Telephone number :

Fax :

Email address :

In return, *exploitant* sends the Protocol for Therapeutic Use and information collection to the prescribing physician and hospital pharmacist, including especially :

- o A patient information note to be given to the patient at the start of treatment (Appendix B) ;
- o Medical follow-up forms (Appendix D) ;
 - Access treatment application form
 - Treatment initiation form
 - Follow-up visit forms
 - Treatment discontinuation form
 - Adverse reactions notification form
 - Pregnancy notification form
- o Pre-printed, pre-stamped envelopes for any correspondence with *exploitant*, if necessary.

4.2.2 Application for accessibility to treatment by the medicinal product

When the prescribing physician wishes to initiate treatment with *medicinal product* in a named patient, he must:

- read the protocol for therapeutic use and information collection,
- check the indication in the cohort ATU,
- check there is no contra-indication,
- fill in the access treatment application form by *medicinal product* and transmit it to the hospital pharmacist concerned who then validates and sends it to *exploitant*.

After reading the application, *exploitant* sends, for each patient, to the prescribing physician and hospital pharmacist, either a favourable notice concerning accessibility to treatment with *medicinal product* bearing the initials of the patient as well as the ATU number allocated to him, or if appropriate a rejection notice duly justified to not include the patient in the cohort ATU (no respect of ATU criteria).

4.2.3. Scheduled visits

Patient follow-up visits are scheduled as follows:

Visits	D0 (initiation) visit	Follow-up visit	Follow-up visit	Follow-up visit	Follow-up visit

4.2.4 D0 visit : treatment initiation

During this visit, the prescribing physician :

- o checks the absence of contra-indications to treatment with *medicinal product* that could have appeared since the inclusion application,
- o gives the patient information note to the patient prior to any prescription of *medicinal product* (Appendix B). In addition, a patient information leaflet is also provided in each box of medicinal product,
- o gives the patient information about treatment with *medicinal product*, its expected adverse reactions and the necessity to comply with the recommended posology, and ensures the patient clearly understands this information,
- o if possible, informs the patient's attending physician about treatment with *medicinal product*,
- o writes a prescription for *medicinal product*,
- o fills in the treatment initiation form (Appendix D) and transmits it to the hospital pharmacist who then sends it to *exploitant*.

4.2.5 Treatment follow-up visits

During each one of the follow-up visits, the prescribing physician :

- o checks the absence of contra-indications to treatment continuation with *medicinal product* that could have appeared or adverse reactions,
- o writes a prescription of *medicinal product*,
- o fills in the corresponding follow-up visit form (Appendix D),
- o fills in the adverse reactions notification form (Appendix D), if appropriate,
- o fills in the pregnancy notification form (Appendix D), if appropriate,
- o fills in the treatment discontinuation form (Appendix D), if appropriate.

Copy of each form is systematically sent to the hospital pharmacist for transmission without delay to *exploitant*.

4.2.6 Treatment discontinuation visit

Any discontinuation of treatment with *medicinal product* is notified using the treatment discontinuation form (Appendix D). The reason for discontinuing treatment is mentioned; if discontinuation is related to the occurrence of an adverse reaction or pregnancy, the corresponding form must be filled in. These forms are transmitted to the hospital pharmacist who then sends them without delay to *exploitant*.

4.3 Role of the hospital pharmacist

In each public or private hospital where a prescribing physician applies for a protocol for therapeutic use and information collection of *medicinal product* in the context of a cohort ATU (cf. 4.2.1), the hospital pharmacist receives the following:

- o the present Protocol for Therapeutic Use and Information Collection,
- o order forms of *medicinal product* to be sent to *exploitant* (Appendix E),
- o pre-printed, pre-stamped envelopes for any correspondence with *exploitant*, if necessary,
- o an adverse reactions notification form, if applicable, to notify to *exploitant*, any adverse reaction reported by a patient when supplying the medicinal product.

The pharmacist systematically sends the treatment initiation form, as well as the follow-up forms completed by the prescribing physician at each patient visit, to *exploitant* at the following address :

contact details of exploitant

Telephone number :

Fax :

Email address :

After receiving a favourable notification from *exploitant* to initiate the treatment, bearing the initials of the patient as well as the ATU number allocated to him/her, the pharmacist may supply the *medicinal product* upon prescription.

The pharmacist supplies *medicinal product* **monthly** upon prescription by the prescribing physician.

Order forms for the *medicinal product* and stock management are the responsibility of the hospital pharmacist.

4.4 Role of the exploitant

Exploitant sends a Protocol for Therapeutic Use and Information Collection to every prescribing physician who asks for it and the hospital pharmacists concerned, as well as to every CRPV centre and Poison Control centres.

It receives all access treatment application forms for *medicinal product* in the context of the cohort ATU.

It ensures that all patients meet the cohort ATU criteria (especially regarding indications and contra-indications).

It sends, by fax, to the prescribing physician and hospital pharmacist, the signed favourable treatment accessibility notice bearing patient identification using the first three letters and first two letters of the patient's surname and the first name respectively, the patient's date of birth and the ATU number allocated to him/her. In case of rejection, a duly justified rejection notice is sent to the prescribing physician and hospital pharmacist. A nominative ATU application may then be submitted to Afssaps for this patient (cf. chapter 6).

It delivers the orders for *medicinal product* transmitted by the hospital pharmacist for patients included in cohort ATU upon reception of order forms.

It gathers all the information collected in the context of the protocol for therapeutic use and information collection, especially the information relative to pharmacovigilance, and acts in compliance with the pharmacovigilance requirements (cf. paragraph 5). It cooperates with the regional pharmacovigilance centre in charge of the national monitoring, if applicable.

It analyses the collected information and transmits a periodic ATU report to Afssaps every... months to Afssaps.

It sends a summary of this report to prescribing physicians and hospital pharmacists concerned, as well as all CRPV and Poison Control centres for information, once it has been validated by Afssaps.

5. PHARMACOVIGILANCE

5.1 Role of healthcare professionals

Who should report ?

Any physician, pharmacist, dentist or midwife observing a serious or unexpected adverse reaction that could be due to the medicinal product with an ATU, whether they prescribed it or not, and any pharmacist knowing of any serious or unexpected adverse reaction which could be due to the medicinal product with an ATU which he delivered, should report it immediately. Any healthcare professional making the same observation may also report.

What should be reported ?

Serious adverse reactions (expected or unexpected)
Unexpected adverse reactions (serious or not)

In addition, it is strongly recommended to report :

- any case of overdose ;
- any case of exposure during pregnancy or lactation ;
- any other effect or situation with a potential or known harmful consequence for health ;
- any observed efficacy loss (especially with vaccines, contraceptives or medicinal products intended for treatment of life threatening disease),
- any reaction judged as relevant for reporting.

Targeted monitoring of some adverse reactions may also be set up for some medicinal products.

Pursuant to Article R.5121-153 of the French Public Health Code, the various definitions are as follows :

ADVERSE REACTION :

A response to a medicinal product or product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

SERIOUS ADVERSE REACTION :

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

UNEXPECTED ADVERSE REACTION¹:

An adverse reaction, the nature, severity or outcome of which is not consistent with the Summary of Product Characteristics (SPC)

MISUSE :

Use which is not compliant with the recommendations of the SPC

ABUSE :

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects

¹To determine the expected/unexpected nature of an adverse reaction, the following is used as a reference:

- For a medicinal product with a nominative ATU :
 - . the SPC approved abroad, if the medicinal product is authorised abroad,
 - . in the absence of an SPC approved abroad: the investigator's brochure or the therapeutic information notice, if applicable (cf. 6.7)
- For a medicinal product with a cohort ATU: the SPC approved in the context of the cohort ATU.

- How to report ?

Adverse events should be reported using the adverse reactions notification form provided in Appendix D, always indicating the ATU number allocated to the patient.

In case of treatment discontinuation, the treatment discontinuation form must be filled in.

In case of pregnancy, the pregnancy notification form must be filled in.

- To whom ?

Adverse events should be reported to the person in charge of pharmacovigilance.

contact details of *exploitant*
Pharmacovigilance department
Telephone number :
Fax :
Email address :

- When to report ?

Immediately in case of serious or unexpected adverse reactions.

At each visit scheduled in the Protocol for Therapeutic Use and information collection in the case of any other adverse event.

5.2 Role of exploitant

It gathers the pharmacovigilance information collected by the prescribing physician and acts in compliance with regulatory pharmacovigilance provisions :

5.2.1 Immediate notification of serious adverse reactions (unexpected and/or expected) to Afssaps which *exploitant* is informed about

Exploitant has to notify the following immediately (at the latest within 15 calendar days following reception) :

- all serious undesirable effects (expected and/or unexpected) occurring in France which it knows of (to Afssaps and a copy to the designated CRPV in charge of monitoring by Afssaps, if applicable),
- as well as any serious undesirable and unexpected effect occurring in any country outside the EU that it knows of.

In case of a serious adverse reaction (irrespective of the country and context of use) or new event that could have an impact on the risk/benefit ratio of the medicinal product and results in the necessity of rapidly transmitting information to users of the ATU medicinal product (prescribing physicians, pharmacists and patients), *exploitant* informs Afssaps about it without delay and transmits any useful document to the relevant units of the agency (ATU unit, pharmacovigilance unit and clinical trials division, if appropriate).

5.2.2. Transmission of periodic ATU reports

Exploitant draws up a periodic ATU report including a description of the conditions for use of the medicinal product and a section relative to pharmacovigilance which includes all adverse reactions and any information useful for the benefit/risk ratio assessment of the medicinal product, according to a periodicity of ... months.

Once it has been validated by Afssaps, *exploitant* sends a summary of this report everyto prescribing physicians and hospital pharmacists concerned, as well as all regional CRPV and the Poison Control centres.

5.3 Role of Afssaps

Afssaps examines the information transmitted by *exploitant* and the regional pharmacovigilance centre in charge of the national monitoring of *the medicinal product*, and takes any measures necessary to ensure the safety of patients and the proper use of *medicinal product*. Afssaps informs *exploitant* about any serious adverse reaction which was directly notified or declared to it within 15 days of the declaration.

In addition, Afssaps validates the periodic ATU report summary produced by *exploitant* prior to circulation.

5.4 Role of the CRPV appointed to be in charge of national monitoring

The CRPV of ... has been appointed to be in charge of the national monitoring of adverse reactions reported with *medicinal product*.

It receives serious adverse reactions and periodic ATU reports transmitted by *exploitant* and has a role of expert in the analysis of this information.

6. NOMINATIVE ATU

In the case of a patient who could not be treated in the context of the cohort ATU, the hospital prescribing physician, through the hospital pharmacist, may apply to Afssaps for a nominative ATU.

The hospital prescribing physician fills in Cerfa form no.10058 01 ("Application for a nominative Temporary Authorisation for Use for a medicinal product"), justifying the application by indicating the anamnesis and the various treatments already used.

This application is accompanied by the initial treatment access application form for *medicinal product* in the context of the cohort ATU and the corresponding rejection notice.

The pharmacist fills in the relevant section on the Cerfa form and sends it by fax to:

AFSSAPS
Autorisations Temporaires d'Utilisation
143-147 bd Anatole France
93285 Saint Denis Cedex
Telephone: 33(0) 1 55 87 36 11
Fax: 33(0) 1 55 87 36 12

7. APPENDICES

Appendix A : Summary of product characteristics (SPC)

Appendix B : Patient information note

Appendix C : Application form for a protocol for therapeutic use and information collection

Appendix D : Medical follow-up forms

- Treatment access application form
- Treatment initiation form
- Patient follow-up visit forms
- Treatment discontinuation form
- Adverse reactions notification form
- Pregnancy notification form

Appendix E : *Medicinal product* order form

Appendix F : Summary statement of the procedure to obtain the medicinal product and patient follow-up procedure

APPENDIX A

Summary of product characteristics (SPC)

APPENDIX B

Patient information note

Date

In the event that the patient is unable to read and clearly understand this information, it is given to members of his family, his legal representative or if applicable, the trusted person.

To be given to the patient prior to any prescription of *the medicinal product*

COHORT TEMPORARY AUTHORISATION FOR USE (ATU)

Medicinal product, dosage, pharmaceutical form

(INN)

The aim of this note is to inform you in order to help you decide, with full knowledge of the facts, whether you accept treatment by the *medicinal product* which has been proposed to you by your physician. In addition to this information note, **please read carefully the patient information leaflet in each** box of *medicinal product*, the text of which is reproduced below, and is also available on the French Health Products Safety Agency (Afssaps) website : www.afssaps.sante.fr.

Please indicate to your physician or pharmacist if you are taking or if you have recently taken another medicinal product, even if this medicinal product has been delivered without prescription.

Medicinal product is available in the context of a so-called "cohort" Temporary Authorisation for Use (ATU) granted by Afssaps on/.../..... which makes the medicinal product available in France prior to its marketing authorisation (MA). *Medicinal product* is already strongly presumed to be safe and effective in the disease you suffer from.

Since this medicinal product does not have a marketing authorisation in France, its use is subjected to a strict monitoring procedure by Afssaps, especially concerning the adverse reactions it may cause. Your physician may interrupt this treatment at any time for inefficacy or safety reasons.

Confidentiality

Your physician will have to complete documents which will be used to collect information, especially relative to the safety of the *medicinal product* during your treatment. This confidential information will be transmitted to *exploitant* and might be subject to computerized processing. In any correspondence concerning you, you will be identified using the first three letters of your surname and the first two letters of your first name as well as your date of birth. Information will be regularly transmitted to Afssaps, in charge of monitoring the use of the medicinal product at national level with the assistance of the Regional Pharmacovigilance Centre (CRPV) of, if appropriate.

Pursuant to Law N°78-17 of 6th January, 1978, amended, the so-called data protection law, you may have access to the computerised information concerning you and exercise your right to correct this information, through your physician, at any time.

Of course, your decision to accept treatment with *medicinal product* is entirely free and you may refuse treatment if you wish.

[Text of the patient information leaflet]

APPENDIX C

Application form for a protocol for therapeutic use and information collection

APPENDIX D
MEDICAL FOLLOW-UP FORMS

Treatment access application form
Treatment initiation form
Patient follow-up visit forms
Treatment discontinuation form
Adverse reactions and pregnancy notification form

APPENDIX E
MEDICINAL PRODUCT ORDER FORM

APPENDIX F

**SUMMARY STATEMENT OF DISTRIBUTION CIRCUIT AND AVAILABILITY OF THE MEDICINAL
PRODUCT AND PATIENT FOLLOW-UP PROCEDURE**

ANNEX F

Template for drafting of Periodic ATU Report

INTRODUCTION

Name of the medicinal product / INN

Name and contact details of the exploitant

Therapeutic indications in the context of the ATU

Period covered by the report / Date of the report / Period to be covered by the next report

Status of the product in other countries (marketing authorisation application, marketing authorisation, "orphan medicinal product" designation, etc.)

1. Data collected during the period considered in the context of a ATU subject to a protocol for use and information collection

ALL THE DATA AVAILABLE MUST BE PRESENTED FOR THE PERIOD CONSIDERED AND AFTER IN THE FORM OF CUMULATIVE DATA.

Description and analysis of all the data collected in the context of the protocol for therapeutic use and information collection, especially the characteristics of the patients treated (population, criteria for use, associations with other medicinal products, etc.) and the number of patients treated in the context of the ATU.

Pharmacovigilance data

ALL THE DATA AVAILABLE MUST BE PRESENTED FOR THE PERIOD CONSIDERED AND AFTER IN THE FORM OF CUMULATIVE DATA.

2.1 Global analysis of the pharmacovigilance data in the context of the ATU in France / Presentation of individual cases

2.1.1 Figures, tables and lists :

Total number of cases

Total number of serious cases and number of fatal cases

Table indicating the number of adverse reactions by organ system

Separate detailed lists of expected adverse reactions and unexpected reactions

The above mentioned information may be presented in the format shown below (cf. addendum next page).

2.1.2 Data analysis :

Global analysis of all the adverse reactions (irrespective of seriousness) observed for each organ system, indicating the time to occurrence, time to regression and evolution ;

Analysis of treatment discontinuation cases related to the occurrence of adverse reactions, including a table presenting the information by organ system ;

Analysis of the fatal cases ;

Analysis of the use of the medicinal product during pregnancy ;

Summary of cases with imputability for each medicinal product according to the formal imputability method or copies of the CIOMS forms.

2.1.3 Overall assessment :

The conclusion should be such as it allows a comparative assessment with the previous period and highlights any new information concerning unexpected adverse reactions or a change in the characteristics of expected adverse reactions.

2.2 Global analysis of the international pharmacovigilance data if the product is available in other countries

Estimated number of patients treated,

Publications collection relative to pharmacovigilance of the medicinal product for the period considered,

Summary of the measures taken for safety reasons by national authorities or by the exploitant (modification of the investigator's brochure or the SPC in another country, information letter to prescribing physicians, press release abroad, etc.)

Nature of the modifications made to the reference medical information concerning the medicinal product safety.

In addition, when the medicinal product with a ATU is authorised abroad within MA, any available PSURs produced for these countries are transmitted to Afssaps in the period of availability of the medicinal product in the context of the ATU in France. If necessary a detailed list of cases can be presented following the model proposed in the addendum below.

3. Clinical trials

All scheduled, ongoing and completed clinical trials, as well as published clinical trials which give additional information concerning the efficacy and safety of the medicinal product, must be mentioned and discussed.

4. Additional information

In particular, any new significant information relative to the medicinal product's efficacy reported to the exploitant during the period covered by this report or after the validity period for information collection for the present report

Any pharmacovigilance data received after the closure date for collection of information for the present report.

5. Conclusion concerning the risk/benefit ratio for the medicinal product in the context of the ATU and conditions for use

ANNEXs to be included in the periodic ATU report

ANNEX 1 : Summary of Product Characteristics (or Reference Document)

ANNEX 2 : CIOMS forms

ANNEX 3 : International PSUR (Periodic Safety Update Report) or detailed list of cases occurring outside France

ADDENDUM of ANNEX F
Template for the presentation of figures and lists (cf. 2.1.1 of periodic ATU report)

Total number of cases	Total number of serious cases
number over the period/total number since beginning of ATU	number over the period/total number since beginning of ATU

Total number of fatal cases
Number over the period/total number since beginning of ATU

Table indicating the number of adverse reactions by organ system

Organ system	Total number of serious AE over the period/ total number since the beginning of ATU	Total number of AE over the period/total number of AE since the beginning of ATU
< name >	< number >	< number >
< name >	< number >	< number >
Total	< number >	< number >

DETAILED LISTS OF PHARMACOVIGILANCE CASES OCCURRING OVER THE PERIOD

In the detailed lists, cases are presented by organ system and must be listed once only, irrespective of the number of undesirable effects reported. All the undesirable effects relating to the same case must be notified; the case will then be listed in the organ system category corresponding to the undesirable effect which is considered as the most serious. A list is established for the French cases and the same template can be used to present cases outside France if necessary (cf. paragraph

2.2).DETAILED LIST OF CASES BY ORGAN SYSTEM

Number/Country if necessary	Origin	Age/Sex	Daily dose	Date of occurrence of the adverse reaction or time to occurrence	Treatment dates or treatment duration	Description of the adverse effect marked with a * if unexpected	Seriousness	Evolution	Comments

ANNEX G

Application form for renewal of cohort **ATU**

• Name of medicinal product :	<input type="text"/>
- Dosage :	<input type="text"/>
- Pharmaceutical ^(a) :	<input type="text"/>
- Active substance(s) :	<input type="text"/>
• Number of cohort ATU	<input type="text"/>
- Date of granting of cohort ATU	<input type="text"/>
• Applicant:	<input type="text"/>
- Company distributing the medicinal product ("exploitant") (name, address) :	<input type="text"/>
- Contact Person : (name, address, telephone number, fax, Email address)	<input type="text"/>
<hr/>	
Signature	
<hr/>	
At	Date

I. Administrative Information:

1.1 The medicinal product is already the subject of a marketing authorisation application (MAA) :

yes
Date of submission to Afssaps ^(b) or the European Medicines Agency ^(b) :

Name of the medicinal product:

no
The holder confirms his commitment to submit a MAA dossier :
 yes no

If the holder confirms his commitment to submit a MAA dossier :

I, the undersigned,, responsible pharmacist for (*name of company*) confirm my commitment to submit a MAA dossier for (*name of medicinal product*), on ... (*date envisaged for submission*), at Afssaps ^(b) or the European Medicines Agency ^(b)

Signature :

1.2 The medicinal product is the subject of clinical trial(s) in France or abroad :

yes
(supply list of clinical trials)

no

a : use standard European Pharmacopoeia terms

b : fill in the appropriate box

c : article L .5121-12 a of the French public health code specifies that a cohort ATU can only be granted if a request for MA has been submitted or if the applicant commits himself to submitting one within a predetermined time. Without this commitment, the application for cohort ATU cannot be accepted.

1.3 The medicinal product has been authorised abroad (MA) during the preceding period of ATU:

yes

(Indicate the countries and names of the corresponding medicinal products, as well as the date of granting of the authorisation)

Country	Name of the medicinal products	Date of MA

Date envisaged for publishing the next periodic summary update reports (PSUR) or equivalent document :

no

1.4 There has been an exceptional, early use abroad (pre-MA) :

yes

Country :

Indication :

Status of use :

no

1.5. Has the medicinal product, for the period of preceding ATU, been designated "orphan medicinal product" in accordance with European regulation (EC) N°141/2000?

yes

Date of designation :

Indication:.....

no

Is a request for designation considered?

yes

no

If yes, date:

II. COHORT ATU

2.1 Current indication for cohort ATU

2.2 Number of people treated by the medicinal product with ATU :

- since the granting of ATU :

- since the last renewal of ATU, if appropriate :

2.3 Quantities of medicinal product delivered during previous authorisation period:

III. REQUEST FOR RENEWAL

3.1 Justification for continuation of ATU :

3.2. Does the application for renewal concern the same conditions of use as those described in the decision for cohort ATU ?

yes

no

If not, describe the differences and the justifications for them^(d) :

^d any information justifying the desired modifications
Afssaps-april 2008 -ATU/notice to applicants

IV. List of documents/information to be enclosed	Yes	No
4.1 Copy of application for MA, if appropriate	<input type="radio"/>	<input type="radio"/>
4.2 If the medicinal product was authorised abroad for the previous period :	<input type="radio"/>	<input type="radio"/>
4.2.1 the copy of this authorisation delivered by the competent authority,	<input type="radio"/>	<input type="radio"/>
4.2.2 the copy of the corresponding summary of product characteristics,	<input type="radio"/>	<input type="radio"/>
4.2.3 last PSUR or equivalent document,		
4.3 Protocol for therapeutic use and information collection envisaged for the period to come, in French language and, if necessary, explaining the modifications requested and their justification in an enclosed letter.	<input type="radio"/>	<input type="radio"/>
4.4 In the event of desired modifications, projects in French language of :		
4.4.1 summary of product characteristics,	<input type="radio"/>	<input type="radio"/>
4.4.2 patient information leaflet,	<input type="radio"/>	<input type="radio"/>
4.4.3 labelling	<input type="radio"/>	<input type="radio"/>
4.4.4 and any information justifying the modifications requested for the ATU	<input type="radio"/>	<input type="radio"/>
4.5 Clinical trials :		
4.5.1. Titles and objectives of the clinical trials in progress and/or planned in France or abroad for the same disease,	<input type="radio"/>	<input type="radio"/>
4.5.2 Concerning the trials performed in France: identity of the principal investigator(s) in France, the designation of the research centre(s) concerned and the progress report of these trials.	<input type="radio"/>	<input type="radio"/>
4.6 The copy of the designation of "orphan medicinal product", obtained for the previous period, if applicable.	<input type="radio"/>	<input type="radio"/>
4.7 Copy of any scientific advice relating to the medicinal product, addressed to the applicant by Afssaps, the European Medicines Agency or any competent authority of another Member State of the Agreement within the EEC, if applicable,	<input type="radio"/>	<input type="radio"/>
4.8 All new information relative to use in early and exceptional circumstances in another country.	<input type="radio"/>	<input type="radio"/>
4.9 File including any new information on the medicinal product and the consequences on its use obtained during the period of preceding ATU.	<input type="radio"/>	<input type="radio"/>
4.10 Last periodic ATU update report established during the period of preceding ATU and a concise analysis of the whole of the periodic ATU reports.	<input type="radio"/>	<input type="radio"/>
4.11 A copy of the summaries of the periodic ATU reports transmitted by the ATU holder to the persons concerned, with the dates of transmission.	<input type="radio"/>	<input type="radio"/>

REQUEST FOR RENEWAL OF COHORT ATU NOTICE OF ADMISSIBILITY

I. SECTION TO BE FILLED IN BY THE APPLICANT

MEDICINAL PRODUCT

• **Name of medicinal product :**

- **Dosage:**

- **Pharmaceutical form ^(a):**

- **Active substance(s):**

• **Applicant :**

Company distributing the medicinal product

("exploitant"):

(Name, address, telephone N°, fax, email)

Contact person :

(Name, address, telephone N°, fax, email adress)

II. SECTION TO BE FILLED IN BY AFSSAPS

Date of reception of request

Date of reception of requested additional elements

Person in charge of file at Afssaps

Name:		Agence française de sécurité sanitaire des produits de santé Direction de l'évaluation des médicaments et des produits biologiques Département de l'Evaluation des médicaments à Statut Particulier et des Essais Cliniques Unité ATU 143 / 147, Boulevard Anatole France 93285 Saint-Denis Cedex France
Email address:		
Telephone number:		
Fax:		

Admissibility

<input type="checkbox"/>	ADMISSIBLE
<input type="checkbox"/>	NOT ADMISSIBLE

Elements to be taken into account by the applicant

<input type="checkbox"/>	MISSING PARTS ^[1]		
<input type="checkbox"/>	AFSSAPS' COMMENTS ^[1]		

Number allotted to the file :

Date:	Signature:
--------------	-------------------

[1] Cf. following page (s)

III. MISSING PARTS	
<input type="checkbox"/>	1. Request form for renewal of cohort ATU
<input type="checkbox"/>	2. Copy of request for MA
	3. If the medicinal product was authorised abroad during the previous period:
<input type="checkbox"/>	3.1. Copy of the authorisation delivered by the competent authority
<input type="checkbox"/>	3.2. Copy of the corresponding summary of product characteristics
<input type="checkbox"/>	3.3. Latest PSUR or equivalent document
<input type="checkbox"/>	4. Protocol for therapeutic use and information collection envisaged for the period to come, in French language and, if relevant, stating any requested modifications and their justification on enclosed document.
	5. In the event of desired modifications, declarations concerning these modifications in French language, of :
<input type="checkbox"/>	5.1. Summary of product characteristics
<input type="checkbox"/>	5.2. Patient Information leaflet
<input type="checkbox"/>	5.3. Labelling
	5.4. Any information justifying the modifications requested for the ATU
	6. Clinical trials
<input type="checkbox"/>	6.1. Titles and objectives of the clinical trials in progress and/or planned in France or abroad for the same disease
<input type="checkbox"/>	6.2. Concerning the trials performed in France : identity of the investigator(s) in France, the designation of the research centre(s) concerned and the progress reports of these trials
<input type="checkbox"/>	7. A copy of the "orphan medicinal product" designation obtained for the previous period
<input type="checkbox"/>	8. A copy of any scientific advice relating to the medicinal product, addressed to the applicant by Afssaps, the European Medicines Agency or any competent authority of another Member State of the Agreement within the EEC,
<input type="checkbox"/>	9. All new information relative to use in early and exceptional circumstances in another country
<input type="checkbox"/>	10. File including any new information on the medicinal product and the consequences on its use obtained during the period of preceding ATU
<input type="checkbox"/>	11. Last periodic ATU report established for the period of preceding ATU and a concise analysis of the whole of the periodic ATU reports.
<input type="checkbox"/>	12. A copy of the summaries of the periodic ATU reports transmitted by the ATU holder to the parties concerned, with the dates of transmission.
<input type="checkbox"/>	13. Other items :
IV. AFSSAPS' COMMENTS	

