National Pharmaceutical Control Bureau (NPCB)
Ministry of Health
MALAYSIA

Berita Ubat-ubatan
NEWSLETTER OF THE DRUG CONTROL AUTHORITY MALAYSIA

Berita Ubat - Ubatan August 2002

Cough Preparations Containing Codeine

At its 137th meeting held on 20 June 2002, the DCA decided on the following steps to be taken for all liquid cough preparations containing codeine:-

1. The registration of all these products will be cancelled with effect from 31 December 2002.
2. The manufacture and sales of these products will be terminated on 1 January 2003.
3. Registration holders are given until the end of this year to finish off their existing stocks.

Note: As at 20 June 2002, 46 such products have been registered with the DCA.

Background:

Cough preparations containing codeine can be used as a substitute for heroin since it is relatively cheaper and more readily available. Although steps have been taken to curb the misuse of codeine, this problem still exists and addiction towards this drug is rampant.

In countries like Egypt, Nepal and Australia, the sale of cough preparations containing codeine is prohibited. In Australia, Dextromethorphan or Pholcodine have been used as a substitute for Codeine. Nevertheless Codeine Linctus is still available and can be sold if it is prescribed on a doctor's prescription.

In Malaysia, alternatives such as Pholcodine and Dextromethorphan are also available. The DCA has already registered 6 products containing Pholcodine in the form of syrup and linctus. Products containing Dextromethorphan/Dextromethorphan hydrobromide are also registered with the DCA. Hence, even though Codeine syrups will be taken off the shelves, this should not affect prescribers since various alternatives are available.

Note: Codeine cough mixture is not listed in the Essential Drugs List issued by World Health Organisation (WHO).

International Visitors & Delegations to NPCB

Name	Country	Date	Purpose of visit
Dr. B. F. Samaranayake Director of Drug Regulatory Authority,	Sri Lanka	18 – 20 June	Study visit
Dr. Budiono Santoso, Regional Adviser in Pharmaceuticals, WHO Regional Office for Western Pacific, Manila	Philippines	10 July 2002	Official visit
Mr. T. Gono Medicine Control Authority of Zimbabwe, Harare	Zimbabwe	18-19 July 2002	Study visit
Dato Paduka Haji Zainal bin Haji Momin Permanent Secretary, Ministry of Health	Brunei Darussalam	18 July 2002	Official visit
Dr. Hj Affendy DSP Hj Abidin Director General of Medical Services, Ministry of Health	Brunei Darussalam	18 July 2002	Official visit
Dayang Aminah bte Hj Md Jaafar Director of Pharmaceutical Services, Ministry of Health	Brunei Darussalam	18 July 2002	Official visit
Abdul Mulok bin Hj Abdul Halim Acting Chief Executive Officer, Ministry of Health	Brunei Darussalam	18 July 2002	Official visit

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MADRAC NEWS

KAVA-KAVA (PIPER METHYSTICUM)
In December 2001, the Drug Control Authority (DCA Meeting No.131) took the decision to withdraw the registration of all products containing acetone-extract kava-kava. This was in line with information received from the Swiss Authorities who had reason to suspect that the liver failure associated with kava-kava was due to the acetone-extract procedure.

However, in line with regulatory action taken in other countries, the DCA has now decided to suspend the registration of all products containing kava-kava with immediate effect. Instructions have been issued to all registration holders to stop all sales and to recall all these products from the market.
(DCA 138 - August 2002)

NONI JUICE (Morinda Citrifolia):
A case has been reported where a patient experienced excessive bleeding intraoperatively during a surgical procedure. On investigation it was found that the patient claimed to have taken high amounts of noni fruit. Although the relationship between the use of noni juice and bleeding has not been established, the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) took a decision to alert medical professionals to be on the look-out for any unusual cases of bleeding which could possibly be associated with the use of products containing noni extracts.

MISOPROSTOL (CYTOTEC): "OFF-LABEL USAGE"
Upon the advice of the DCA, Pharmacia Corp (M) has issued a "Dear Doctor" letter advising against the off-label use of intravaginal/oral misoprostol in pregnant women for the induction of labour as the safety has not been established. However, in the US, the off-label use of misoprostol for the induction of labour has been allowed and is approved for use in combination with mifepristone to induce abortion in pregnancies of = 49 days.

PURE RED CELL APLASIA: SUSPECTED ASSOCIATION WITH EPOETIN ALFA (EPREX)
Pure red-cell aplasia (PRCA), a selective failure of the erythroid elements in bone marrow resulting in a normochromic, normocytic anemia, has been reported to be associated with the use of a recombinant human erythropoietin (rHuEPO). The mechanism underlying PRCA is not well understood. The anemia in patients with rHuEPO-induced PRCA is much more severe than the anemia in patients with renal failure that prompted the rHuEPO therapy. In addition, most patients with rHuEPO-induced PRCA become permanently transfusion dependent and may be resistant to other rHuEPO products.

In Malaysia, MADRAC has to date received one report on PRCA where a patient received Eprex starting February 2000 and two months later, the patient was found to have red cell hypoplasia on bone marrow biopsy. The patient had to undergo blood transfusion for the treatment.

The product registration holder, Janssen Cilag has informed all prescribers on the issue of PRCA and has made the necessary arrangements to follow up each patient who has been confirmed to have PRCA by bone marrow testing.

INDOMETHACIN-INDUCED RECTOVAGINAL FISTULA IN A POSTPARTUM PATIENT
Indomethacin suppositories are commonly used for the relief of musculoskeletal pain in patients with concomitant peptic ulcer disease to alleviate local gastrointestinal irritation. The use of inhibitors of prostaglandin synthesis such as nonsteroidal anti-inflammatory drugs (NSAID) locally to suppress labour is uncommon.
The first case of indomethacin-induced rectovaginal fistula (RVF) complicated by fecal incontinence has been described in a postpartum patient after the use of indomethacin suppository per vaginum for suppression of labour by Malaysian doctors.
A 39 year old female at 30 weeks' gestation presented with preterm labour associated with Escherichia coli septicemia, because of fetal distress underwent a caesarean section with an indomethacin suppository given per vaginum preoperatively. Twelve hours after insertion, severe swelling of the labia and posterior vaginal wall was evident. The lesion progressively deteriorated, resulting in a large vaginal ulcer with purulent discharge.
Ten days later, the patient complained of fecal incontinence and fecal discharge per vaginum where examination revealed a large RVF measuring 6cm in diameter and the anal sphincter was noted hypotonic. The vaginal ulcer crater was treated with sitz baths and saline dressings.
At three months, the ulcer crater healed, with partial recovery of the anal sphincter and the patient has been planned for an anal sphincter and RVF repair.

Ref: Abdul Wahid FS, Qureshi A, Cheong SK. Indomethacin-induced rectovaginal fistula in a postpartum patient. Dis Colon Rectum 45(6): 843-844, June 2002.

Malaysian Guidelines for the Reporting and Monitoring of Adverse Drug Reactions
These guidelines have just been developed and address the requirements and procedures for reporting ADRs to the Drug Control Authority by health professionals and product registration holders.
These guidelines are available on the web at the following websites www.bpfk.gov.my or www.madrac.gov.my/madrac
Any comments/queries to these guidelines can be forwarded to the Head, Surveillance and Pharmacovigilance Division, National Pharmaceutical Control Bureau or through e-mail to ah@bpfk.gov.my

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A Brief Report on the Role of the Clinical Trials Regulatory Unit of the National Pharmaceutical Control Bureau, Ministry of Health, Malaysia

Introduction

Over the past few years, the Clinical Trials Regulatory (CTR) Unit, which is a sub-unit of the New Chemical Entity (NCE) Unit of the National Pharmaceutical Control Bureau (NPCB) has played an important role in propagating clinical trials in Malaysia. As secretariat to the National Clinical Research Committee (NCRC), the CTR unit has been involved in organizing and executing all the main activities planned by the NCRC.

Activities of the CTR Unit

The main activities are:-
· to ensure that investigational products (IP) are of quality and safe for participants of clinical trials before the clinical trials import license (CTIL) is issued.

· to ensure that the application of CTIL is in compliance with the current guidelines and regulations in Malaysia.

Amongst other activities carried out by the CTR unit in an effort to facilitate and promote clinical trials in Malaysia are:-

i) Development of Guidelines

Several sub-committees were formed to formulate guidelines. The guidelines include those listed below:

a) Malaysian Guidelines for Good Clinical Practice (GCP) (1999).
b) Guidelines for Application to Conduct Drug-Related Clinical Trials in Malaysia (1999).
c) Malaysian Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (2000).
d) Guidelines for Application of Clinical Trials Import Licence and Permit in Malaysia (2000).

ii) Organize seminars, workshops and conferences

The CTR unit was involved in helping to organize several training activities such as:-

a) Good Clinical Practice (GCP) workshops (5 workshops in the year 2000/2001).
b) Asia-Pacific Clinical Trials Conference in the year 2001.
c) Good Laboratory Practice (GLP) seminar/workshop (2 in the year 2000/2001).

iii) Improvement of CTIL processes.

The CTR unit has re-evaluated and reformed the processes involved (Refer to Figure 1). Currently, the timeline is shortened (4-8 weeks) and the requirements are streamlined. Consequently, the applications to perform clinical trials in Malaysia has increased in recent years (Refer to Figure 2).

Future Plans

The CTR unit of NPCB is planning several other activities in an effort to further promote clinical trials especially in new areas such as herbal and biotechnology research, as well as to make Malaysia one of the attractive sites for clinical trials in the Asia-Pacific region. Activities which have been planned are as follows:-

a) The development of GCP inspection program. This program will involve inspection of the infrastructure (facilities and sites) as well as compliance with GCP and GLP requirements.

b) Guidelines for Clinical Research on Herbal and Biotechnological Products in terms of quality and safety requirements.

c) Updates on serious adverse events reporting and monitoring with required databases.

d) Further strengthening of the CTR unit.

Conclusion

With the current efforts made in improving the infrastructure, the conduct of clinical trials, as well as the regulatory guidelines and legislation, we hope to attract more quality clinical trials into Malaysia.

Further information pertaining to the application of clinical trial import licence can be obtained / downloaded from the NPCB website (http: // www.bpfk.gov.my)

Slimming Products Found To Be Adulterated

Who would have thought that herbal slimming products could actually lead to death? The questions "Do natural remedies work? How safe are the herbal products?" frequently cross our minds but never would we for a moment think that unscrupulous traders would adulterate herbal remedies with Fenfluramine, which was withdrawn by the Drug Control Authority in 1997 following reports of cardiac valvular problems.

The recent scare started in April in Singapore with the shocking discovery of Fenfluramine in SLIM 10, a Chinese traditional medicine available in Singapore but not registered with the Drug Control Authority of Malaysia. This adulterated product has been linked to one death in Singapore, while in Japan, a similar product was reported to have claimed several lives. The deaths were due to liver toxicity believed to be caused by the adulterant.

Surveillance has been conducted by the National Pharmaceutical Control Bureau on registered traditional medicines indicated for slimming to detect adulteration with active pharmaceutical ingredients such as Fenfluramine, Phentermine and Sibutramine. Thus far, 28 products have been confirmed to be free from adulteration with these ingredients.

However, five (5) products tested were found to contain adulterants. The products identified were:
i. Bestrim - adulterated with Fenfluramine, Nicotinamide and Caffeine.
ii. FB Slymer - adulterated with Fenfluramine
iii. Jian Tze Soh Fu Tea - adulterated with the banned herb Magnolia officinalis. This ingredient is known to cause kidney failure.
iv. Biotrim - adulterated with Sibutramine.
v. FB Capsule - adulterated with Sibutramine.

The registration of these products have been cancelled in Malaysia and the product registration owners instructed to withdraw these products from the market.
On a similar note, the US FDA released a press statement on 13 August 2002 warning the nation to avoid two Chinese diet pills, Chasu Jianfei Diet Capsules and Chasu Gempi, which apparently contained Fenfluramine and hence posed a potential public health risk.

SOURCES OF PRODUCTS REGISTERED WITH DCA AS AT AUGUST 2002

COUNTRY	NUMBER OF REGISTERED PRODUCTS				
	POISONS	NON POISONS	TRADITIONAL MEDICINES	COSMETICS	TOTAL
SOUTH AFRICA	18	5	1	0	24
AUSTRALIA	500	520	363	152	1535
AUSTRIA	58	11	2	0	71
BANGLADESH	0	1	0	0	1
BELGIUM	206	25	8	78	317
BULGARIA	0	0	1	0	1
CANADA	200	54	20	51	325
CHINA	8	17	2375	0	2400
CHILE	5	0	0	0	5
CYPRUS	153	18	0	0	171
CZECH REPUBLIC	16	0	0	0	16
DENMARK	155	22	0	0	177
EGYPT	0	8	3	0	11
ENGLAND	556	329	19	26	930
FINLAND	59	7	2	0	68
FRANCE	302	96	21	0	419
GERMANY	227	102	17	267	613
WEST GERMANY (FRG)	326	142	13	93	574
GREECE	17	3	0	0	20
HONG KONG	0	5	24	0	29
HUNGARY	74	17	0	0	91
ICELAND	0	2	0	0	2
INDIA	281	85	228	8	602
INDONESIA	112	123	391	227	853
IRELAND	121	64	0	0	185
ITALY	200	52	3	126	381
JORDAN	21	0	4	0	25
JAPAN	89	78	14	38	219
KOREA, SOUTH	148	34	30	0	212
MALAYSIA	2816	3205	5425	281	11727
MEXICO	4	2	0	0	6
MONACO	0	1	0	0	1
NETHERLAND/HOLLAND	97	29	2	5	133
NEW ZEALAND	46	9	27	0	82
NORWAY	7	15	0	0	22
PAKISTAN	2	4	0	0	6
PHILIPINES	36	52	1	0	89
POLAND	0	2	0	0	2
PORTUGAL	17	5	0	0	22
PUERTO RICO	15	1	0	0	16
SCOTLAND	4	6	0	0	10
SINGAPORE	144	117	14	0	275
SLOVENIA	15	0	0	0	15
SLOVAK REPUBLIC	2	0	0	0	2
SPAIN	82	15	0	105	202
SRI LANKA	0	0	6	0	6
SWEDEN	113	38	22	0	173
SWITZERLAND	355	83	9	0	447
TAIWAN	89	27	131	0	247
THAILAND	281	285	7	62	635
TURKEY	12	3	0	0	15
UNITED KINGDOM	79	8	0	0	87
U.S. OF AMERICA	429	538	521	119	1607
YUGOSLAVIA	35	5	0	0	40
TOTAL REGISTERED	**8532**	**6270**	**9704**	**1638**	**26144**

Visit by Dr. Budiono Santoso, Regional Adviser in Pharmaceuticals, WHO Regional Office for the Western Pacific

On 10th July 2002, Dr. Budiono Santoso, Regional Adviser in Pharmaceuticals, WHO Regional Office for the Western Pacific, Manila, Phillipines, visited the National Pharmaceutical Control Bureau (NPCB) which has been designated as the WHO Collaborating Centre for the Regulatory Control of Pharmaceuticals since 1996.

The terms of reference for his visit were:-

(i) To learn various programme activities undertaken by the NPCB as the WHO Collaborating Centre;
(ii) To review collaborative activities with WHO; and
(iii) To explore other areas of collaboration.

On hand to receive Dr. Budiono was Mdm. Hasiah Abdullah, Deputy Director of NPCB and several senior officers from various divisions of this Institution. Dr. Budiono was briefed on the organizational set-up of the NPCB, its functions, activities and achievements, the training of WHO Fellows and various aspects of regulatory control such as on-line registration of cosmetics. Following the briefing, a discussion was held on ways to strengthen the collaboration between NPCB and WHO.

In his closing remarks, Dr. Budiono noted that NPCB has indeed attained remarkable achievements, which, among others were:-

(i) The launching of the Online Cosmetics Registration effective February 2002;
(ii) The development and use of drug regulatory software;
(iii) The implementation of the recently updated Guidelines for Application of Clinical Trials Import Licence and Permit in Malaysia; and
(iv) NPCB becoming a member of the Pharmaceutical Inspection Cooperation (PIC/S), which implies that the GMP certification issued by NPCB is internationally recognized by the members of PIC/S.

Dr. Budiono pointed out that there are many areas that other countries may learn from NPCB to strengthen their drug regulatory control.