Agence nationale de sécurité du médicament et des produits de santé

Saint-Denis, 19 September 2012

NATIONAL DRUG COMMISSION

Minutes of the meeting of Tuesday, June 26, 2012

Were present :

Members of the National Pharmacovigilance Commission:

Mr. Caron (Chair)
Mr. Vial (Vice-President)
Mr. MALLARET (President of the National Commission on Narcotic Drugs and Psychotropic) Ms. FALIP (representative of the Directorate General of ANSM) Ms. Baumelou-TORCK

BERNARD
Mr. CAMENEN
Mr. Carlier Ms.
DUGAST
Mr. ESCHALIER
Mr. Giroud Ms.
GUY
Mr. HAZEBROUCQ
Mr. Javaudin
Ms. PASTOR JOHN
WOOL-CESSAC Ms. Ms.
Ms. LaRoche LEMER

Ms. Lillo IT LOUET (alternate for Mrs JONVILLE-BERA)
Mr. MEILLIER (alternate to Ms PAULMIER-BIGOT)
Mr MERLE
Ms. PERAULT-POCHAT
Mr. SAILLER
Mr. Saviuc
Mr. TESTED
Ms. VEYRAC (Mrs. SGRO of alternate)

CRPV :
Ms. ZENUT

ISSUES CONSIDERED BY LABORATORIES

MSD France: National Monitoring of Arcoxia® (Etoricoxib): Total one year marketing

BIOCODEX: Presentation of data from the reassessment of the benefit / risk Stresam® (Etifoxine)

MANAGEMENT OF CONFLICTS OF INTEREST

No situation of major conflict of interest was retained or declared during the meeting of the National Pharmacovigilance Committee of 26 June 2012.

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I - INTRODUCTION AND ADOPTION OF THE REPORT OF THE CNPV 22/05/2012

The minutes of the CNPV of 22 May 2012 was adopted without amendment

II - FOLLOW NATIONAL ARCOXIA® (Etoricoxib): BALANCE SHEET TWO YEARS OF MARKETING

CRPV reporter: CRPV Clermont Ferrand

Trade name	ARCOXIA®
DCI	etoricoxib
ATC	M01AH05
Pharmaceutical form	film-coated tablets 30 mg and 60 mg
pharmacological class	Anti-inflammatory and antirheumatic, no steroids, coxibs
Registration Procedure	mutual recognition (RMS = UK)
Date of Marketing Authorization	26/08/2008
Marketing Authorization Holder	MSD France
Date of commercialization in France	12/03/2010
SMR / ASRM	Moderate / absence of therapeutic advance (V)

1 -Reminder

In the European Union, the first marketing authorization of Arcoxia® (etoricoxib) was granted February 3, 2002 in the UK. A mutual recognition procedure was started in March 2002 for the indications osteoarthritis (60 mg / d), rheumatoid arthritis (90 mg / day) and gout (120 mg / d).

In France, given the increased cardiovascular risk in particular myocardial infarction and stroke found in clinical trials of other coxibs, the granting of the marketing authorization has been delayed in order to provide additional data in particular MEDAL program studies. The objective of these studies was to specifically assess the safety of cardiovascular and digestive use of the product.

The marketing authorization of Arcoxia® were granted in France on 26 August 2008 for the forms 30 mg, 60 mg, 90 mg and 120 mg: - the

indication " *symptomatic treatment of osteoarthritis* " for shapes 30 and 60 mg
marketed since 12 March 2010

- in the *symptomatic treatment of rheumatoid arthritis* with an extension of indication in 2012 in t *reatment short term moderate pain associated with dental surgery* to form 90 mg. This form has not been commercialized and still has his MA. Indeed, the company submitted in 2011 a sunset exemption.

- in the treatment of acute gout attack for the form 120 mg. This marketing authorization has lapsed in France default marketing.

The transparency of the HAS commission had granted reimbursement forms to 30 mg and 60 mg (moderate SMR and ASMR no), refused the refund form to 120 mg and the laboratory was then withdrew its claim for the form 90 mg. At European level, a risk management plan was set up with a variation in France. The main objective is enhanced monitoring of the risks identified as thrombotic cardiovascular complications, digestive, cardio-renal, kidney, skin, risks related to exposure during pregnancy, and the risk exposure in children less than eighteen years, and patients with renal impairment in hepatic impairment ..

Afssaps, as part of a national RMP has set up a national monitoring pharmacovigilance, validated information materials to prescribers and patients and asked the lab to conduct a study of use. The main objective of the study is to describe in a real situation, the use of Arcoxia® with collection of data on dosage, duration of treatment, and the grounds of limitation. This study was the start agreement in March 2012 and the first patient was enrolled June 8, 2012, with a year late.

2 - Pharmacovigilance Analysis of comments

Methodology

The analysis focuses on the cases reported in France during the rst two years of marketing, for which etoricoxib is classified as suspicious. The cases considered are those from the National Pharmacovigilance Database (BNPV) until 30 March 2012 and those registered by the company until 31 March 2012. In addition, a review of the literature data and data PSURs was conducted, particularly for identified risks.

Results

In total, after removing duplicates, 207 comments were taken into account (56 cases from CRPV and 151 lab) with 311 adverse effects. These observations concern 72% of women and 28% men, mean age of 63 + 14 years old. Thirty percent of cases were classified as "serious". When evolution is known cases evolve mainly to a recovery without sequelae (87%). Indicate, when specified, is essentially osteoarthritis (53%) or joint pain without information on arthritic origin or not (19%). When the dosage is known, it is 30 mg / d in 51% of cases and 60 mg / d in 47%.

The most frequently reported adverse events belong to the Body-Class Systems (SOC) to:

- General disorders: 55 adverse events (17.7%) including 35 predominantly peripheral edema,
- Gastrointestinal: 48 adverse events (15.4%) 19 whose signs and symptoms,
- Cardiac disorders adverse events 42 (13.5%) including 17 coronary arterial disorders,
- Vascular disorders: 33 adverse events (10.6%) including 22 hypertensive disorders.

analysis:

The analysis was performed according to the risks identified then by SOC.

- Cardiovascular thrombotic events :

Arterial thrombotic risk: 9 arterial thrombotic side effects have been reported (5 myocardial infarction, acute coronary syndromes 2 and 2 ischemic stroke). Nationally, 7 of 9 patients had at least one cardiovascular risk factor.

venous thrombotic risk: 5 adverse venous thrombotic events were reported in 4 patients in the national monitoring (2 pulmonary embolism, deep vein thrombosis and 2 1 occlusion of retinal vein). Data from the MEDAL study 1 and the MEDAL Program 2 show a similar incidence of arterial thrombotic events, IDM, stroke, pulmonary embolism and vascular death between etoricoxib (60 and 90 mg) and 150 mg diclofenac. The meta-analysis of Trelle 3 (31 randomized trials, 117 218 patient-years) suggests that etoricoxib does not increase the risk of MI and stroke compared to placebo (indirect comparison). However, this study suggests an increased risk of cardiovascular death with etoricoxib with diclofenac as compared to placebo no significant increase in deaths from all causes. Regarding venous thrombotic risk, Literature data on some NSAIDs including etoricoxib evoke the existence of confounding factors and does not conclude on this risk.

- The renovascular events reported include: edema 35, 22 cases of hypertensive disorders including symptomatic 3, 7 heart failure, acute renal failure 5 and 3 cases of nephrotic syndrome for which the etiology is multifactorial. according MEDAL 1 etoricoxib is associated with an increase in blood pressure compared to diclofenac without increased incidence of thrombotic cardiovascular events. He was described of discontinuation due to hypertension with etoricoxib regardless of the dose compared to diclofenac 150 mg.

According to data from clinical studies, the risk of edema, congestive heart failure and renal dysfunction appear dose-dependent but etoricoxib 60 mg is not different from diclofenac 150 mg.

- The digestive complications 3 include gastrointestinal bleeding which 1 associated with peritonitis 1, 1 associated with haematemesis 1 gastroduodenitis, 1 oral hemorrhage associated with one bloody vomiting, melena 1, 2 uncomplicated duodenal ulcers; all these events is the expected profile with NSAIDs.

According to the MEDAL program, compared to diclofenac 150 mg ago, significantly less impact for uncomplicated upper GI events for etoricoxib and no difference for complicated upper GI events and digestive down events 2.

- Hypersensitivity reactions include 13 cases of drug eruption including 1 case Lyell syndrome with concomitant Voltaren ® and 1 case of angioedema.

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1 Combe B, Swergold G, J McLay, McCarthy T, C Zerbini, Emery P, et al. Cardiovascular safety and gastrointestinal tolerability of etoricoxib vs diclofenac in a randomized controlled clinical trial (The MEDAL study). Rheumatology 2009; 48: 425-432. 2 Cannon CP, Curtis SP, FitzGerald GA, Krum H Kaur A Bolognese JA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long- term (MEDAL) program: a randomized comparison. Lancet 2006; 368: 1771-1781.

3 Trelle S, Reichenbach S, Wandel S, B Tschannen, Villiger PM, Egger M, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011; 342: c7086 doi: 10.1136 / bmj.c7086.

Other side effects, liver damage were analyzed. In 4 cases, there is an acute cytolytic liver damage. Eleven cases of hepatic failure have been reported internationally. Although these cases are not very informative, there are treatments and associated pathologies, the term "liver failure" has been added in the SPC.

The rapporteur has not detected a signal for other SOC.

3 - Discussion and conclusions of the rapporteur CRPV

According to data from spontaneous reporting, the profile of reported adverse events was generally similar to that expected and there is no new data vis-à-vis the risks identified safety. Given spontaneous reports, the indication is not strictly respected, especially regarding the consideration of cardiovascular risk factors. We must await the results of the prescription study in France, for which we deplore a year late, to objectively evaluate this consideration. According to studies, and in comparison with diclofenac, CRPV rapporteur believes that the thrombotic cardiovascular risk etoricoxib is similar, that the risk of hypertension is higher but no increase in cardiovascular events that renovascular risk of etoricoxib 60 mg is stackable and digestive benefit is only present for uncomplicated upper GI events.

The CRPV rapporteur proposes in these conditions to reduce the national monitoring while maintaining a specific monitoring of liver disease, nephrotic syndrome, venous thromboembolic accidents and literature data.

The CRPV also proposed analyzing the results of pharmaco-epidemiological study of use in France and the monitoring of Arcoxia form ® 90 mg in case of commercialization.

4 - Discussion and conclusions of the National Pharmacovigilance Committee

He was asked the laboratory reasons for refusal of marketing authorization of etoricoxib FDA. The FDA requested studies (including use of study) that the lab found difficult to achieve. Before this failure to provide the requested studies, the marketing authorization has not been granted. When asked the reason for refusal of marketing authorization by the Canadian agency, the laboratory could not answer.

The laboratory was asked about the reason for the delay of one year of study for use in France; the answer is that the delay was linked to administrative roundtrips to validate the protocol. The agreement of the National Council of the Medical Association and the PPC was given in March 2012.
Regarding a link between adverse effects and treatment duration, it appears that the cardiovascular risk is present from the first dose and increases with time. According to the laboratory, the average length etoricoxib treatment is about 30 days.

After the departure of the laboratory representatives:

- Members of CNPV commented on the possibility of recommending etoricoxib second line. In the absence of direct comparative study between NSAIDs, however it does not appear feasible to recommend one NSAID over another

- An additional risk of misuse, assuming the form 90 mg is marketed, was raised by members of CNPV. The treatment of dental pain is indeed indicated for a period of 3 days, while existing packaging seem ill-suited to this duration. In case of refund of etoricoxib 90 mg with the Transparency Commission (CT) of the HAS, it was explained to members of the CNPV the data Arcoxia pharmacovigilance national monitoring ®

and the opinion of the ANSM would be forwarded to the HAS.
The lab had said in this connection that special packaging is being recorded.

- According to IMS data (dispensation dispensary France from February 2009 to February 2012) ketoprofen is the first NSAID dispensed (20%) and diclofenac second (15%). It was recalled that diclofenac is also an NSAID for which cardiovascular risk seems more important than for others. A European work is currently underway on this subject. Dispensations Arcoxia ® are for their declining (-20% between 2011 and 2012) and represent a fraction of NSAIDs dispensations in France (about 1%).

- Finally, it was discussed the need to remember the rules of good use of NSAIDs in general, especially as some NSAIDs are nonprescription. Information on NSAIDs and coxibs ANSM present on the site are obsolete and an update is required and will be made in the future.

5. Conclusions

Members of the CNPV voted unanimously:
- For a national monitoring relieved of etoricoxib with an analysis of the literature, unpublished data provided by the laboratory, and pharmaco-epidemiological study data generated in France.
- To monitor the form to 90 mg if the lab files a claim and provided it is granted by the Transparency Committee of the HAS.

- To remember the rules of good use of NSAIDs with a specific point on coxibs.

III - REVALUATION PROFIT / RISK STRESAM® (Etifoxine) BALANCE SHEET DATA JOB SECURITY (2000-2012)

CRPV reporter: CRPV Lyon

1. Introduction

Trade name	STRESAM®
DCI	etifoxine
dosage form, dosage	50 mg capsule
pharmacological class	Other anxiolytic (N05BX03)
Registration Procedure	National marketing authorization Date = 06.19.1979
Notice of Transparency / Notification Date	low SMR (Notice HAS 14/12/2011)
Marketing Authorization Holder	Biocodex laboratory
Marketing outside France	Marketing authorization in 40 countries, including 4 of the European Union (Bulgaria, Luxembourg, Malta and Romania)
Mode of delivery	List I, prescription limited to 12 weeks

The etifoxine hydrochloride is an anxiolytic acting differently benzodiazepines. This would facilitate drug potentiating GABAergic inhibition directly the activity of GABA-A receptors via a site allosteric modulator different from that of benzodiazepines and / or by stimulating the production of neurosteroids which potentiate the activity of the GABA-A receptors. Etifoxine is listed under " *psycho-somatic manifestations of anxiety such as dystonia autonomic, including cardiovascular term* "Made with low medical service.

Etifoxine was the subject of a pharmacovigilance survey presented to the Technical Committee of 12 October 1999 which led to add dermatological side effects in the SPC and acute reactions hypersensitivity.
Under the revaluation of record earnings risk STRESAM®, the laboratory offers in section 4.8 of the SPC, specify the nature rashes (adding "maculopapular rash, erythema multiforme, pruritus, facial edema"), and to add "liver damage often in combination: cytolysis liver, hepatitis and elevated liver enzymes (GGT, ALT, AST) ".

2. Methodology

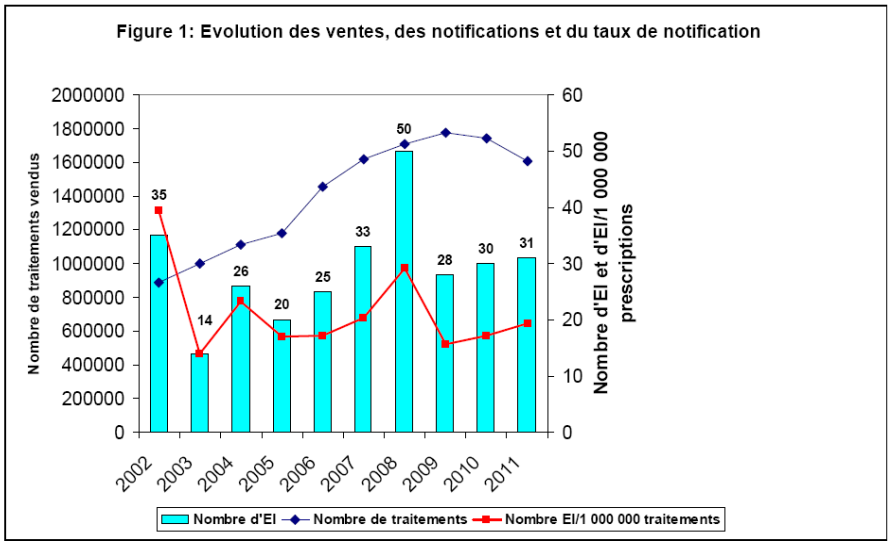
The analysis focused on all the side effect (etifoxine coded suspect or interaction) between the network of RAPC 01/01/2000 and 30/04/2012, and laboratory between the 01/01 / 2000 and 31/12/2011. Prior notification of BNPV to 2000 have been for some side effects. The cases for which other causes (drug or non-drug) was more evident depending on the nature of the adverse reaction or narrative were excluded from the analysis.

Sales and prescriptions were evaluated from data provided by the laboratory for the years 2002 to 2011: GERS data for sales and EPPM data of winter 2011 for the average prescription (34.71 days) and average daily dose (2.86 tablets). The number of treatments sold during this period was calculated from these data.

3. Results

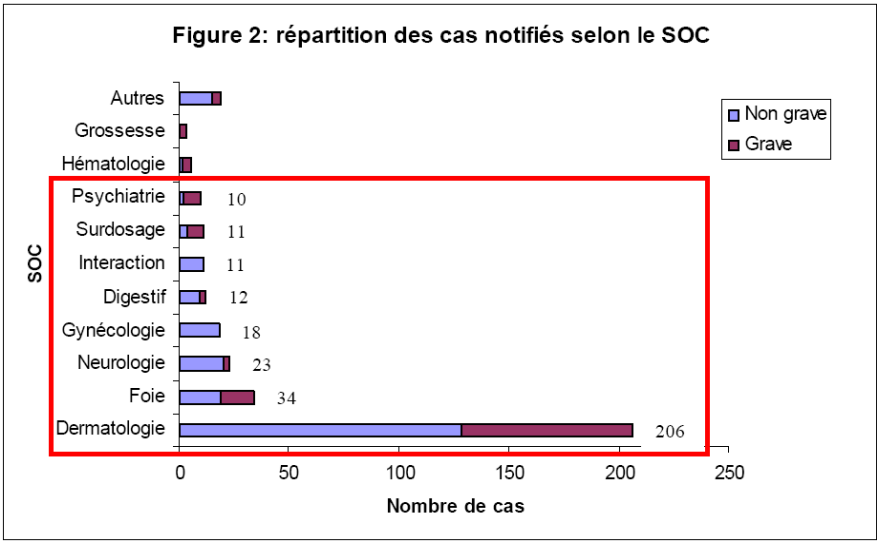
A total of 352 of the 419 cases reported during this period were retained, including 125 severe cases (36%). This is relatively young patients (mean age 40.5 years). The indication and dosage are met for the majority of cases where this information is known. The incidence of reported cases is very low and fairly constant over the study period of about 14 to 40 cases per million treatment for all cases, and 3 to 14 cases per million for severe cases, while sales doubled between 2002 and 2009.

Figure 1: Evolution des ventes, des notifications et du taux de notification



The reported side effects are mainly dermatologic conditions and hypersensitivity reactions (58.5%) and liver damage (9.7%), neurological (6.5%), gynecological (5.1%), digestive (3.4%), psychiatric (2.8%), drug interactions (3.1%) and overdose (3.1%).

Figure 2: répartition des cas notifiés selon le SOC



Dermatological adverse reactions and hypersensitivity reactions (n = 206)

It is basically of cases of rash (69.9%), and severe drug eruption (12.1%), hypersensitivity reactions (8.7%), vasculitis (3.4%) or other types of skin reactions (5.8%). Bullous or severe drug reactions, not listed in the SPC, include possible DRESS syndrome (n = 5), bullous drug eruptions type of erythema multiforme (n = 10), Stevens-Johnson syndrome (n = 5) or Lyell's syndrome (n = 1), a fixed drug eruption, and erythroderma

The 5 cases of DRESS syndrome occurred after 8-21 days of treatment. In 2 cases, no co-suspect combination therapy was found. In three other cases, the co-suspect treatment was associated NSAID or tetrazepam. A cure or improvement in treatment discontinuation is mentioned in all cases. The 10 cases of erythema multiforme occurred after 2-56 days of treatment. In 5 cases, no treatment was associated or was known as that can cause bullous drug eruption. In the remaining 5 cases, the co-treatment was suspect an NSAID (n = 2) or an anti-infective (n = 3). All these cases have evolved toward healing without sequelae or improvement in treatment discontinuation.

The 5 cases of Stevens-Johnson syndrome occurred after 7 to 16 days of treatment. In 3 cases, no co-suspect treatment known to cause bullous drug eruption was found. In the other 2 cases, the co-suspect treatment was associated an anti-infective or antihypertensive. All these cases have evolved toward healing without sequelae or improvement in treatment discontinuation.

In the one case of toxic epidermal necrolysis, chronology of Etifoxine is imprecise and recent exposure to NSAIDs was found.

Vasculitis diseases or pseudo serum (n = 7), also not listed, occurred with an evocative median of 10 days after the start of treatment. Three cases were considered serious. In 4 cases, no treatment

were associated, or any known combination therapy to cause vasculitis was found. Skin biopsy was consistent with vasculitis in 2 cases. Skin tests were negative in 1 case. All these cases have evolved toward healing without sequelae or improvement in treatment discontinuation.

Among the 18 cases of acute hypersensitivity reactions, two cases of anaphylaxis have been reported, including one for which Etifoxine is the only suspect.

hepatic adverse events (n = 34)
Based on the 29 reported cases of acute liver injury, the hepatotoxic potential of Etifoxine appears likely on the following arguments:

- homogeneity of liver disease such (cytolytic in 79% of evaluable cases)
- within suggestive onset (≤ 2 months 93% of evaluable cases)
- Liver biopsy suggestive of drug involved in 2 cases
- notion of a case with positive rechallenge,
- etifoxine only suspect or not associated with a hepatotoxic drug in 19 cases (64%),
- accountability etifoxine at least plausible in 66% of cases.

neurological adverse events (n = 23) and psychiatric (n = 10)
The 23 cases of neurological manifestations are represented by headache (n = 5), visual disturbances (n = 2), sleep disorders like insomnia (n = 2), drowsiness (n = 4) of nightmares (n = 1) or sleepwalking (n = 1), dizziness (n = 3), speech disorders (n = 1), tremor (n = 1), extrapyramidal syndrome (one severe case), worsening of restless legs syndrome (n = 1) worsening of myasthenia representing an against-indication for the use of etifoxine (2 severe cases) .. the 10 cases psychiatric events (12 adverse events, serious cases 8) correspond to the increase of anxiety (n = 1), confusion (severe 1), the behavioral type of aggressiveness or agitation / excitation (4 including 3 serious), hallucinations (n = 1), depressive disorders (n = 1), suicidal ideation (1 gross), suicide attempts (2 bass) and suicide. Among the 4 cases of suicidal behavior, one mentioned the occurrence of suicidal thoughts after the recent introduction of Etifoxine, the other 3 being associated with concomitant introduction of an antidepressant.

gynecological adverse events (n = 18)
In 16 cases, there is bleeding, occurred within 1 month after the start of treatment in 9 cases (unknown time in 7 cases) in patients taking oral contraceptives the long course in 13 cases. A disappearance of bleeding is emphasized in treatment discontinuation in 10 (unknown behavior in 6 cases). The concept of a recurrence of bleeding after rechallenge is mentioned in 5 cases. The two other cases correspond to amenorrhea and oligomenorrhea.

In the absence of cases of bleeding in other sites or well validated cases of haematological disorders or hemostasis, a possible mechanism leading to decreased effectiveness of oral contraception by Etifoxine might be suggested .

gastrointestinal adverse effects (n = 12)
Of these, 4 correspond to diarrhea paintings appeared in the 2 months of the start of treatment (n = 3) or more months (n = 1), with highlight to colonoscopy, combined with a biopsy of a lymphocytic colitis (n = 3) or subacute inflammatory colon lesions (n = 1). A case is marked by recurrent colitis after the resumption of etifoxine. In 2 cases, Etifoxine is the only suspect drug.

Other side effects of interest
Other cases of interest, four serious cases reported severe thrombocytopenia (platelets <10 G / l) in patients aged 72 to 89 years. The time to onset is said that in one case (3 days). Etifoxine is the only suspect drug in one case. Regression stopped treatment is noted in 3 cases, but was associated with a corticosteroid therapy or immunoglobulins in 2 cases. It is unknown in one case with initial evolution rather evoking idiopathic thrombocytopenic purpura.

Overdose (n = 11)
These cases involve 11 patients with mean age of 21.8 years (14 to 37 years). The supposed ingested doses of etifoxine known in 7 cases, are from 500 to 2000 mg (median: 1000 mg). In 5 cases, there is a poly-intoxication. Clinical signs are present in 10 cases (11 symptoms) including drowsiness in 5 cases (including 3 with associated taking sedatives).

drug interactions (n = 11)

A drug interaction is suspected in 11 cases with:

- abnormal prothrombin in 5 patients under AVK with decreased INR in 4 cases (unspecified in 1 case), which can translate inefficiency of the AVK. In 3 cases, the INR was normalized to stopping Etifoxine (unknown behavior in 2 cases);

- a failure of oral contraception with occurrence of pregnancy in 4 cases;
- an increase of TSH in a patient previously balanced by levothyroxine observed 3 months after starting treatment with Etifoxine and normalizing after shutdown;
- Withdrawal signs methadone recorded 12h after the Etifoxine outlet.

These data could suggest a loss of effectiveness of some drugs associated Etifoxine without a mechanism to be proposed. Enzyme induction nevertheless seems unlikely if one refers to the withdrawal observation methadone, due to a very short time to onset.

4. Conclusions and rapporteur's proposals

The rapporteur CRPV, analyzed data:

- Confirm the risk of skin conditions and of acute hypersensitivity reactions,
- Reveal side effects not mentioned in the SPC, to be particularly taken into account in the reassessment of the benefit / risk because of their potential severity, despite a very low incidence, and who already already require a mention in the SPC. It's about :

- some severe drug reactions such as DRESS (5 cases and 2 where Etifoxine is the only suspect), erythema multiforme (10 cases, including 5 which is reasonably Etifoxine the only suspect) and Stevens-Johnson syndrome (5 cases including 3 where etifoxine reasonably the only suspect);
- Rare cases of vasculitis or serum pseudo-disease (7 cases including 4 which is reasonably Etifoxine the only suspect);

- the possibility of severe anaphylactic reactions or anaphylactic shock;
- acute liver hepatocellular, sometimes severe (25 cases with arguments to retain responsibility for Etifoxine), including 1 case reported in 1996 and requiring liver transplantation, and 1 case with concept of positive rechallenge;

- cases of functional bleeding in women usually in pill (16 cases including 5 with notion of positive rechallenge);

- very rare cases of lymphocytic colitis (4 cases, 1 with concept of positive rechallenge)

- Identify potential signals that warrant monitoring: decrease of the activity of warfarin or oral contraception;

- Show no significant risk of neurological or psychiatric adverse events
- Justify that the wording of section 4.9 "Overdose" by mentioning the risk of drowsiness and removing the need for a gastric lavage in case of mass outlet.

Proposals to amend the RCP

Device class or organ	***few***	***very rare***	***Proposal CRPV reporter***
Nervous system	*Drowsiness light early in treatment, disappearing spontaneously during the pursuit of it.*		
Skin conditions and subcutaneous tissue	*Rash: rash maculopapular erythema multiforme, pruritus, facial edema.*	*Allergic reactions: urticaria, angioedema.*	Add these effects with unknown frequency: - anaphylactic shock - DRESS syndrome - Stevens-Johnson syndrome - vasculitis and serum sickness-like reaction - change in erythema multiforme Erythema multiforme

liver disorders	*Hepatic often in combination: elevated liver enzymes, hepatitis.*		Add this effect with a frequency not delete "often in combination"
investigations	*Elevated liver enzymes (γ- GT, AST, ALT).*		To delete
Disorders of organs reproducing and breast			Add frequency not known: - breakthrough bleeding in women taking oral contraceptives
Gastrointestinal disorders			lymphocytic colitis

5. <u>Conclusion CNPV</u>

The CNPV draws attention to the new liver and skin reactions, rare or very rare but potentially serious, justifying as part of a risk-benefit ratio that the benefit of Etifoxine be clearly demonstrated.

Pending the opinion of GTNPA's earnings Etifoxine in the treatment of anxiety, as an alternative to benzodiazepines, and the final opinion of the AMM commission on the benefit-risk ratio of 'etifoxine the CNPV act unanimously in favor of an update of the CPR STRESAM ® as proposed by the CRPV reporter.

In the case of a favorable opinion on the benefit-risk etifoxine, VNPF also wishes that drug interaction signals (AVK; oral contraceptives) were investigated in the laboratory.

<u>Post-CNPV NOTE:</u>
This case was examined by the MA board of 13 September 2012, which concluded that the benefit / risk remains favorable Stresam®.

The Commission is in favor of maintaining the indication of Stresam® in "psycho-somatic manifestations of anxiety" and supports the application of the SPC update, further study and investigation of drug interactions.

IV - PRESENTATION OF THE NEW RULES ON TEMPORARY RECOMMENDATIONS OF USE

The law of 29 December 2011 introduced the ability to supervise out-marketing uses by Temporary recommendations of Use (RTU). It is a continuation of the Decree No. 2005-1023 of 24 August 2005 on the proper use of contract governing the use of off-AMM list of drugs off-GHS [1]

(Treatment protocols) and Article L.162-17-2-1 the Code of Social Security (PLFSS [2]) on the notwithstanding support requirements outside refundable field in the context of ALD [3] and rare diseases (Article 56). It broadens the contours in applying to all drugs prescribed in the city and in the hospital and strengthens the security component by adding the requirement of a patient monitoring provided by the (s) Laboratory (s) (s) concerned.

An RTU is developed by ANSM when two co-existing conditions:
- there is an uncovered therapeutic needs is to say that there is no appropriate alternative medication with an MA or a cohort ATU in the indication concerned; and

- the risk / benefit of the drug is deemed favorable, especially from published scientific evidence of safety and efficacy.

The evaluation of the level of evidence of the effectiveness and extent of the expected clinical benefit is achieved based on the principles of scientific evaluation in medicine, taking into account the methodological characteristics of the studies and all available results related to the effectiveness of the drug in the given situation. The requirement may nevertheless be adapted to specific situations, such as rare diseases. When it comes to data from published studies, they should preferably have been presented in peer-reviewed journals.

When a therapeutic need is identified, but there are insufficient data to assess the risk / benefit ratio, the favored regulatory framework for the prescription is the clinical trial.

The RTU has appended a collection of protocol monitoring patients on efficacy data, tolerance and actual use of the product. RTU is temporary; it is valid for 3 years.

[1] GHS: homogeneous group stay

[2] PLFSS: Bill funding social security [3] ALD: long-term illness