Advisory on the use of cough and cold medicines in children

In view of concerns raised on the recent recall in the United States of over-the-counter cough and cold products marketed for infants and toddlers, and the ensuing recommendations from the public advisory committee meeting convened by the US Food & Drug Administration (FDA) on the safe use of these medicines in young children, HSA has provided an interim advisory to healthcare professionals on the appropriate use of these products while we continue to review the scientific data. These recommendations were included in the Dear Healthcare Professional Letter issued on 30 October 2007 and posted at the MOH Health Professional portal at http://www.hpp.moh.gov.sg.

Table 1: Interim recommendations on use of cough and cold medicines in various age groups of children

<table>
<thead>
<tr>
<th>Category / Drug</th>
<th>Under 6 months</th>
<th>6 months to 2 years</th>
<th>2 years &amp; above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines¹</td>
<td>Not recommended</td>
<td>Use only when benefits have been assessed to outweigh risks</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Cough suppressants²</td>
<td>Not recommended</td>
<td>Use only when benefits have been assessed to outweigh risks</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Cold and flu products³</td>
<td>Not recommended</td>
<td>Use only when benefits have been assessed to outweigh risks</td>
<td>Use with caution</td>
</tr>
</tbody>
</table>

Active ingredients discussed during the meeting between US FDA and its expert panel for which adverse event reports were analysed:
1. Brompheniramine, chlorpheniramine, diphenhydramine
2. Codeine, dextromethorphan, diphenhydramine
3. Ephedrine, guaifenesin, phenylephrine, pseudoephedrine

Background

The recent recall in the US in October 2007 involved 14 brands of cough and cold preparations (containing antihistamines and decongestants) targeted for infants and very young children. They were voluntarily recalled by drug companies due to the danger of overdosage and misuse in this group of patients. Examples of such products are Concentrated Infants' Tylenol Drops Plus Cold & Cough, Dimetapp Decongestant Plus Cough Infant Drops, and Decongestant Infant Drops.

HSA confirms that these products are not licensed for sale or use in Singapore.

The US FDA also convened an expert advisory committee in October to deliberate on the efficacy and safety of cough and cold products when used in children under six years of age. In view of the lack of efficacy data in young children balanced against the occurrences of rare but serious adverse drug reactions (ADRs) associated with the use of these products, the expert panel recommended stronger cautionary labels on these products and not to use them in children under six years old. FDA will deliberate on the panel’s recommendations before coming to a conclusion on this issue.

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GlaxoSmithKline (GSK) has issued a Dear Healthcare Professional Letter to alert our healthcare professionals on reports of myocardial ischaemia associated with the use of salbutamol (Ventolin®) as a tocolytic agent. GSK also advised healthcare professionals to exercise caution when using salbutamol for premature labour, to carefully monitor patient’s cardiovascular function including ECG, and to discontinue the drug if signs of myocardial ischaemia develop.

### Background
Salbutamol, a selective beta2-adrenoreceptor agonist, is available in several dosage forms with varied uses. Parenteral preparations of salbutamol are registered for the management of uncomplicated premature labour in the last trimester of pregnancy though it is known that salbutamol tablets may sometimes be used for this purpose.

The advice by GSK follows a company-initiated review of the available data from published literature, clinical trials and spontaneous reports of myocardial ischaemia in association with salbutamol. The review found eight spontaneously reported cases in the company database and nine reports in published literature, suggestive of a causal association with myocardial ischaemia when salbutamol was given for the treatment of premature labour.

### Summary of spontaneous reports and literature
The reported events included myocardial ischaemia, myocardial infarction, chest pain and ECG abnormalities indicative of myocardial ischaemia. All the events were reported with the use of intravenous salbutamol except one which was reported with the use of salbutamol tablets. Five cases required hospitalisation and one was considered life-threatening.

The time to onset ranged between 1.5 hours to 4 days with most of the cases occurring within the same day as treatment initiation. No significant pre-disposing factors could be identified for the development of ischaemic events besides preterm labour. In four of the cases, it was specifically stated that the patients had no known risk factors. One patient had a paternal history of cardiovascular disease while another had a possible pre-existing coronary vascular occlusion.

About half of the cases reported a positive dechallenge on salbutamol discontinuation. One case documented ST depression on the re-introduction of salbutamol one year after the first incident of myocardial ischaemia. However, most of the cases did not provide information on rechallenge. Where specified in the reports, actions taken after the occurrence of the adverse event include the discontinuation of salbutamol and treatment with nifedipine, heparin, aspirin, nitroglycerin and verapamil.

### Conclusions and recommendations
Although the effects of sympathomimetics may be exaggerated in preterm labour due to high background sympathetic drive, hyperventilation, dehydration and haemodilution through the use of intravenous fluids, the association between myocardial ischaemia with salbutamol use in preterm labour cannot be ruled out as the reported cases were well-documented and contained no significant pre-disposing factors for the development of ischaemic events other than preterm labour.

To date, HSA has not received any spontaneous local ADR report of myocardial ischaemia associated with the use of salbutamol in preterm labour. Nevertheless, healthcare professionals are advised to be cautious when using salbutamol for this purpose, and to report any serious adverse reactions suspected to be due to its use in pregnancy to the Pharmacovigilance Unit of HSA. The local package inserts of parenteral and oral Ventolin® products has been updated to include this new safety information.

### Review of data by US FDA
A review of the adverse reports from the US FDA associated with the antihistamines (diphenhydramine, brompheniramine and chlorpheniramine), and the decongestants (pseudoephedrine, phenylephrine, and ephedrine) over 1969–2006 revealed that most of the ADRs occurred in children under two years old and overdosage and drug toxicities were the common causes. A further analysis of the adverse events associated with pseudoephedrine, chlorpheniramine, diphenhydramine and dextromethorphan from 2002–2007 showed that serious events and deaths related to the nervous system (e.g. seizures), cardiac and respiratory system were associated with both overdoses as well as labeled doses of cough and cold medicines. There is also a potential risk of overdose when using multiple cough and cold products.

### Local situation
HSA has not received any local reports of fatal adverse drug reactions associated with cough and cold medicines. However, taking into consideration the findings by US FDA and the lack of efficacy data of cough and cold medicines used in children, HSA has provided healthcare professionals with an interim advisory on the use of cough and cold medicines in young children. This advisory takes into consideration guidelines developed by other regulatory agencies, and the previous review conducted by HSA and its Pharmacovigilance Advisory Committee in 2005 on the use of promethazine in children under two years of age.

### References

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**Association of salbutamol and myocardial ischaemia in premature labour**
A rising from the emerging concerns associated with gadolinium-based contrast agents (GBCAs) and the potential increased risk of nephrogenic fibrosing dermopathy (NFD) and nephrogenic systemic fibrosis (NSF), the Health Sciences Authority (HSA) and its Pharmacovigilance Advisory Committee have reviewed the safety profile and use of these products, particularly in patients with renal dysfunction.

**Brief overview**

Gadolinium-based contrast agents (GBCAs) are approved by HSA for use in magnetic resonance imaging (MRI). Seven GBCAs are registered in Singapore: gadodiamide (Omniscan®, GE Healthcare), gadopentetate dimeglumine (Magnevist®, Bayer Schering Pharma), gadoterate meglumine (Dotarem®, Guerbet), gadobutrol (Gadovist®, Bayer Schering Pharma), gadobenate dimeglumine (Multihance®, IDS Pharmaceutical Division), gadoversetamide (Optimark®, Tyco Healthcare) and gadoxetic acid (Primovist®, Bayer Schering Pharma).

HSA has been closely monitoring the association of NFD/NSF with these contrast agents since May 2006, following the first alert by GE Healthcare on NFD/NSF reported with the use of Omniscan® in patients with severe renal impairment. An article was published in July 2006 issue of the Adverse Drug Reaction News Bulletin to alert healthcare professionals of these adverse reactions.

Following the first alert on Omniscan®, more global reports of NFD/NSF were subsequently received for Omniscan® (more than 150 cases), as well as Magnevist® (78 cases) and Optimark® (11 cases). More recently, isolated cases associated with other GBCAs were also reported. All these reports occurred only in patients with renal dysfunction and is associated with swelling and tightening of the skin in the extremities which may develop over a period of days to several weeks. The mechanism by which a GBCA can cause NFD/NSF has not been elucidated but the current understanding is that GBCAs are associated with different levels of NFD/NSF risk based on their physicochemical and pharmacokinetic properties.

HSA has issued a Dear Healthcare Professional Letter (DHCPL) in December 2007 to all registered physicians to alert them to the above safety information, as well as advise on appropriate use of these drugs. For details of the DHCPL, please log on to the MOH Health Professionals Portal at http://www.hpp.moh.gov.sg.

**Summary of recommendations**

- Use of Omniscan® or Magnevist® is contraindicated in patients with severe renal failure (GFR < 30mL/min/1.72m²).
- The risk for the development of NFD/NSF in patients with moderate renal impairment is unknown, therefore Omniscan® and Magnevist® should be used with caution in patients with moderate renal impairment (GFR 30–59mL/min/1.73m²), especially if any gadolinium-based contrast media have been previously administered.
- Omniscan® and Magnevist® should be used in neonates and infants only if the benefits outweigh the risks as these patients have immature kidney functions.
- The other GBCAs should be used in patients with severe renal impairment (GFR < 30mL/min) only when absolutely necessary where the benefits outweigh their risks. Any possible alternative imaging tests that do not require GBCA, the clinical need for GBCA use, the relative risk for the patient, the type of agent to be used and any history of prior GBCA exposure should be considered when using the other GBCAs in severe renal impaired patients.
- There is no robust evidence to show that haemodialysis can prevent or treat the development of NFD/NSF, but haemodialysis shortly after GBCA administration in patients currently receiving haemodialysis may be useful in removing the agent from the body, and there is some preliminary evidence that suggests NFD/NSF is less likely to develop in patients receiving early and adequate haemodialysis. If it is to be performed, the US and European authorities have recommended that at least two episodes of haemodialysis, the first commencing within 24 hours of administration of GBCA, performed in patients at risk who receive any of the GBCAs.
Risk of torsade de pointes and QT prolongation with haloperidol

Haloperidol is a butyrophenone antipsychotic agent and its indications include the management of psychoses, schizophrenia and manic states and management of aggressive and agitated behavior. Haloperidol injection has been registered in Singapore since 1994 and is licensed only for intramuscular administration.

Recent safety alert issued by the US FDA

The US Food and Drug Administration (FDA) has recently issued a safety alert which highlights the potential increased risk of QT prolongation and torsade de pointes (TdP) with the use of intravenous (IV) administration of haloperidol.

Although injectable haloperidol is approved by the FDA only to be used as an intramuscular injection, there is considerable evidence from the medical literature that IV haloperidol is a relatively common ‘off-label’ clinical practice, primarily to treat cases of severe agitation in intensive care units.

There are at least 28 case reports of QT prolongation and TdP in the medical literature, some with fatal outcome in the context of off-label IV administration of haloperidol. Additionally, case control studies performed have demonstrated a dose-response relationship between intravenous haloperidol dosing and subsequent TdP.

Johnson & Johnson (sponsor of the proprietary brand of haloperidol, Haldol® in the US) recently conducted two post-marketing studies analysing QT prolongation and TdP with the administration of haloperidol (both oral and injectable). In the first study, Johnson & Johnson performed a search of their Benefit Risk Management worldwide safety database. The results revealed 73 cases of TdP, of which 11 of these cases led to fatalities. Eight of these fatalities involved the IV administration of haloperidol. The second study involved a post-marketing investigation that examined reports of cardiac events that involved haloperidol received by the company as of 30 July 2005. Thirteen of these haloperidol related cardiac events reported involved the occurrence of TdP, QT prolongation, ventricular arrhythmia and/or sudden death.

Label amendments in the US

Based on these recent findings, the labelling of Haldol® products in the US were revised to include the following warnings:

- Higher doses and IV administration of haloperidol appear to be associated with a higher risk of QT prolongation and TdP.
- Although cases of sudden death, TdP and QT prolongation have been reported even in the absence of predisposing factors, particular caution is advised in treating patients using any formulation of haloperidol who:
  - have other QT prolonging conditions, including electrolyte imbalance (particularly hypokalaemia and hypomagnesemia),
  - have underlying cardiac abnormalities, hypothyroidism, or familial long QT syndrome, or
  - are taking drugs known to prolong the QT interval.
- Because of this risk of TdP and QT prolongation, ECG monitoring is recommended if haloperidol is given intravenously.

Additionally, Johnson & Johnson’s recent amendments to Haldol®’s labelling now include that Haldol® is not approved for intravenous administration.

Conclusion

HSA has not received any local reports of prolonged QTc or TdP involving the use of haloperidol, and will continue to monitor the situation. The FDA, in its safety update, stated that based on case reports alone, it was unable to estimate the frequency with which QT prolongation or TdP occur following administration of haloperidol and will continue to monitor post-marketing reports for such adverse events and further regulatory actions and communications will be effected as additional information becomes available.

It advised that healthcare professionals should take into consideration the above new safety information when making individual treatment decisions for their patients.

References

The Pharmacovigilance Unit, HSA has received reports of adverse reactions resulting from use of adulterated cosmetic products. The cases below relate to the experience of some patients.

Local case reports

The cosmetic product, Beauty Express® Miracle Pigmentation Scar Cream was tested by HSA to contain betamethasone dipropionate 0.023%, a potent steroid, following reports of adverse drug reactions to the product. A few female patients who purchased the product from a retail shop in Singapore as skin whitener for skin pigmentation developed rashes, redness and skin sensitivity on their face after using the creams for several years. These patients became very dependent on the cream and suffered flares of skin redness and soreness whenever they stopped application of the creams. Clinically, the rashes on their face were very suggestive of “steroid facies” as the skin on their face were red and atrophied with surface telangiectasia. The reporting physician suspected steroid facies and symptoms of steroid withdrawal syndrome when they stopped using the cream. Steroid facies is caused by prolonged use of fluorinated topical steroids on the face. Other side effects of topical fluorinated steroids on the face include perioral and periorbital dermatitis (which manifest as aceneiform eruptions around the mouth and eyes).

Betamethasone dipropionate is a very potent corticosteroid as compared to other topical corticosteroids such as hydrocortisone and betamethasone valerate. It can result in Cushing’s syndrome, skin atrophy and hyperglycaemia. Prolonged and widespread use may also result in reversible hypothalamic-pituitary-adrenal (HPA) axis suppression.

The local company marketing Beauty Express® Miracle Pigmentation Scar Cream was prosecuted by HSA for adulterating the product with betamethasone dipropionate.

When diagnosing an adverse reaction in patients, healthcare professionals are encouraged to take a detailed medical history which may take into consideration the patient’s use of cosmetic products.
1. **Adefovir (Hepsera®, GSK)** Caution: Elderly. Warning: Lactic acidosis (in the absence of hypoxemia), sometimes fatal, usually associated with severe hepato- and hepatic steatosis may occur, hence treatment with nucleoside analogues should be continued whenever serum aminotransferase levels, progressive hepato- or metabolic lactic acidosis of unknown etiology occur & caution should be exercised when prescribing nucleoside analogues to any patient (particularly obese women) with hypothyroidism, or other pre-existing liver disease. New ADRs: Vomiting, mild to moderate increases in serum creatinine levels, hypophosphatemia & a decrease in carnitine concentrations.

2. **Alendronate (Fosamax®, MSD)** Cautions: Discontinuation should be considered in patients with a history of peptic ulcer of jaw (ONJ) or other conditions that impair bone turnover. Contraindication: Elderly. Warning: Cardiogenic & congestive heart failure reported. Cautions: Patients with known or suspected heart disease. Pre-treatment cardiovascular examination (echocardiography, electrocardiogram) & continued monitoring of CV function is recommended. Not recommended in patients with elevated transaminases (>5 times ULN). Concomitant use with other PDE III inhibitors such as miremiline, amrinone, enalapril, lisinopril, cilazapril, & felodipine is not recommended. Patients treated with the benefits of concomitant use of anagrelide with acetylsalicylic acid in patients with a platelet count >1500 x 10^9/L &/or a history of haemorrhage should be assessed before starting treatment. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not be given anagrelide.

3. **Anagrelide (Agrylin®, IDS)** Elderly patients had twice the incidence of serious adverse events, mainly cardiac-related events. Contraindication: Moderate/severe hepatic impairment or moderate/severe renal impairment (CrCl <50ml/min). Potential risks & benefits of anagrelide therapy in patients with mild hepatic impairment should be assessed before treatment is started. Warning: Cardiogenic & congestive heart failure reported. Cautions: Patients with known or suspected heart disease. Pre-treatment cardiovascular examination (echocardiography, electrocardiogram) & continued monitoring of CV function is recommended. Not recommended in patients with elevated transaminases (>5 times ULN). Concomitant use with other PDE III inhibitors such as miremiline, amrinone, enalapril, lisinopril, cilazapril, & felodipine is not recommended. Patients treated with the benefits of concomitant use of anagrelide with acetylsalicylic acid in patients with a platelet count >1500 x 10^9/L &/or a history of haemorrhage should be assessed before starting treatment. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not be given anagrelide.

4. **Baclofen (Lioresal®, Novartis)** Signs & symptoms of overdosage have been reported with doses ≥5mg/day in patients undergoing chronic haemodialysis as baclofen concentrations in plasma are elevated. Cautions: i) Patients such as those with impaired renal &/or hepatic function &/or Parkinson's disease. ii) Discontinuation of overdosage as lowering of convulsion threshold may occur & seizures have occasionally been reported; iii) Abruption when combined with anticonvulsant drugs. Clinical characteristics of withdrawal of intrathecal Lioresal® may resemble autonomic dysreflexia, infection (sepsis), malignant hyperthermia, neuroleptic malignant syndrome, or other conditions associated with a hypermetabolic state or widespread rhabdomyolysis. Drug interactions: Synthetic opiates, alcohol, morphine & levodopa. Careful monitoring of respiratory & cardiovascular functions is essential, especially cardiopulmonary disease & respiratory muscle weakness. ADRs: Hypotension, paresthesia & erectile dysfunction.

5. **Cabergoline (Dostinex®, Pfizer)** Warnings: Chest x-ray is recommended when assessing the risk of severe osteoporosis or osteoporotic fractures. Contraindication: Moderate/severe hepatic impairment or moderate/severe renal impairment (CrCl <50ml/min). Potential risks & benefits of anagrelide therapy in patients with mild hepatic impairment should be assessed before treatment is started. Warning: Cardiogenic & congestive heart failure reported. Cautions: Patients with known or suspected heart disease. Pre-treatment cardiovascular examination (echocardiography, electrocardiogram) & continued monitoring of CV function is recommended. Not recommended in patients with elevated transaminases (>5 times ULN). Concomitant use with other PDE III inhibitors such as miremiline, amrinone, enalapril, lisinopril, cilazapril, & felodipine is not recommended. Patients treated with the benefits of concomitant use of anagrelide with acetylsalicylic acid in patients with a platelet count >1500 x 10^9/L &/or a history of haemorrhage should be assessed before starting treatment. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not be given anagrelide.

6. **Carbogine (Dostinex®, Pfizer)** Cautions: Elderly. Warning: Cardiogenic & congestive heart failure reported. Cautions: Patients with known or suspected heart disease. Pre-treatment cardiovascular examination (echocardiography, electrocardiogram) & continued monitoring of CV function is recommended. Not recommended in patients with elevated transaminases (>5 times ULN). Concomitant use with other PDE III inhibitors such as miremiline, amrinone, enalapril, lisinopril, cilazapril, & felodipine is not recommended. Patients treated with the benefits of concomitant use of anagrelide with acetylsalicylic acid in patients with a platelet count >1500 x 10^9/L &/or a history of haemorrhage should be assessed before starting treatment. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not be given anagrelide.

7. **Clobetasol (Univate®, Apex Pharmacy)** Contraindication: Treatment of dermatoses, peri-anal & genital pruritus in children <1yr, including dermatitis & nappy eruption. Severe ADRs are likely to happen if adenosine 5'-monophosphate or more frequent application is used.

8. **Clocetasol (Univate®, Apex Pharmacy)** Contraindication: Treatment of dermatoses, peri-anal & genital pruritus in children <1yr, including dermatitis & nappy eruption. Severe ADRs are likely to happen if adenosine 5'-monophosphate or more frequent application is used.

9. **Clobetasol (Univate®, Apex Pharmacy)** Contraindication: Treatment of dermatoses, peri-anal & genital pruritus in children <1yr, including dermatitis & nappy eruption. Severe ADRs are likely to happen if adenosine 5'-monophosphate or more frequent application is used.
Voluntary withdrawal of clobutinol (Silomat®) cough syrup

Clobutinol (Silomat®, Boehringer Ingelheim) was licensed in Singapore in 1999. It is an orally active non-opioid antussive agent, and is indicated for the treatment of irritative, non-productive cough and inflammatory disorders of the airways.

In September 2007, Boehringer Ingelheim voluntarily withdrew Silomat® from the Singapore market as a precautionary measure due to concerns of a potential increased risk of cardiac arrhythmias that could be associated with the active ingredient.

Published experimental data have indicated the potential of clobutinol affecting the hERG (human ether-a-go-go related gene) potassium channels. Preliminary findings from a recent clinical trial with clobutinol in adult healthy volunteers have shown a prolongation of the QTc interval in the ECG. As clobutinol is indicated for a non-serious disease condition and in view of the potentially life-threatening adverse effects, HSA agreed with the actions of Boehringer Ingelheim to withdraw clobutinol from the worldwide market. A Dear Healthcare Professional Letter (DHCPPL) was issued by the company to alert healthcare professionals to the findings and the decision to recall and suspend the sales of Silomat®. For details of the DHCPPL, please log on to the Health Professionals Portal at http://www.hpp.moh.gov.sg.
Protaminin (Trasylol®, Bayer HealthCare) is an antifibrinolytic agent used to reduce blood loss and the need for blood transfusion in adult patients at risk of blood loss who are undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery. It has been registered in Singapore since 1994.

Recent safety findings

Recent findings have raised concerns regarding the safety issues associated with the use of aprotinin in cardiac surgery. Earlier observational studies have suggested that aprotinin may increase the risk of mortality when compared against other antifibrinolytic agents. The latest Canadian study, BART (Blood conservation using antifibrinolytics: A randomized trial in high risk cardiac surgery patients), a trial comparing the safety and efficacy of aprotinin (2 million units bolus + 2 million units in pump prime + 2 million units via infusion over 4 hours) against epsilon-aminocaproic acid (10g bolus + 250 mL NaCl in pump prime + 2g/hr infusion) or tranexamic acid (30mg/kg bolus + 2mg/kg/hr in pump prime + 16mg/kg/hr infusion) suggested an increase in all-cause mortality among patients in the aprotinin arm of the study compared to the other two drugs: the 30 days mortality of aprotinin compared to the two drugs were relative risks of 1.5 at p=0.06 and p=0.08. Although statistical significance was not reached, a trend towards an increase in mortality in the aprotinin-treated group was present throughout most of the trial.

International measures

As a result of the findings of the BART study, and in consultation with the German Federal Institute for Drugs and Medical Devices (BfArM), the US Food and Drug Administration (FDA), Health Canada and other regulatory authorities, Bayer HealthCare® decided to temporarily suspend the worldwide sales of Trasylol® until the final data from the study can be compiled and evaluated.

HSA’s action and advisory

In consultation with the Health Sciences Authority (HSA), the sales of Trasylol® was temporarily suspended in Singapore on 6 November 2007 pending further evaluation of information from the BART study. A final regulatory decision on Trasylol® will be made in due course and healthcare professionals will be informed accordingly.

As an interim measure, HSA has worked with Bayer to allow supply of Trasylol® through restricted access under certain conditions, to a small group of patients who have been assessed by their physicians to have no other therapeutic options, and where the benefits of the drug may outweigh its risks. Physicians are required to discuss the risks associated with using Trasylol® and obtain written consent from either the patient or the next of kin should the patient be incapable or incompetent in doing so before prescribing Trasylol®.

References