

Welcome to the STABILIS users for this nineteenth Newsletter !

# INFOSTAB

**DECEMBER 2012**

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*The parliament building of Budapest by night.*

SUMMARY

## **Test your knowledge on stability**

### **News from congresses**

News from the first ECOP Congress, Budapest, Hungary  
September 2012

### **New monographs**

Carfilzomib, Tigecycline

### **New references from international publications**

Bendamustine, Bortezomib, Carboplatine, Oxytocin,  
Trastuzumab

### **New documents on Infostab website**

### **Statistics**

Focus on Colombia

### **Answer to the test**

## Test your knowledge on stability !

Which of the following intravenous infusions must be protected from light ?

- Fluoro-uracil
- Dacarbazine
- Carmustin
- Irinotecan
- Fotemustin

*See the answer on page 8*

## News from the first ECOP Congress, Budapest, Hungary, September 2012

The First Congress of the European Society of Oncology Pharmacists (ESOP) took place in Budapest, Hungary, September 27-29, 2012. Around 500 participants from 52 countries attended the Conference.

Stability studies had an important part in the Congress with two practical sessions, a debate around the Dose Banding Concept and many posters.

The practical session «New horizons - Which stability data can we rely on and how are they done ?» took place on Thursday 27 September with two oral communications, the first one of **Pr Alain Astier** from the University Hospital Henri Mondor, Créteil, France. « **Practical stability studies - A powerful approach to decrease the cost of monoclonal antibodies** ».

Pr Astier, specialized in the stability studies of monoclonal antibodies, presented the works of his team. He explained the complex methodologies used to study these compounds and the main results with the extended stabilities of cetuximab and bevacizumab (at least 3 months), and rituximab (6 months). He also presented the recent study (also in poster) which demonstrated

the possibility to send trastuzumab by pneumatic conveying system to the wards without any degradation (if the air is previously removed from the bags), see details in the poster session. This research will be extended to other monoclonal antibodies. The poster can be downloaded on the Infostab website.

The main aspect of the conclusion was that these extended stabilities permit to propose the Dose Banding and in advance batch preparation especially for rituximab with the optimisation of the workload of the pharmacy and important money savings.



*Pr Alain Astier during his presentation.*

The second speaker of this practical session was Dr Iben Larsson from Denmark « Obtaining valid stability data for cytotoxics - An international matter ». She emphasized the very limited stability data given by the Summary of Products Characteristics (SPC) and the need of stability performed by hospital pharmacists. To prevent all countries from spending a lot of resources on performing identical stability studies, she recommended that the best solution should be the coordination for the generation of reliable stability studies at European level.



*Marco Bellerio (Italy), Rainer Trittler (Germany) and Iben Larsson (Denmark) involved in the presentation of posters and oral communications.*

**The Practical interactive session « Extended stability of anticancer drugs - The dream becomes a reality ? »** took place at the end of the afternoon. The first presentation was « **Extended stability of rituximab, bortezomib and azacitidine - Application in the daily practice in haematology** » by **Dr J Vigneron**. The main lines of this lecture were presented in the last stability newsletter (see the meeting of the SOBRAFO in Brasilia). The extended stability of rituximab infusion bags (6 months), bortezomib in syringes (5 weeks) and azacitidine (8 days in the freezer at -20°C) were presented with their applications in the daily practice. These extended stability studies allow the preparation in advance with many advantages.

- waiting time of the patient diminished or eliminated
- preparation during the afternoon
- stress of the pharmacy staff decreased
- the organisation of the nursing staff enhanced
- save money

The content of this lecture has been published in the last issue of the European Journal of Oncology Pharmacists (*EJOP 2012; Volume 6, Issue 2*).

The second presentation was done by Dr Rainer Trittler from the University Hospital of Freiburg « **Benefits of extended drug stability and compatibility data in clinical practice** ».

He presented the results of a systemic survey to explore the view of the German hospital pharmacies on extended stability studies. He obtained the answers of 105 hospital. More than 90% of them were working with extended stability data and only 8.3% used only the Summary of Product Characteristics. The conclusion was «Our survey shows that extended stability studies play an important role in clinical practice of German hospitals. The benefits for the hospital pharmacy can be minimising costs and waste.»

### **Debate around the Dose Banding concept**

On the second day of the congress, in the afternoon, a debate was organised around the Dose Banding Concept: «Clinical/practical:This house believes that Dose Banding is a major issue for quality, practical and economical reasons.»

Two speakers were in favor of the DB concept : Pr Graham Sewell and Pr Etienne Chatelut

**Pr Graham Sewell**, one of the creator of the Dose Banding Concept, presented his experience and the main lines of the concept : « 14 years of Dose-Banding: Evidence and clinical experience ».

The Dose Banding concept is :

- the standardization of the doses of chemotherapy at  $\pm 5\%$  of the dose calculated according to the Body Surface Area (BSA)
  - the preparation in advance
  - the administration of one or several syringes or bags to administer the dose .
- (ex 3 syringes of fluorouracile 400, 300 and 250 mg to administer 950 mg).

**The Dose-Banding Concept can be applied to drugs which have extended stability.** The pharmacy can carry out batch preparation of prefilled syringes or bags. This approach allow the prospective analysis by UV-Vis spectroscopy with drug identification and assay and prospective sterility tests.

Prospective microbiological monitoring with broth simulation, finger-dab plates etc must be performed according to Good manufacturing Practices.

Currently 65% of outpatients are now banded. The production of banded dose approx 38000 per year.

In his conclusion, Pr Sewell emphasized that there is a scientific rationale of the DB and after 14 years of clinical experience, the DB is widely adopted in UK and UK prescribers support the concept. There is a clear benefit for the patient care, the safety and the quality.

The advantages are numerous :

- Batch preparation
- Automated compounding
- Industry prepared licenced infusions
- Control of pharmacy nursing workload
- Average waiting time reduced
- Prospective end- product testing
- Medication errors reduced or eliminated
- Drug wastage minimised or eliminated

The second speaker in favor of the DB concept was Pr Etienne Chatelut. He exposed the pharmacokinetics arguments.

He has compared the pharmacokinetics between the Body Surface Area calculation and the Dose Banding. The following molecules were compared: cisplatine, docetaxel, paclitaxel, doxorubicine, irinotecan and topotecan.

3 standardized doses band were administered to the patients according to the BSA.

It seems that that a difference occur in the pharmacokinetic only for paclitaxel.

After the two presentations in favor of the Dose Banding Concept, Pr Klaus Meier from Germany and Pr C Dittrich from Austria gives their opinions against the DB Concept.

After the presentations of the 4 leaders, many questions were asked by the audience by pro and con pharmacists.

A vote was organized with a majority of pharmacists convinced by the arguments in favor for the DB. However, around only 20 % of the audience already used the DB in their daily practice.

## The poster session

91 posters were presented from the teams of 24 countries.

France (16), Italy (15), Chian, Spain, (7), TAIwan (5), Germany (4), Hungary, Portugal, Egypt, Belgium (3), Australia, Japan, Korea, Slovenia, Denmark, USA, Poland, Estonia, Netherland, Brazil (2), Syria, Iran, Russia, Mongolia (1).

Very interesting posters with innovative stability studies were presented.

**« Rituximab can be sended by conveying systems if the air has been removed from the infusion bag. »**

Presented in the poster : Pneumatic conveying systems and physical stability of monoclonal antibodies - example of rituximab

**Vieillard V, Rilcy K, Magneux C, Bellanger A, Astier A, Paul M.** *Henri Mondor Hospital, Creteil, France and Pitié Salpêtrière Hospital, Paris, France.*

Aggregation can be induced by mechanical stress which can occur during transport and could induce loss of efficacy and/or toxic effects such as immunogenicity. The objective of this study was to verify if the pneumatic conveying systems could be used to send bags containing the Mab rituximab to the clinical services.

The authors have demonstrated that , without head space or bubbles into the bags, up to 8 travel cycles can be carried out with no modification in comparison with the control. In the opposite, in the presence of air, significant modifications were found after 4 cycles since two populations were found by dynamic light scattering. Moreover, modifications of the FTIR spectra were also observed suggesting alteration of the secondary structure. These results demonstrated that aggregation during the pneumatic transport is strongly dependant on the presence of air/liquid interface.

In practice, a pneumatic conveying system can be safely used for the transport of diluted rituximab (and probably other monoclonal antibodies) but the presence of air into the bags must be avoided.



The «Great Market of Budapest» built by Gustave Eiffel in 1900

« **Reconstituted bendamustine at 2.5 mg in water for injection was stable at 4°C for 8 hours.** »

This new information was presented in the poster « Stability of **bendamustine** reconstituted with water for injection at 2.5 mg/mL and diluted with 0.9 or 1.5% sodium chloride. »

**Vigneron J, Sobalak N, May I, Demore B**  
- University hospital of Nancy, France.

The poster can be downloaded (see in «Documents available on the Infostab website»)

« **Bortezomib solutions at 2.5 mg/mL used for subcutaneous injections is stable in glass vials for 30 days at 4°C** »

Presented in the poster :

Chemical stability of bortezomib solutions in original manufacturer vials

**Bosch-Ojega C, Sanchez-Rojas MF, Espinosa-B** Faculty of science of Malaga and University Hospital «Virgen Del Rocío» Seville, Spain

This study allows to prepare in advance of this concentrated solution and will have many advantages for the daily practice of the centralized units.

**The stability of oxaliplatin infusions depends on the formulation of the lyophilisate**

Presented in the poster:

Stability of **lyophilized oxaliplatin** formulation in polyolefin bags containing 5% dextrose injection.

**Trojniak M, Palozzo AC, Franceschinis E, Realdon N.** From the institute of oncology and the university of Padova in Italy.

In this study, the authors have demonstrated that the stability of oxaliplatin is concentration-dependent. They compare the stability of solutions at 5 mg/mL, 2mg/mL and 0.5 mg/mL. The stability of the 5 mg/mL was in accordance with the previous stability studies with a concentration above 95% of the initial concentration after 2 months.

When the solution is diluted to 0.5 or 0.7 , the stability is dramatically decreased.

In this oxaliplatin formulation, lactose was used as excipient and the presence of this compound result in the formation of the new Pt (DACH) complex at significant levels which may be the cause of the instability of the diluted ready to use oxaliplatin solutions.

The solutions at 0.5 and 0.7 mg/mL stored in polyolefine infusion bags were chemically unstable within 7 days and 14 days respectively at 2-8°C. The poor stability of diluted solutions, prepared from this lyophilized formulation, does not allow the preparation in advance and the storage in pharmacy departments.

« **Trastuzumab infusions are stable for 6 months !** »

This stability study was performed by the team of the University Hospital of Créteil, France.

**Vieillard V, Da Silva R, Astier A, Escalup L,**



*The famous Gerbeaud Confectionery*

### « Trastuzumab infusions are stable for 6 months ! »

This stability study was performed by the team of the University Hospital of Créteil, France.

**Vieillard V, Da Silva R, Astier A, Escalup L, Paul M.**

Physicochemical stability of diluted trastuzumab solutions stored 6 months at 4°C.

The study was carried out by using various protein characterization methods: size exclusion HPLC, dynamic light scattering, turbidity, cation exchange HPLC, UV spectrometry and peptide mapping. Trastuzumab was diluted in normal saline and stored in polyethylene infusion bags (Freeflex®) at 4°C during 6 months. No modification of trastuzumab characteristics were observed until the 6 months of storage whatever the method used. This excellent stability could authorise the safe anticipated preparation by pharmacy centralised units.

### **Solutions of eribulin mesylate were stable for 2 weeks.**

This study presented in the last Stabilis newsletter was presented as a poster.

Eribulin solutions in open vials, syringes or polypropylene bags at clinically relevant concentra-

tions were physically compatible and chemically stable for at least 14 days at 4°C and 20°C with and without protection from light.

This work was recently published in *Ann Pharm Fr* 2012 ; 70, 5: 249-255.

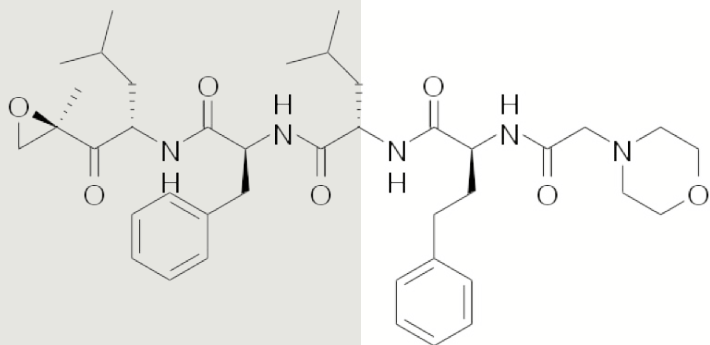
**Extended stability of antibiotic in elastomeric container** was presented for the administration at home.

Innovative strategy for antibiotics administration using elastomeric pump -stability studies And preliminary pharmacokinetics evaluation (see documents on *Infostab* website in the next section).

A poster from a Chinese team presented the **stability of epirubicin hydrochloride solutions prepared from three different formulations** (concentrated solutions and dry powder). The three epirubicin solutions were stable when stored at 2-8°C under dark conditions during at least 40 days and the average content of epirubicin could achieve more than 93% of the initial concentration.

## New Monographs

### Carfilzomib



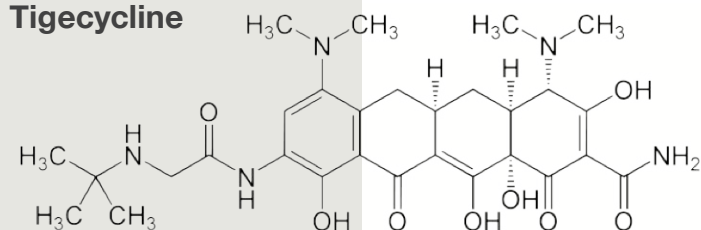
Carfilzomib is a next-generation proteasome inhibitor that is being developed as a potential treatment for patients with multiple myeloma and solid tumors.

Carfilzomib 2 mg/ml reconstituted solution with water for injection is stable for 24 hours at 2-8°C and for 4 hours at room temperature (15-30°C), in manufacturer vial or in polypropylene syringe.

When diluted in 5% dextrose injection PVC bags, the stability is the same as previously.

*Onyx Pharmaceuticals : Summary of Product Characteristics, 2012*

### Tigecycline



Tigecycline is the first clinically-available drug in a new class of antibiotics called the glycylicyclines. It is structurally similar to the tetracyclines in that it contains a central four-ring carbocyclic skeleton and is actually a derivative of minocycline.

Tigecycline is bacteriostatic and is a protein synthesis inhibitor by binding to the 30S ribosomal subunit of bacteria and thereby blocking entry of Aminoacyl-tRNA into the A site of the ribosome during prokaryotic translation.

Tigecycline is physically incompatible with amphotericin B, amphotericin B lipid complex, diazepam, esomeprazole and omeprazole.

*Pfizer : Summary of Product Characteristics, 2012*

## New references from international publications

### Bendamustine

Bendamustine 2.5 mg/ml reconstituted solution with water for injection is stable for 8 hours at 2-8°C.

*ECOP Congress, Budapest, Hungary 2012*

### Bortezomib

Reconstituted bortezomib 2.5 mg/ml was physically and chemically stable at 4°C in the dark at least for 30 days in the original manufacturer vial.

*ECOP Congress Budapest Hungary 2012*

### Carboplatine

Solutions of carboplatin diluted in 5% dextrose (0.5 or 5 mg/ml) were stable for at least 7 days in refrigerated conditions or at room temperature.

*Krankenhauspharmazie 2001 ; 7: 331-333.*

### Oxytocin

Oxytocin parenteral solutions in the final concentration of 0.02UI/ml and diluted in normal saline are stable for at least 30 days under frozen and refrigerated conditions for 30 days. At room temperature, the oxytocin solutions were stable for at least 21 days.

*AAPS Pharm Sci 2012 ; 6, 1 : 49-54*

### Trastuzumab

Diluted trastuzumab (0.8 and 2.4 mg/ml) was strongly stable after storage up to 6 months at 4°C.

*ECOP Congress, Budapest, Hungary 2012*

# New documents in Infostab website

[www.infostab.fr](http://www.infostab.fr)

See in « Publications » and « Stability and compatibility ».

**1. J. Vigneron\*, N. Sobalak\*, I. May\*, B. Demoré\*\***

**Stability of bendamustine reconstituted with water for injection at 2.5 mg/mL and diluted with 0.9% or 1.5% sodium chloride at 0.25 and 0.60 mg/mL**

\*Pharmacy department, University Hospital, Nancy, France - \*\*SRSMC, UMR 7565, Université de Lorraine – CNRS Faculté de Pharmacie  
*Poster presented during "ECOP" congress, Budapest, Hungary, September 2012*

**2. M. Moine<sup>1</sup>, V. Vieillard<sup>1</sup>, A. Astier<sup>1</sup>, M. Paul<sup>1</sup>**  
**Stabilité physico-chimique du Bevacizumab 5 mg/mL dilué dans du Chlorure de Benzalkonium 0.1 mg/mL**

<sup>1</sup> : GH Henri Mondor, Service Pharmacie, 51 av du Mal de Lattre de Tassigny, 94010 Créteil  
Poster presented during "CSH" congress, Ajaccio, France, September 2012

**3. V. Vieillard<sup>1</sup>, R. Da Silva<sup>1</sup>, A. Astier<sup>1\*</sup>, L. Escalup<sup>2</sup>, M. Paul<sup>1</sup>.**

**Physicochemical stability of diluted trastuzumab solutions stored 6 months at 4°C**

<sup>1</sup> : Department of Pharmacy, Henri Mondor Hospital Group and \* UMR 7054, School of Medicine, Paris 12, University. Créteil France

<sup>2</sup> : Department of Pharmacy, Curie Institute, Paris, France

*Poster presented during "ECOP" congress, Budapest, Hungary, September 2012*

**4. V. Vieillard<sup>1</sup>, K. Rilcy<sup>1</sup>, C. Magneux<sup>2</sup>, A. Bellanger<sup>2</sup>, A. Astier<sup>1\*</sup>, M. Paul<sup>1</sup>**

**Pneumatic conveying systems and physical stability of monoclonal antibodies: Example of rituximab**

<sup>1</sup> : Department of Pharmacy, Henri Mondor Hospital Group and \* UMR 7054, School of Medicine, Paris 12, University. Créteil France

<sup>2</sup> : Department of Pharmacy, Pitié Salpêtrière Hospital Group, Paris, France

Poster presented during "ECOP" congress, Budapest, Hungary, September 2012

**5. C. Bosch-Ojeda<sup>a</sup>, M.F. Sánchez-Rojas<sup>a</sup>, M. Espinosa-Bosch<sup>b</sup>**

**Chemical stability of Bortezomib solutions in original manufacturer vials**

<sup>a</sup> : Department of Analytical Chemistry, Faculty of Sciences, University of Málaga, 29071, Málaga, Spain

<sup>b</sup> : Department of Pharmacy, General Hospital, University Hospital "Virgen dell Rocío", 41013, Sevilla, Spain

*Poster presented during "ECOP" congress, Budapest, Hungary, September 2012*

**6. Scott E. Walker<sup>2,3</sup>, Lauren F. Charbonneau<sup>1</sup>, Shirley Law<sup>2</sup> and Craig Earle<sup>3</sup>**

**Stability of Azacitidine solutions in sterile water for injection**

<sup>1</sup> : Odette Cancer Centre Department of Pharmacy,

<sup>2</sup> : Sunnybrook Health Sciences Centre Department of Pharmacy,

<sup>3</sup> : Cancer Care Ontario Institute for Cancer Research and the <sup>4</sup>Faculty of Pharmacy, University of Toronto, Toronto, Ontario.

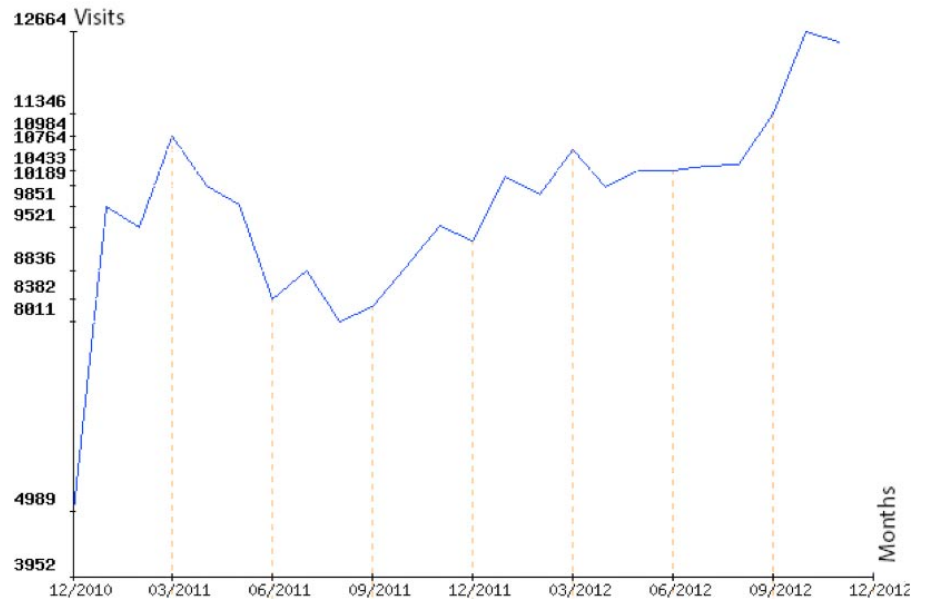
*Poster presented during "NOPS" congress, Saskatoon, Canada, October 2012*



# Statistics

The statistics show a constant decrease of the French language with an increase of the English and Spanish language. The Spanish language increases not only with an increase of the users in Spain but also in South America.

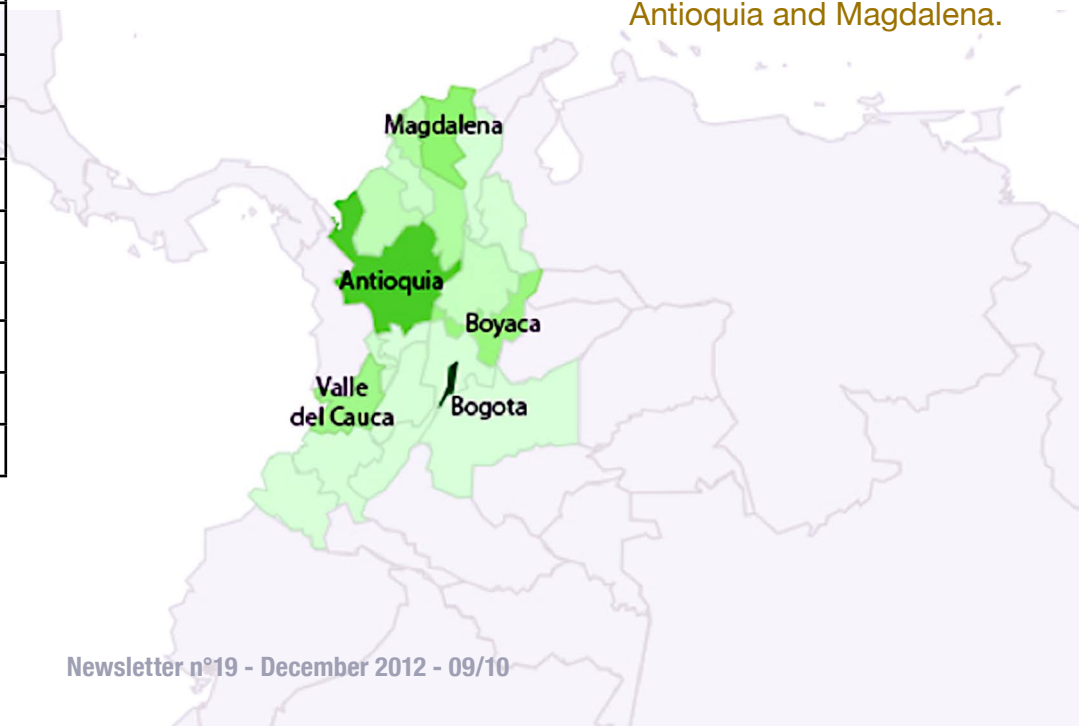
Language	Percentage
French	51.7 %
English	9.5 %
German	6.4 %
Spanish	6.1 %
Dutch	4.1 %
Italian	3.7 %
Portuguese	2.4 %
Turkish	2.0 %
Polish	1.2 %
Finnish	1.0 %
Croatian	1.0 %
Russian	1.0 %
Greek	1.0 %
Latvian	0.9 %
Danish	0.9 %
Czech	0.8 %
Hungarian	0.8 %
Slovenien	0.8 %
Swedish	0.8 %
Rumanian	0.8 %
Norwegian	0.8 %
Estonian	0.8 %
Slovak	0.7 %
Lithuanian	0.7 %



The number of users have significantly increased during the past 3 months with more than 12000 users in October and November with a maximum daily peak at 600 users in October !

The Country Focus of this newsletter is on Colombia which has dramatically increased the number of users this year. 1175 users in 2011 and 2979 since the beginning of 2012, a increase of more than 150% !

The main town using Stabilis are Bogota, Antioquia and Magdalena.



# Answer to the test

- Fluoro-uracil
- Dacarbazine
- Carmustin
- Irinotecan
- Fotemustin

All these drugs are sensitive to light exposure. However, in clinical practice, the infusion of fluorouracile and irinotecan do not need to be protected from light.

Irinotecan infusions are stable for 3 days diluted in 0.9% sodium chloride or 5% dextrose without protection of light according to the manufacturer.

Dacarbazine, carmustine and fotemustine are very sensitive with a rapid degradation. The photodegradation of dacarbazine is indicated by the apparition of a pink colour.

## References :

Akimoto K, Kaway A, Ohya K et al.

**Photodegradation reactions of CPT-11, a derivative of camptothecin, part i: chemical structure of main degradation products in aqueous solution.**

*Drug Stability 1996 ; 1: 118-122.*

Dodds HM, Craik DJ, Rivory LP.

**Photodegradation of irinotecan (CPT-11) in aqueous solutions : identification of fluorescent products and influence of solution composition.**

*J Pharm Sci 1997 ; 86, 12: 1410-1416.*

Stevens MFG, Peatey L.

**Photodegradation of solutions of the antitumour drug DTIC.**

*J Pharm Pharmacol 1978 ; 30: 47P.*

Dine T, Khalfi F, Gressier B, Luyckx M, Brunet C, Ballester L, Goudaliez F, Kablan J, Cazin M, Cazin JC.

**Stability study of fotemustine in PVC infusion bags and sets under various conditions using a stability-indicating high-performance liquid chromatographic assay.**

*J Pharm Biomed Anal 1998 ; 18: 373-381.*

Fredriksson K, Lundgren P, Landersjo L.

**Stability of carmustine - kinetics and compatibility during administration.**

*Acta Pharm Suec 1986 ; 23: 115-124.*

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