DECEMBER 2010

MADRAC

Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia
This newsletter is also available on our website: http://www.bpfk.gov.my

REGULATORY MATTERS

AVANDIA® (ROSIGLITAZONE) & COMBINATION PRODUCTS: RESTRICTION OF USE DUE TO CARDIOVASCULAR RISK

Since its approval in the United States in year 1999 and in the European Union in the subsequent year, rosiglitazone has been identified to be associated with the adverse events of fluid retention and heart failure. Hence, this drug is always under tight vigilance by international regulatory agencies. In September 2010, the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) has proposed to the Drug Control Authority (DCA) to contraindicate the use of rosiglitazone and its combination products in patients with established NYHA Class I to IV heart failure and in patients with known ischaemic heart disease due to the associated risk of congestive heart failure. This proposal was approved by the DCA in its 232nd meeting on 30 September 2010 and the final recommendation of restriction was approved in its 234th meeting on 22 November 2010.

More information on the background of this safety update is available in the April 2010 issue of MADRAC bulletin.

Rosiglitazone In Malaysia

Rosiglitazone is first approved in Malaysia in year 2000 as an adjunct to diet and exercise to improve glycaemia control in patients with type 2 diabetes mellitus. There are 11 products containing rosiglitazone in Malaysia, with GlaxoSmithKline (GSK) as the sole product holder. Products marked with (*) are listed in the Ministry of Health Drug Formulary.

Product Name	Active Ingredients	Strengths Available
Avandia®	Rosiglitazone	2mg, 4mg*, 8mg*
Avandaryl®	Rosiglitazone/Glimepiride	4mg/1mg, 4mg/2mg, 4mg/4mg
Avandamet®	Rosiglitazone/Metformin	1mg/500mg, 2mg/500mg, 4mg/500mg, 2mg/1000mg, 4mg/1000mg

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To report an adverse drug reaction:
1. Visit http://www.bpfk.gov.my;
2. Click on "MADRAC (Adverse Drug Reactions)" on the left toolbar; and
3. Click on "Reporting Online".

Alternatively, please contact:

National Centre for Adverse Drug Reactions Monitoring
Centre for Post Registration of Products
National Pharmaceutical Control Bureau
Ministry of Health
Lot 36, Jalan Universiti,
46730 Petaling Jaya,
Selangor.

Tel : +603-7883 5400
Fax : +603-7956 7151

Chronology of NPCB's Actions on Rosiglitazone

Date	Events
Dec 2007 & May 2008	Package insert was updated to include a new Boxed Warning emphasizing the risk of rosiglitazone causing or exacerbating heart failure and the contraindication in patients with established NYHA Class III or Class IV heart failure.
23 Feb 2010	A press statement was released to strengthen the safety information.
24 Sept 2010	A press statement was released to inform about the new restriction, whereby rosiglitazone is not to be initiated in any new patient. Existing patients should seek medical advice to evaluate the appropriateness to continue treatment with this drug.
30 Sept 2010	The DCA has approved the recommendation to contraindicate the use of rosiglitazone in patients with established NYHA Class I to IV heart failure and in patients with known ischaemic heart disease.
22 Nov 2010	The DCA has approved the final recommendation on the restriction of this drug. This will be discussed under the subheading '**Current Regulatory Actions by DCA**'.

Usage in Malaysia

In general, the usage of rosiglitazone has declined in both government and private sectors since the controversy regarding its safety in year 2007. In private sector, many of the prescriptions have been changed to pioglitazone, whereas in the government institutions, the usage is very limited as it is placed under the A* category (can be initiated by consultants or specialists for specific indications only). The high cost is another deterrent to the extensive use of this drug.

ADR Reports

To date, the National Centre of ADR Monitoring has received 46 reports for rosiglitazone-containing products, out of which 25 were suspected to cause cardiovascular adverse events. In most cases, it is difficult to ascertain the association of cardiovascular risk with rosiglitazone because most diabetic patients are on multiple medications and they are also pre-disposed to these risks due to the nature of their disease.

Current Regulatory Actions by DCA

a) Updates of package inserts in the following sections.

- **Black Boxed Warning**

  - Rosiglitazone is contraindicated in patients with established NYHA Class I to IV heart failure and in patients with known ischaemic heart disease, particularly in those taking nitrates.
  - Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. Patients on rosiglitazone should be monitored carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnoea, and/or oedema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered.

- **Contraindications**
- **Warnings & Precautions**
- **Indications**

b) Dissemination of **Dear Health Care Professional (DHCP) letter** to all prescribers to convey the updates stated above.

These regulatory actions are effective from 13 December 2010.

Reference:

1. EMA. Press Release: European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2010/09/human_pha_detail_000020.jsp&murl=menus/medicines/medicines.jsp&mid [23 Sept 2010]
2. FDA MedWatch. Avandia (rosiglitazone): REMS – Risk of cardiovascular events. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm226994.htm [23 Sept 2010]

SIBUTRAMINE: CANCELLATION OF REGISTRATION DUE TO SAFETY CONCERN

In December 2010, the Drug Control Authority (DCA) has decided to cancel the registration of all products containing sibutramine due to the associated safety concerns. Prior to this, in October 2010, the DCA had announced the suspension of these products and all product holders were instructed to immediately stop any import and wholesale transactions, as well as to withdraw their products from all point of sales within 30 days of suspension date. A press statement on this issue was released on 11 October 2010.

This regulatory action follows the new data obtained from the Sibutramine Cardiovascular OUTcomes (SCOUT) study conducted by Abbott Laboratories for their product Reductil®. This study demonstrated a 16% increase in the relative risk of major adverse cardiovascular events (a composite of non-fatal heart attack, non-fatal stroke, resuscitation after cardiac arrest and cardiovascular death) in patients treated with Reductil® compared to patients taking a placebo. At the end of the trial (60 months), patients in the Reductil® group lost a modest amount of body weight compared to patients in the placebo group (2-4kg more or 2.5%). It is not clear if this effect on weight loss can be maintained when the treatment is stopped.

This is a follow-up report for the issue published in the MADRAC bulletin April 2010.

Sibutramine in Malaysia

Sibutramine is registered in Malaysia as an adjunctive therapy to diet and exercise within a weight management program in patients who are obese (BMI ≥ 30kg/m^2), and in patients who are overweight (BMI ≥ 27kg/m^2) if other obesity-related risk factors are present. Sibutramine is contraindicated in patients with history of coronary artery disease (angina, myocardial infarction), congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or transient ischaemic attack), with inadequately controlled hypertension, as well as aged 65 years and above.

Sibutramine was authorised in Malaysia since 2003, available in strengths of 10mg and 15mg. There were 11 registered products containing sibutramine prior to the suspension under the tradenames of Reductil® (Abbott), Sibutrim® (Glenmark), Sibutramine Sandoz® (Imeks Pharma), Slenfig® (Pahang Pharmacy) and Fenslim® (Ranbaxy).

Regulatory Actions

Following preliminary results of SCOUT, the DCA, on 25 January 2010, had instructed all product holders to incorporate the SCOUT study summary description in the package inserts and to issue a Dear Health Care Professional (DHCP) letter to all prescribers. In October, suspension was imposed in light of the final results of SCOUT, and most recently, cancellation of registration was recommended.

ADR Reports

Through the National Centre of ADR Monitoring, a total of 38 reports for sibutramine had been received. Among these, six reported on cardiovascular events (8 events), which are myocardial infarction (3 events), palpitations (3 events) and ST segment elevation (2 events). Four patients recovered without sequalae while the outcomes for the two remaining patients were unknown.

Recommendations

Patients who are currently on treatment with sibutramine are advised to consult their doctors for alternative weight management plan. The DCA will not register any product containing sibutramine starting from the date of cancellation.

Reference:

1. FDA MedWatch. Meridia (sibutramine): Market withdrawal due to risk of serious cardiovascular events. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm228830.htm [8 Oct 2010]
2. EMA. Press Release: European Medicines Agency recommends suspension of marketing authorization for sibutramine. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2010/09/human_pha_detail_000011.jsp&murl=menus/medicines/medicines.jsp&mid=&jsenabled=true [21 Jan 2010]

SAFETY ISSUES OF CURRENT INTEREST

LAMICTAL® (LAMOTRIGINE): RISK OF ASEPTIC MENINGITIS

In August 2010, the National Centre of ADR Monitoring received notification of the risk of aseptic meningitis associated with the use of Lamictal®. This causality is based on the US Food and Drug Administration's (FDA) identification of 40 cases of aseptic meningitis in paediatric and adult patients taking Lamictal® since the drug's approval in December 1994 through November 2009.

In Malaysia, Lamictal® is indicated for the treatment of epilepsy in adults and children above 2 years of age, as well as bipolar disorder in adults above 18 years of age.

Aseptic meningitis is an inflammation of the protective membranes (meninges) that cover the brain and spinal cord not caused by bacterial infection. Symptoms of meningitis may include headache, stiff neck, fever, chills, nausea, vomiting, rash, drowsiness, confusion, altered mental stage, altered consciousness and abnormal sensitivity to light.

Data Summary

Data summary of the 40 cases of aseptic meningitis received in the US is as follows.

No.	Aspects	Descriptions
1	Signs and symptoms	• Headache, fever, nausea, vomiting, nuchal rigidity, rash, photophobia, myalgia.
2	Time to onset	• 1 to 42 days (mean of 16 days).
3	Outcome	• 1 reported death (not related). • 35 cases required hospitalisation.
4	Dechallenge	• In most cases, symptoms resolved after discontinuation.
5	Rechallenge	• 15 cases reported a rapid return of symptoms following re-initiation, i.e. within 30 minutes to 24 hours (mean of 5 hours). • Symptoms were frequently more severe after re-exposure.
6	Lab data	• Cerebrospinal fluid (CSF) analysis was characterised by a mild to moderate pleocytosis, normal glucose levels, and mild to moderate increase in protein.
7	Underlying conditions	• Some patients also suffered from systemic lupus erythematosus or other autoimmune diseases. • Some patients have new onset of signs and symptoms of involvement of other organs (predominantly hepatic and renal), which may suggest that in some cases, meningitis were part of a hypersensitivity or generalised drug reaction.

Local Scenario

The Drug Control Authority (DCA) has registered 26 products containing lamotrigine under the trade names Lamictal® (GlaxoSmithKline), Lamotrix® (Komedic), Lameptil® (Novartis), Lamitor® (Pahang Pharmacy), Apo-Lamotrigine® (Pharmaforte), Lamotaxyl and pms-Lamotrigine (both Ranbaxy). Lamictal® Dispersible Tablet 5mg & 25mg and Lamictal® Tablet 50mg & 100mg are listed in the Ministry of Health Drug Formulary as Category A items (to be initiated by consultants or specialists only).

Up to November 2010, the National Centre of ADR Monitoring had received 109 reports associated with the use of lamotrigine. None of these reported on meningitis.

GSK (Malaysia) is updating the package insert to include 'aseptic meningitis' as a *very rare* adverse reaction of the nervous system, observed during 'other clinical experience'.

Recommendations

Patients on lamotrigine should be advised to contact their healthcare professionals immediately if they experience signs and symptoms of meningitis so that treatment can be promptly initiated. Healthcare professionals are encouraged to report adverse events related to the use of this medicine to the National Centre of ADR Monitoring, NPCB.

Reference:

1. FDA MedWatch. Lamictal® (lamotrigine): Label change – Risk of aseptic meningitis. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm222269.htm [12 Aug 2010]

TYGACIL® (TIGECYCLINE): INCREASED MORTALITY RISK

In September 2010, the National Centre of ADR Monitoring was made aware of the association of Tygacil® with increased mortality risk when compared with other antibiotics following the decision of the US Food and Drug Administration (FDA) to revise the label of Tygacil®.

The increased risk was most apparent in patients treated for hospital-acquired pneumonia (HAP), especially ventilator-associated pneumonia (VAP). Other risk factors include treatment for complicated skin and skin structure infections (cSSSI), complicated intra-abdominal infections (cIAI) and diabetic foot infections.

Tygacil® is approved by the Drug Control Authority (DCA) for the treatment of cSSSI and cIAI in patients 18 years of age and older. It is noteworthy that this product is not indicated, despite the wide use, for the treatment of HAP, including VAP, as well as diabetic foot infection.

Data summary

This result was obtained from a pooled analysis of 13 clinical trials. The trials were grouped by type of infection (approved and unapproved indications), and the overall mortality of Tygacil® vs. pooled control agents was compared.

Overall, death occurred in 4.0% (150/3788) of patients receiving Tygacil® and 3.0% (110/3646) of patients receiving comparator antibiotics. An adjusted risk difference between the two arms for all-cause mortality, based on a random effects model stratified by trial weight, was 0.6% (95% CI 0.1, 1.2).

The cause of excess death is often difficult to ascertain, but it is highly probable to be related to progression of infections. In general, Tygacil® is considered bacteriostatic. However, it has demonstrated bactericidal activity against isolates of *S. pneumoniae* and *L. pneumophila*. One possible reason for the mortality difference is that in certain severe infections, Tygacil®'s bacteriostatic mechanism may put it at some disadvantage, although for approved indications, cure rates with Tygacil® were generally similar to that seen with the bactericidal active control agents.

Local Scenario

Tygacil® (Tigecycline) 50mg Lyophilized Powder for Intravenous Infusion by Wyeth is the only product containing tigecycline that is registered in Malaysia. This product is not listed in the Ministry of Health Drug Formulary.

Up to November 2010, the National Centre of ADR Monitoring had received four reports with the use of tigecycline, with a total of six events. The adverse events include bradycardia, coagulation disorder, liver function tests abnormal, nausea, neutrophilia and vomiting. Three patients recovered without sequelae and the last patient who suffered from coagulation disorder and liver function tests abnormal had not recovered at the time of reporting.

Wyeth is currently updating the product leaflet of Tygacil®. A Dear Health Care Professional (DHCP) letter will be issued to inform healthcare practitioners on this safety update.

Recommendations

Healthcare professionals should be aware that the greatest increase in risks of death was seen when Tygacil® is used in patients with VAP, which is an unapproved use. An alternative antibiotic should be considered in patients with severe infections.

Reference:

1. FDA MedWatch. Tygacil® (tigecycline): Label change – Increased Mortality Risk. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm224626.htm [1 Sept 2010]

RELATED PUBLICATIONS

ALLOPURINOL-INDUCED ADVERSE CUTANEOUS DRUG REACTIONS

A Review of MADRAC (Malaysian Adverse Drug Reactions Advisory Committee) Report from 2000 – 2009

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Background:
Allopurinol is a widely used medicine in Malaysia and was the 35th most commonly prescribed medicine in 2008.[1] It is a common cause of adverse cutaneous drug reactions (ACDRs) with some reports citing it as the commonest agent causing severe adverse cutaneous drug reaction (SACDR).[2,3,4] Despite that, it is often prescribed for inappropriate indications.[5,6,7]

Objectives:
The main objective was to review the reported patterns of allopurinol induced ACDRs. Secondary objectives included reviewing the outcome of these reactions and the indications of allopurinol usage.

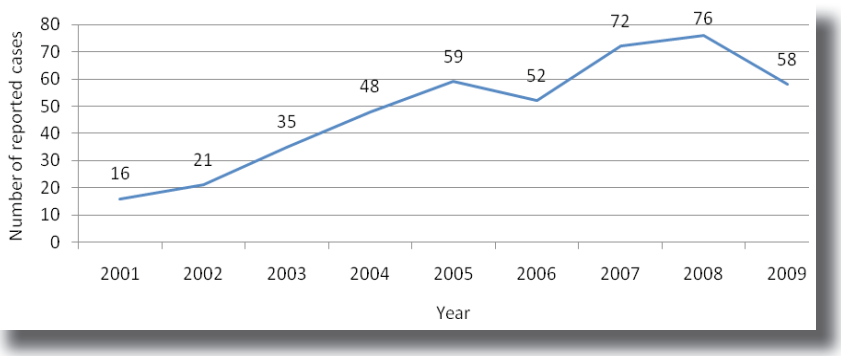
Methods:
This was a retrospective review of all ACDRs associated with allopurinol ingestion reported to MADRAC (Malaysian Adverse Drug Reactions Advisory Committee) from January 2001 till December 2009. Severe ACDR included Stevens-Johnson Syndrome, toxic epidermal necrolysis and DRESS syndrome.

Results:
Allopurinol induced ACDRs were reported in 437 patients and the incidence was increasing from 2001 till 2009 (Figure I). The commonest ACDRs described were Steven Johnson Syndrome (26.9%), followed by maculopapular exanthem (23.2%) and Toxic Epidermal Necrolysis (5.7%) (Figure II). Allopurinol induced ACDRs were severe reactions in 36.8%. The main indication for allopurinol usage was for gouty arthritis (59%), followed by asymptomatic hyperuricaemia (34%), non-specific arthritis or arthralgia (3%), renal calculi (2%) and during chemotherapy (2%). Fifteen (3.4%) mortalities were reported. Six of the deceased (40%) were prescribed allopurinol for asymptomatic hyperuricaemia.

Discussions:
The rising incidence of allopurinol induced ACDRs could be due to the increment of allopurinol presciption or ACDRs reporting rate among the practitioners. A large proportion of the reported ACDRs was severe and a significant number of them succumbed to the reactions. Inappropriate usage of allopurinol had been reported to be between 46.9% to 86.4% in various series.[5,6] Asymptomatic hyperuricaemia and non-specific arthritis or arthalgia are definite inappropriate indications and not all gouty athritis are indicated for allopurinol initiation. In our series, the actual inappropriate usage of allopurinol in this series was more than 36%. If we were able to control the inappropriate usage of allopurinol, we would have been able to prevent at least 36% of these ACDRs and 6 mortalities between 2001 to 2009.

Conclusions:
The incidence of allopurinol induced ACDRs are increasing with a significant proportion of them being severe reactions causing significant number of mortalities. A large portion of these reactions and mortalities are preventable if steps are made to avoid inappropriate usage of allopurinol.

Figure I: Number of Allopurinol induced ACDRs reported to MADRAC from 2001-2009



Source: National Pharmaceutical Control Bureau

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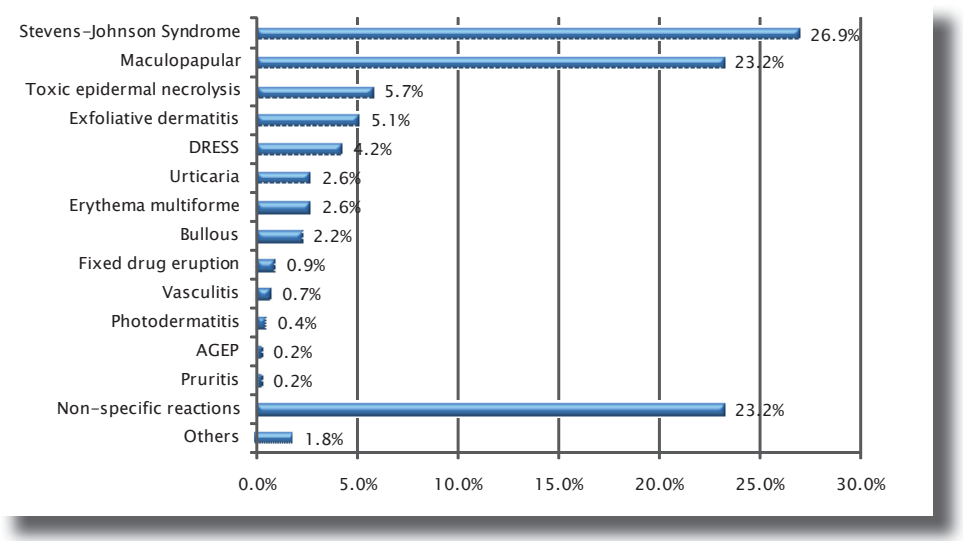
Figure II: Allopurinol induced ACDRs reported to MADRAC from 2001-2009



**DRESS : Drug Rash with Eosinophilia and Systemic Symptoms
AGEP : Acute Generalized Exanthematous Pustulosis

Source : National Pharmaceutical Control Bureau

MALAYSIAN ADR FORMS: BEST AMONG 10 COUNTRIES

The cover article in the recent issue of Reactions Weekly, entitled 'ADR reporting forms need to be harmonized' described that the ADR reporting form used in Malaysia (sometimes referred to as 'the blue form') appeared to be the most complete form in terms of the information asked for, based on the criteria deemed to be crucial for causality assessment. Reactions Weekly is a bulletin published weekly, 50 times a year, and it includes news from the Uppsala Monitoring Centre, WHO.

The following article is adopted from **Reactions Weekly**, 9 Oct 2010, No.1322.

ADR Reporting Forms Need To Be Harmonized

Bandekar MS, *et al*. Quality check of spontaneous adverse drug reaction reporting forms of different countries. Pharmacoepidemiolody and Drug Safety. 15 Sept 2010.

There exists a *need to harmonize the ADR reporting forms* of all countries, as discrepancies in these forms lead to incomplete data capture by WHO, resulting in *inappropriate causality assessment of ADRs and possible signal detection*, declare researchers from India. They suggest that the development of guidelines for creating an effective spontaneous ADR reporting form *is the need of the hour*.

The researchers compared ADR reporting forms for 10 different countries* obtained via the internet, and scored them on 18 different elements (for a total possible score of 18), such as patient information, and adequacy of space and columns to capture information required for causality assessment.
*Australia, Canada, India, Kenya, Malaysia, Pakistan, South Africa, Tanzania, the UK and the US

All of the forms analyzed asked for detailed patient information, such as sex, age, weight, list of suspected drugs, outcome of the reaction, and start and stop date of the suspected drugs and reaction. However, information about patients' allergic status was not requested in the ADR forms of Kenya, Pakistan and the UK, and pregnancy status was required only in the forms from Kenya and Pakistan.

Information about dechallenge, which the researchers say is *most important* for causality assessment was not asked for in the ADR forms of Australia, Pakistan, South Africa and the UK. In addition, information about rechallenge was not requested on the forms for Australia, Kenya or Pakistan.

The ADR form of Malaysia scored the highest on the points system, with 16 out of a possible 18 points.

NEWS & UPDATES

NEW REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNISATION (AEFI)

A concise reporting form specifically for AEFI reporting has been developed to assist the monitoring of mild adverse reactions experienced by patients after vaccination.

This new AEFI form can be used to document any adverse events associated with any type of vaccines. Patients are supposed to fill in the form if they experience adverse events thought to be related to the vaccines. They should then return the form to the clinic where they received the vaccination. Healthcare professionals in the clinic, in turn, should complete the form with relevant product details and send it in to the National Pharmaceutical Control Bureau (NPCB) via post or fax.

At the moment, the AEFI form is used in the newly launched Ministry of Health Human Papillomavirus (HPV) vaccination program and copies of the forms are available in all states' *Bilik Gerakan HPV*. The goal is to extend its use in various vaccination programs and it will then be available in all hospitals and clinics in Malaysia.

Patients and healthcare professionals are encouraged to report as these data will be useful in detecting any possible signals related to the use of vaccines.

HOW CAN WE SERVE YOU BETTER?

As the secretariat of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC), the Pharmacovigilance Section would like to seek for your opinion on what we can do to serve you better. Please take a moment to share your thoughts with us as this could help us to improve our service to you as well as to ensure better medication use.

All comments are welcomed. Our contact details are as follows:

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