

## CLASSIFICATION OF SEDATING ANTIHISTAMINES

### TASK

To examine the safety of sedating antihistamines and produce a report suggesting the most appropriate schedule for both combination and single ingredient formulations of sedating antihistamines marketed in NZ.

### BACKGROUND

Allergic conditions affect about 20-30% of individuals. A survey of hay fever sufferers found, that 54% were self medicating with over the counter preparations and one third of these patients had experienced drowsiness because of their therapy. Antihistamines are one of the options for the symptomatic treatment of allergic disorders such as seasonal and perennial allergic rhinitis and chronic urticaria. However, the use of traditional antihistamines such as diphenhydramine, chlorpheniramine, triprolidine and promethazine is often associated with a number of adverse effects, of which sedation is the most pronounced. These adverse effects can interfere with the performance of daytime activities and place the patient at risk of accidents in situations such as driving and operation of machinery. Drivers killed in car accidents due to their own error were found 1.5x more likely to have used a first generation antihistamine than other drivers, who died in MVAs and who were not found responsible for the accident.

Clinical trials have demonstrated, that as a group, the second generation antihistamines have a much more favourable therapeutic index and a significantly lower incidence of sedative effects than their predecessors. Unlike the classical antihistamines, many of the newer agents have a greater affinity for the H<sub>1</sub> receptor but do not readily cross the blood brain barrier and are thus relatively devoid of undesirable central effects such as sedation, fatigue, etc. However there are differences between the individual newer antihistamines.

### METHODS OF ASSESSING SEDATION

#### **What is sedation**

Sedation reflects the (measurable) impairment of superior cognitive functions such as attention, memory, coordination and psychomotor performance, which can severely impair daytime activities such as school performance, car driving ability and many other tasks, where concentration and a high degree of alertness and skill are required.

#### **How can we reliably measure the sedative effect of a new drug**

A large number of trials with an even larger number of tests have been carried out to assess the sedative effect of the newer H<sub>1</sub> antagonists. However, many of these tests lack validity and the results are not reproducible. In a study, that involves only the test drug and placebo, data showing no change in test scores may indicate either that the drug does not produce impairment, or that the tests lacked sufficient sensitivity to detect the impairment. Inclusion of a positive control guarantees the sensitivity of the test battery. The positive control should be an antihistamine known to cause impairment, given at the lowest dose that will produce changes in test scores. It is important to recognise, that the purpose of the inclusion of the positive control is not to draw direct comparisons with the test drug. The study drug should be compared to placebo and the positive control should be used to ensure the sensitivity of the psychometric assessment in that study.

Several methods are available to evaluate whether an antihistamine produces sedation:

A) Subjective assessment

Subjective reporting of sedation is not a particularly reliable measure. Antihistamines may alter the awareness of sleepiness, thus rendering results of subjective assessment scales unreliable.

B) Objective assessment

Standardised objective performance tests are available for assessment of ability to concentrate or react to external stimuli and for evaluation of sensorimotor coordination, reaction time, memory, CNS arousal and information processing. These tests may be influenced by subjects' motivation level, performance strategy, test familiarity, boredom, memory or amount of practice. A school or work environment can be simulated and simulated driving tests have proved useful. Objective tests using EEG monitoring have the advantage that they are not influenced by subjects' intelligence, motivation, practice or boredom, although they may be influenced by physiological factors such as hypoglycemia.

The following is a summary table of tests employed to investigate sedation (reproduced from Hindmarch):

**Tests for measures of performance**

A) Psychomotor performance

- A1: Actual car driving
- A2: Simulated car driving
- A3: Simulated car tracking

B) Sensorimotor coordination speed

- B1: Adaptive tracking
- B2: Critical tracking
- B3: Continuous tracking
- B4: Visuomotor coordination
- B5: Choice reaction time
- B6: Simple reaction time
- B7: Reaction time
- B8: Pursuit rotor

C) CNS arousal, information processing

- C1: Critical flicker fusion
- C2: Digit symbol substitution task
- C3: Mental arithmetic
- C4: Letter cancellation
- C5: Stroop colour test
- C6: Logical reasoning
- C7: Visual search task

D) Memory

- D1: Short term memory
- D2: Continuous memory task

E) Sensory skills

- E1: Vigilance task
- E2: Attention task
- E3: Continuous attention task
- E4: Dynamic visual acuity
- E5: Simulated assembly line task

- F) Motor ability
  - F1: Finger tapping
- G) Physiological
  - G1: Electroencephalograph (EEG)
  - G2: Continuous EEG
  - G3: Multiple sleep latency test
  - G4: Evoked potentials
  - G5: Actigraphy
- H) Subjective ratings
  - H1: Visual analogue rating scales
  - H2: Profile of moods scale
  - H3: Stanford sleepiness scale

Of the above listed tests the following tests have been shown to be particularly useful: Tests of car driving feature in many studies and appear to be sensitive to the sedative effect of the antihistamines. It has been suggested, that the ability of the driver to control weaving of the car, measured as the standard deviation of the lateral position, is an indicator of drug induced sedation.

A task, which often features in studies investigating the central effects of the antihistamines, is the critical flicker fusion task (CFF). CFF has consistently demonstrated the reduction in cognitive capacity following traditional antihistamines, as well as detecting changes with newer antihistamines, where other tests have failed to detect impairment.

Choice reaction time is one of the most popular tests of sensory motor performance. The total reaction time is regarded as the sum of two separable components: the stimulus recognition reaction time used as a measure of attentional monitoring and the motor reaction time used as a measure of the efficiency of the response output system. Measurements of CRT provide information on the constant, very rapid adjustments individuals must make to their environment, which require them to attend to several potential stimuli at once. There is a high degree of construct validity inherent in reaction time measures. The sensitivity of the test is highlighted by the fact that it is one of the few tests that detected impairments with antihistamines such as cetirizine.

The P300 test represents the endogenous component of the auditory evoked potential.

The multiple sleep latency test is used throughout the day to provide an objective index of sleepiness.

Use of actigraphy enables the investigator to detect impairments in motor performance throughout the day and overcomes the problems associated with fixed interval testing.

Unfortunately, correlation between subjectively and objectively identified impairment of CNS function is imperfect: some people may be impaired and yet not perceive any problems, and conversely, others may complain of somnolence yet be able to perform psychomotor tests adequately.

## COMMONLY USED ANTIHISTAMINES IN NEW ZEALAND

In the evaluation of the world wide database the following criteria were used to include a study for safety analysis:

Studies, which allow for proper conclusions to be drawn, should have a large power, be double blind, placebo controlled and should ideally include a positive control.

Objective CNS performance tests should be conducted at baseline and over a period long enough to ensure clearance of the drug given. The CNS effects of the drug tested should be measured after single dosing and after repeated dosing, in order to represent either situation. Most studies are conducted on healthy volunteers, which implies that the results can be extrapolated to the group of allergy sufferers. This is probably the case, but it remains to be proven. Patients with CNS disease, who may be more sensitive to the sedative effects of antihistamines, are excluded.

### 1) Triprolidine

#### Preparations:

- Actifed – 1.25mg/5ml elixir or 2.5mg tablets, recommended dose 2.5mg tid-qid
- AllerAct D Day and Night tab

#### Relevant studies include:

- *Kerr et al. (1994)* conducted a double blind, placebo controlled, cross over study on eighteen healthy volunteers comparing single doses of mizolastine, terfenadine 60 mg, triprolidine 10 mg and placebo. The test battery included critical flicker fusion (CFF), choice reaction time, tracking and other objective tests plus subjective assessment tests at 1, 3, 5, 8 and 24 h post dose. Triprolidine caused subjective sedation and reduced the CFF threshold and reaction time to a degree comparable with the effects of blood alcohol concentrations of 50 mg%.
- *Brookhuis et al. (1993)* investigated the effects of a 5-day-administration of either ebastine, triprolidine 10mg or placebo on car driving performance. 15 healthy male volunteers participated in this double blind study, which was designed to test for effects of both acute and repeated administration. Driving performance was tested on day 1 and 5 and showed a significant amount of weaving and delay in following the speed manoeuvres of a leading car in the triprolidine group compared with placebo.
- *Valk et al (1997)* performed a randomised double blind three way cross over study whereby 18 men received either loratadine 10mg, triprolidine 5mg or placebo. Objective tests (vigilance, complex tasks) and subjective tests, tailored to the specific tasks of aircrew were applied under hypobaric conditions. Loratadine and placebo did not cause any impairment of alertness or performance from 1-6 hr after ingestion, whereas triprolidine did.

#### Conclusions:

Triprolidine's sedative effects are well known, so much so, that it features in most studies as positive control for sedation.

Triprolidine administered as a single dose as low as 5mg or as a repeated dose (10mg od for 5 days) has consistently been shown to impair CNS function in objective and subjective psychomotor tests.

Recommendation: It should be classified as a sedating antihistamine.

## 2) Diphenhydramine

### Preparations:

- Ergodryl- 25mg per capsule , dose 1 capsule repeatedly q1/2h max 6 per day
- Benadryl dry cough- 12.5mg per 5ml, dose 10ml=25mg qid
- Panadol Night- 25mg per tablet, dose 2 tablets=50mg nocte

### Relevant studies include:

- *Gengo et al. (1990)* performed a randomised, double blind, placebo controlled, cross over study with 15 healthy volunteers. Single doses of cetirizine (20mg, 10mg and 5mg), diphenhydramine 50mg (positive control) and placebo (negative control) were administered. At 0, 2, 4, 6, 8, and 24 hours after the dose automobile driving simulator performance, digit symbol substitution, trails B maze tracking and subjective feelings of drowsiness were measured. No differences between placebo and any of the three doses of cetirizine could be detected, however, diphenhydramine produced impaired mental performance and drowsiness.
- *Simons et al. (1996)* compared the CNS effects of single doses of six H1 antagonists on 15 healthy subjects. Measures of sedation were the P300 latency test and a subjective somnolence score. Only diphenhydramine increased the P 300 latency significantly compared to baseline and placebo. Subjective somnolence was significantly greater than baseline and placebo after cetirizine, ketotifen and diphenhydramine. The conclusion was that effects on cognitive function differ from the effect of inducing subjective somnolence.
- *Weiler et al.* performed a randomised, double blind, placebo controlled cross over trial with 40 licensed drivers with allergic rhinitis. The comparators included single doses of fexofenadine 60 mg, diphenhydramine 50 mg, alcohol (0.1% blood alcohol concentration) and placebo. The endpoints measured were a) coherence, i.e. a continuous measure of the ability to match the varying speed of the vehicle ahead, and b) subjective drowsiness, lane keeping and emergency response to an unexpected vehicle blocking the lane. Diphenhydramine impaired coherence more than alcohol. Lane keeping was impaired after alcohol and diphenhydramine. Self reported drowsiness did not predict lack of coherence.
- *Witek et al. (1995)* conducted two single dose, cross over studies. In the first, the authors validated their methodology in 18 healthy subjects by examining the response to diphenhydramine 50mg, terfenadine 60mg and placebo. In the second trial single doses of diphenhydramine 50mg and 25mg, chlorpheniramine 4mg and placebo were given and the relative effects were measured with the help of psychometric tests such as choice reaction time, hand steadiness, divided attention task and with a subjective drowsiness scale. All assessments were made before and 1, 3, and 5 hours after drug administration. In the first trial diphenhydramine 50mg produced significant impairment relative to placebo in both objective and

subjective assessments. Responses following terfenadine did not differ from placebo. In the second study all three regimens produced subjective and objective impairments to a significantly greater degree than placebo. The general rank order of effects was diphenhydramine 50mg, followed by diphenhydramine 25mg, followed by chlorpheniramine 4mg.

- *Roth et al. (1987)* compared the sedative effects of loratadine 10 and 40mg with those of diphenhydramine 50mg tid and placebo for 2 days each in a double blind crossover study involving 16 healthy adults. Mean latency to sleep was reduced significantly with diphenhydramine compared with placebo, whereas neither loratadine dose reduced sleep latency. Reaction time, vigilance, digit symbol substitution and other tasks demonstrated a significant impairment after diphenhydramine compared to both loratadine doses.
- *Schweitzer et al. (1994)* compared the sedative effects of cetirizine (10mg od), diphenhydramine (50mg tid) and placebo during a 3 day period in a randomised, double blind study with 12 atopic volunteers. Sedation was measured with the multiple sleep latency test (MSLT) and a simulated line assembly task (SALT) on days 1 and 3. Both MSLT and SALT showed no differences between placebo and cetirizine on treatment day 1 while there was significant impairment in the diphenhydramine group. However on day 3 all three groups performed equally well. Subjective sleepiness testing was done using the visual analogue scale. Again on day one subjects rated themselves more sleepy with diphenhydramine compared with placebo and cetirizine, but by day 3 there were no significant differences in sleepiness between the groups. The authors conclude that cetirizine does not produce acute impairment of alertness and performance, unlike diphenhydramine, which does. The absence of significant differences on day 3 between the groups is explained by development of tolerance to the sedative effects of diphenhydramine.
- *Mattila et al. (1986)* investigated the sedative effects of single and repeated doses of diphenhydramine 50mg bid, temelastine 100mg bid and placebo for 5 days. Thirteen healthy subjects were included in this double blind cross over trial and underwent objective (digit symbol substitution, flicker fusion, tracking, choice reaction etc.) and subjective (visual analogue scale etc.) tests on day 1, 4 and 5. On day 1 diphenhydramine impaired performance in the critical flicker fusion, attention test, digit symbol substitution and tracking. On day 4 there was still impairment in critical flicker fusion and tracking, though less than on day 1. The authors concluded that diphenhydramine loses most of its sedative effect with repeated dosing.

#### Conclusions:

Diphenhydramine is known for its sedative properties and is often used in studies as positive control.

Diphenhydramine has been shown to consistently impair objective and subjective measures of CNS performance at single doses as low as 25mg. Studies investigating the effect of repeated dosing show less measurable impairment and therefore suggest development of tolerance.

Recommendation: However as most patients in clinical practice use diphenhydramine as a one off dose, it should be classified as a sedating antihistamine.

### 3) Chlorpheniramine

#### Preparations:

- Codral 4 Flu- 2mg per tablet, dose 2 tablets=4mg qid
- Day and Night Cold and Flu- 2mg per night capsule, dose max 2 capsules=4mg at night
- Histafen- 8mg or 12mg capsules, dose 1 capsule bid
- Orthoxicol day and Night- 2mg per night caplet, dose 2 caplets=4mg nocte
- Vicks Headclear cap
- Coldrex Flu Strength- 2.5mg per capsule, dose 2 capsules=5mg tid
- Demazin- 6mg of Dexchlorpheniramine per tablet, dose 1 tablet bid  
- 1.25mg per 5ml syrup, dose 15ml= 3.75mg qid

#### Relevant studies include:

- *Sannita et al.* conducted EEG monitoring in a cross over, placebo controlled study in healthy male volunteers receiving single doses of cetirizine 10mg or 20mg, chlorpheniramine 4mg and placebo. An increase of the 6,5-14.5 Hz EEG power, which is interpreted as early EEG sign of sedation, was observed after chlorpheniramine or cetirizine 20mg.
- *Witek et al.* conducted two single dose, cross over studies. In the first, the authors validated their methodology in 18 healthy subjects by examining the response to diphenhydramine 50mg, terfenadine 60mg and placebo. In the second trial single doses of diphenhydramine 50mg and 25mg, chlorpheniramine 4mg and placebo were given and the relative effects were measured with the help of psychometric tests such as choice reaction time, hand steadiness, divided attention task and with a subjective drowsiness scale. All assessments were made before and 1, 3, and 5 hours after drug administration. In the first trial diphenhydramine 50mg produced significant impairment relative to placebo in both objective and subjective assessments. Responses following terfenadine did not differ from placebo. In the second study all three regimens produced subjective and objective impairments to a significantly greater degree than placebo. The general rank order of effects was diphenhydramine 50mg, followed by diphenhydramine 25mg, followed by chlorpheniramine 4mg.
- *Meador et al. (1989)* examined the effect of single doses of chlorpheniramine 8mg, terfenadine 60 mg and placebo on the latency of the P3 evoked potential, which represents cerebral processing speed. 24 healthy adults were included in this double blind cross over study. The results showed significant slowing of the P3 potential with chlorpheniramine compared to placebo and terfenadine.

#### Conclusions:

Chlorpheniramine was generally thought to be one of the less sedating first generation H1 antagonists.

Chlorpheniramine causes impairment of objective and subjective measures of CNS function at single doses as low as 4mg. Studies testing the effect of repeated dosing are very limited and the result interpretation is controversial.

Recommendation: As for diphenhydramine, most patients in clinical practice use chlorpheniramine as a one off dose and therefore it should be classified as a sedating antihistamine.

#### 4) Promethazine

Preparations:

- Avomine- 25mg per tablet, dose 25mg od
- Phenergan- 10mg or 25mg tablets, dose 20mg tid
- Goodnight-25mg tablets, dose max 2 tablets= 50mg nocte
- Tixylix – linctus 1.5mg tid
- Phensedyl dry family cough – syrup, dose 3.6 mg tid, max.7.2mg tid
- Coldrex Night Relief – liquid, dose 20mg nocte

Relevant studies include:

- *Nicholson et al (2000)* studied the effects of fexofenadine on digit symbol substitution, tracking, vigilance tasks, objective sleepiness (multiple sleep latency test) and subjective sleepiness. Six healthy volunteers in a placebo controlled, double blind, cross over design received either single doses of fexofenadine (120, 180 and 240mg), promethazine 10mg (as positive control) or placebo. The performance tests were conducted from 1h pre ingestion to 8 h post ingestion. There were no changes of performance or sleepiness with any dose of fexofenadine at any time compared with placebo. Promethazine, compared both with placebo and fexofenadine, impaired performance on the digit symbol substitution task, vigilance task and tracking task, increased objective and subjective sleepiness.
- *Hindmarch et al. (1999)* performed a double blind, placebo controlled cross over study with 24 healthy volunteers. The comparators included single doses of fexofenadine 80mg, 120mg and 180mg, loratadine 10mg, promethazine 30mg (as a positive control) and placebo. The test battery included critical flicker fusion (CFF), choice reaction time (CRT) and assessment of subjective sedation (LARS), all performed at 1.5, 3, 6, 9, 12 and 24 h post dose. Activity levels were monitored with wrist actigraphs over 24h. Fexofenadine at all doses tested was not statistically different from placebo in any of the tests used and loratadine did not cause any significant impairment of cognitive function. Significant impairments were found following promethazine, such as reduction in CFF up to 12 h post dose, increase in recognition reaction time and increase in sleep like activity on actigraph.
- *Kahn (1979)* reported on cases of sudden infant death syndrome and a possible association with medication including phenothiazines. One of the 7 children described, suffered respiratory arrests after receiving promethazine for a slight cough. Another study (full text not yet seen) suggests a similar association.

Conclusions:

Promethazine is known for its sedative properties and has been widely used for paediatric sedation. In the studies investigating the sedative properties of H1 antagonists it has been used as a positive control.

Promethazine 10 mg in single doses has been shown to impair performance on objective and subjective psychomotor tests. There are no studies of the effects of repeated dosing.

Additionally there is debate about a possible association with SIDS. As the literature available is rather limited, this debate cannot presently be resolved.

It is a common practice that children under the age of two in NZ are given promethazine by their parents for night sedation and/or for cough in the belief that there are no known serious adverse effects. It is of concern that promethazine preparations are easily available over the counter and are also prescribed by GP's for infants without a warning.

Recommendation: Therefore it appears prudent for promethazine to be classified as a sedating histamine. Caution should be exercised when prescribing to infants and the datasheet should contain a warning about a possible association with SIDS.

## 5) Acrivastine

Recommended daily dose:

8mg tid

Relevant trials include:

- *Ramaekers et al. (1994)* conducted a double blind, cross over, placebo controlled study on 18 healthy volunteers. The comparators were single doses of acrivastine 8, 16 and 24 mg, the combination of acrivastine 8mg with pseudoephedrine 60mg, terfenadine 60, 120 and 180mg, diphenhydramine 50mg and placebo. Drug effects were assessed by subjecting the participants to two repetitions (at 1.5-2.75 h and at 3.25-4.5 h post dose) of two driving tests (highway driving and car following). Acrivastine 8mg had a small, but significant effect on highway driving in the first trial but no effects in the second trial. Acrivastine 16mg significantly impaired driving in both tests in the first trial, but not in the second trial. Acrivastine 24mg impaired both tests in both trials. The combination of acrivastine with pseudoephedrine did not cause any significant impairment of performance. The authors concluded that acrivastine in therapeutic doses (8mg) had little effect on driving performance, but that higher doses severely impaired driving performance. Our interpretation of the results is, that acrivastine had no effect on some of the driving tests, because it has a short duration of action and the first test was timed to be closer to the peak concentration, which is usually achieved in 1 hour.
- *Cohen et al. (1985)* performed a double blind, cross over study on 12 healthy subjects. Acrivastine 4, 8 and 16mg was compared with triprolidine 2.5 and 5mg and placebo. Adaptive tracking and reaction times were measured 1.5, 3 and 5 hours post ingestion. Acrivastine caused no impairment while triprolidine increased reaction times and decreased the tracking score. No subjective sedation was detected after acrivastine.

Conclusions:

Acrivastine is a derivative of triprolidine.

Glaxo Smith Kline have submitted an application for acrivastine to be registered in NZ as a nonsedating antihistamine.

There are very few trials, that have investigated the effects of acrivastine at a single dose. Acrivastine has a very short half life and the majority of performance tests in the studies were not adequately designed to investigate the time of the peak concentration. In spite of that, there is evidence, that single doses of acrivastine have a sedative effect and impair CNS function. The effect of repeated administration at the daily recommended dose of acrivastine of 8mg tid has not been investigated in studies so far. Further studies with proper methodology are needed.

Recommendation: Acrivastine should be classified as a sedating antihistamine.

## 6) Hydroxyzine

### Preparations:

- Serecid- 10mg, 25mg, 50mg capsules, dose 25mg tid, max 100mg qid

### Relevant studies include:

- *Seidel et al (1987)* studied sleepiness and performance in a randomised, double blind, parallel design, placebo controlled study with sixty healthy volunteers receiving single doses of either cetirizine 5mg, 10mg, 20mg, hydroxyzine 25mg or placebo. Multiple sleep latency tests were performed every 2 hours and a vigilance performance test twice during the day. Subjects receiving cetirizine in doses of 5 to 20 mg did not differ from placebo controls in any objective or subjective measures of daytime alertness. Subjects receiving hydroxyzine were significantly more sedated and showed slower reaction times than the placebo controlled group for at least 4 hours after treatment. Self rated feelings of sleepiness, impairment and fatigue did not differ significantly between groups. The conclusion is that hydroxyzine subjects may not have been aware of their impaired performance.
- *Walsh et al. (1992)* investigated twelve healthy subjects in a double blind, placebo controlled cross over design. Subjects received cetirizine 10mg, hydroxyzine 25mg or placebo as a single dose. Performance was measured during eight 50 min test periods on a simulated assembly line task over 9 hours after ingestion. Performance decrements were consistently measured with hydroxyzine but not with cetirizine.
- *Gengo et al. (1987)* conducted a randomised, placebo controlled cross over study on 12 healthy volunteers to investigate the effects of single doses hydroxyzine 25 mg, its metabolite cetirizine 10mg and 20mg, and placebo. CNS effects were measured with critical flicker frequency, Stroop word testing and visual analogue scales for up to 36 h post dose. Hydroxyzine produced a significant change compared with placebo in all three CNS parameters. Neither cetirizine 10mg or 20mg produced any significant changes in CNS parameters. Both the intensity and time course of CNS effects were related significantly to hydroxyzine blood concentrations.
- *Simons et al. (1995)* studied the CNS effects of cetirizine 10mg, hydroxyzine 50mg, diphenhydramine 50mg, and placebo administered as a single dose to 20 healthy subjects in a double blind cross over study. The P300 latency and a visual analogue scale for somnolence were recorded at baseline and at 2 1/2 h post dose. Neither cetirizine nor placebo significantly increased the mean P300 latency or

somnolence compared with baseline, although increases were seen in some subjects after each of these treatments. Hydroxyzine increased the P300 latency and the subjective somnolence compared with baseline and with placebo.

- *Goetz et al. (1989)* conducted a double blind, cross over study on 16 healthy volunteers. Comparisons were drawn between hydroxyzine 25mg bid, terfenadine 60mg bid and placebo for 5 days. Hydroxyzine but not terfenadine significantly prolonged both simple and choice reaction time and produced significant drowsiness. During the 5 days of hydroxyzine, neither objective nor subjective symptoms demonstrated development of tolerance. No correlation was found between subjective symptoms and prolongation of reaction times by hydroxyzine.

#### Conclusions:

Hydroxyzine is known for its sedative properties and has been widely used as a sedative for agitated patients and for premedication.

Hydroxyzine has been shown to impair performance on objective and subjective CNS tests both after administration of single doses, as well as after repeated doses within the daily recommended dosing regimen.

Recommendation: Hydroxyzine should be classified as a sedating antihistamine.

## 7) **Fexofenadine**

#### Preparations:

- Telfast- 60mg capsules, 120mg tablets, dose 120mg od

#### Relevant clinical studies include:

- *Vermeeren et al. (1998)* conducted a double blind cross over study with 24 healthy volunteers. The comparators included fexofenadine 120mg od or 60mg bid, fexofenadine 240 mg od or 120 mg bid, clemastine 2mg bid and placebo, all administered over 5 days. Psychomotor tests (critical tracking, choice reaction time, sustained attention) and a standardised actual driving test were undertaken between 1.5 to 4 hours after administration of the morning dose on days 1, 4 and 5. On day 5 subjects were additionally challenged with a moderate alcohol dose. Fexofenadine did not impair driving performance. Driving performance was better with twice daily 120mg fexofenadine compared to placebo. Both dosing regimens of 240 mg per day appeared to attenuate the adverse effects of alcohol on driving. The first dose of fexofenadine on day 1 impaired the critical tracking task without other significant impairments on objective psychometric tests. In the discussion of the results the authors argue based on the engineering model of tracking performance, that this tracking error is due to a mild stimulant effect of fexofenadine. The laboratory tracking error did not translate into a tracking error on driving, on the contrary, the mild stimulation improved control of the vehicle. The arguments in the discussion appear plausible.
- *Nicholson et al (2000)* studied the effects of fexofenadine on digit symbol substitution, tracking, vigilance tasks, objective sleepiness (multiple sleep latency test) and subjective sleepiness. Six healthy volunteers in a placebo controlled, double blind, cross over design received either single doses of fexofenadine (120, 180 and 240mg), promethazine 10mg or placebo. The performance tests were conducted from 1h pre ingestion to 8 h post ingestion. There were no changes of

performance or sleepiness with any dose of fexofenadine at any time compared with placebo. As a result the authors concluded, that fexofenadine may be considered for use in individuals involved in skilled activity such as air crew.

- *Hindmarch et al. (1999)* performed a double blind, placebo controlled cross over study with 24 healthy volunteers. The comparators included single doses of fexofenadine 80mg, 120mg and 180mg, loratadine 10mg, promethazine 30mg and placebo. The test battery included critical flicker fusion (CFF), choice reaction time (CRT) and assessment of subjective sedation (LARS), and were performed at 1.5, 3, 6, 9, 12 and 24h post dose. Activity levels were monitored with wrist actigraphs over 24h. Fexofenadine at all doses tested was not statistically different from placebo in any of the tests used and loratadine did not cause any significant impairment of cognitive function. Significant impairments were found following promethazine.

#### Conclusions:

Fexofenadine is the active metabolite of terfenadine and has been marketed widely as being completely devoid of sedative effects.

A number of studies with both placebo controls and positive controls have been conducted using fexofenadine at doses higher than the recommended dose. Within these dose ranges fexofenadine lacks any clinically relevant sedative activity and does not impair cognitive and psychomotor performance both after administration of single as well as repeated doses.

Recommendation: It should be classified as a non sedating antihistamine.

## 8) **Trimeprazine**

#### Preparation:

- Vallergan Forte- 30mg/ 5ml syrup, dose 10mg qid, max 100mg per day

#### Relevant studies include:

- *Burtles et al. (1983)* studied lorazepam, diazepam, trimeprazine and placebo on 100 children in a double blind study. The conclusion was that all three drugs appeared satisfactory as premedicants.
- *Ong et al. (1996)* compared the degree of sedation in 191 children receiving oral premedication for daystay surgery. The comparators included chloral 40mg/kg, midazolam 0.2mg/kg, promethazine 1mg/kg, trimeprazine 3mg/kg or placebo. The children were assessed using four categories: asleep or drowsy, awake but calm, crying or anxious, and oversedated. Trimeprazine and chloral produced the best degree of sedation in 1-5y olds (n=146). The sedative effect of trimeprazine lasted longer into the postoperative period. The older age group (n=45) did not require deep sedation and did well on midazolam.
- *Routledge et al (1999)* examined the CSM/MCA data base of adverse reactions to antihistamines. Up to 31.Dec. 1997 there were 127 reports on adverse reactions to trimeprazine, 3 of them fatal. Of the 25 reports of cardiovascular disorder, sinus

bradycardia was the commonest single disorder (8), with hypotension (6) and syncope (3) also reported.

- *Loan et al. (1985)* reported on 4 cases of an adverse cardiovascular response to oral trimeprazine as a premedication in children. Although none of the cases had a fatal outcome, all of them were characterised by bradycardia, hypotension and two required atropine and adrenaline infusion respectively.

#### Conclusions:

Due to its sedative properties trimeprazine is widely used as premedication for children.

Trimeprazine's sedative properties have been established in anaesthetic trials.

As with promethazine, in NZ trimeprazine is given by parents to children under two years of age as a night sedation or prior to travel in the belief, that it has no serious adverse effects. The possibility of adverse cardiac effects exists (see above).

Recommendation: It should be classified as a sedating antihistamine. Trimeprazine should be avoided in children under two years of age. There should be a warning in the datasheet about potential adverse cardiac effects.

### **9) Azatadine**

#### Proprietary/ OTC preparations:

- Zadine- 1mg tablets, dose 1mg bid, max 2mg bid

#### Examples of relevant studies:

- *Biehl (1979)* conducted two studies of a randomised, double blind Latin square design. In the first trial with 27 subjects, 2mg azatadine was compared with another antihistamine Sch12169 (2mg) and placebo. In a second trial with 32 subjects, higher doses of azatadine (4mg and 8mg) were compared with dexchlorpheniramine 4mg and placebo. Objective tests included coordination tests, reaction tests, finger tapping and driving simulation. Azatadine did not produce significant impairment on psychomotor testing at either the standard 2mg or the maximum recommended 4mg per day. Azatadine 8mg caused impairment of performance compared to placebo of a similar order to that observed after dexchlorpheniramine 4mg. The authors conclude that at the recommended dosage of 2mg per day azatadine is not likely to impair driving ability.
- *Levander et al. (1985)* compared the peripheral and central effects of hydroxyzine 20mg, azatadine 3mg and clemastine 3mg and placebo on 24 healthy volunteers in a double blind design. Central sedative effects were analysed using a set of computerised neuropsychological tests ( finger tapping, reaction time, tracking, trail making) and analogue ratings administered between 2 and 5 hours post ingestion.. A compound score, reflecting the balance between peripheral and CNS effects, showed hydroxyzine to have relatively more peripheral antihistamine effect and less sedative effect than azatadine and clemastine.

#### Conclusions:

There are very few studies that have investigated the sedative properties of azatadine.

Single dose administration of azatadine 3mg was shown in one of two available studies to cause significant impairment of CNS performance. There are no studies investigating the effect of repeated dosing. The results are conflicting and a cautious approach would be to regard it as a sedating antihistamine.

Recommendation: Azatadine should be classified as a sedating antihistamine.

## 10) Cetirizine

### Preparations:

- Zyrtec- 10mg tablets, dose 10mg od, max 10mg bid

Cetirizine is a metabolite of hydroxyzine and is marketed as having better antihistaminic properties and less sedative properties. As the sedative effect of cetirizine has been a subject to ongoing controversy, we have listed the relevant studies in more detail to facilitate comparisons of these studies.

### Relevant trials include:

- *Schweitzer et al. (1994)*

Methods: n=12, atopic individuals, randomised, double-blind, cross over , repeated dosing over 3 days

Comparators: cetirizine 10mg od  
diphenhydramine 50mg tid  
placebo

Outcomes: multiple sleep latency test  
simulated assembly line task  
sleep actigraphy  
visual analogue scale for sleepiness

Times of tests: day 1 and 3  
1 to 9 hours post ingestion

Results: cetirizine caused no impairment in any of the tests  
diphenhydramine caused significant impairment in all tests on day 1, but not on day 3

Critical appraisal: a well designed study

- *Gengo et al. (1990)*

Methods: n=15, healthy individuals, randomised, double blind, cross over, single dosing

Comparators: cetirizine 5mg, 10mg, 20mg  
diphenhydramine 50mg  
placebo

Outcomes: driving simulation  
digit symbol substitution  
trais B maze tracking  
visual analogue scale for drowsiness

Times of tests: from 2 to 24 hour post ingestion

Results: driving – cetirizine caused no impairment while diphenhydramine did  
digit symbol substitution – 20 mg cetirizine caused a small

but significant impairment while  
diphenhydramine caused marked  
impairment

maze tracking – no impairment with any of the treatments  
visual analogue scale – cetirizine caused no impairment while  
diphenhydramine did

Critical appraisal : a well designed study

- *Walsh et al. (1992)*

Methods: n=12, healthy individuals, randomised, double blind, cross over,  
single dosing

Comparators: cetirizine 10mg  
hydroxyzine 25mg  
placebo

Times of tests: 30min to 9 hours post dosing

Outcomes: simulated assembly line task  
visual analogue scales for sedation

Results: simulated assembly line task - cetirizine caused no impairment  
while hydroxyzine did  
visual analogue scales - no significant difference between the  
three

Critical appraisal: a well designed study

- *Nicholson et al. (1998)*

Methods: n=6, healthy individuals, randomised, double blind, cross over,  
single dosing

Comparators: cetirizine 5mg, 10mg, 15mg  
promethazine 10mg  
placebo

Times of tests: 30min to 7.5 hours post dosing

Outcomes: sleep latency  
digit symbol substitution  
tracking  
vigilance  
visual analogue scale for sleepiness

Results: sleep latency - no change with cetirizine 5mg, patches of  
reduction with cetirizine 10 and 15 mg but no  
sustained decrease throughout the day such as  
with promethazine  
digit symbol substitution - no change with any of the  
treatments  
tracking – no impairment by 10 mg cetirizine, but cetirizine 5  
mg and 15 mg caused impairment 30 min after  
ingestion, while promethazine caused impairment  
5.5 h after ingestion  
visual vigilance task – no significant changes with cetirizine 5  
and 15mg, but cetirizine 10 mg slowed  
down reaction time, promethazine  
impaired performance as well

visual analogue scale – no meaningful impairment with cetirizine while promethazine caused significant subjective sleepiness

- Critical appraisal :
- a very small study with large variations in individual results, difficult to draw conclusions
  - presentation of test results very fragmented and difficult to get an overview
  - impairments measured in the cetirizine group show no dose reponse relation, neither do they correspond to cetirizine's pharmacokinetic properties.
  - the results of this study need to be viewed with great caution

• *Simons et al. (1996)*

Methods: n=15, healthy individuals, randomised, double blind, cross over, single dosing

Comparators: astemizole 10mg  
cetirizine 10mg  
ketotifen 2mg  
loratadine 10mg  
terfenadine 60mg  
diphenhydramine 50mg  
placebo

Times of tests: 2 to 2.5 hours post ingestion

Outcomes : P 300 latency  
visual analogue scale of sedation

Results: P 300 – only diphenhydramine increased the latency significantly compared to placebo  
visual analogue scale – cetirizine, ketotifen and diphenhydramine caused significant impairment to baseline and placebo

Critical appraisal : Only one objective measurement was taken on a variety of drugs that differ in their pharmacokinetic properties. Therefore it is likely that some peak effects were missed. These results need to be viewed with great caution.

• *Seidel et al ( 1987)*

Methods: n=60, healthy individuals, randomised, double blind, parallel, single dosing

Comparators: cetirizine 5mg, 10mg, 20mg  
hydroxyzine 25mg  
placebo

Times of tests : 2 to 10 hours post ingestion

Outcomes: multiple sleep latency test  
vigilance tests  
visual analogue scale of sedation

Results: cetirizine at any dose did not differ from placebo in objective or subjective tests while hydroxyzine caused impairment in objective tests only

- Critical appraisal : well designed study
- *Ramaekers et al (1992)*

Methods : n=16, healthy individuals, randomised, double blind, cross over, single dosing

Comparators : cetirizine 10mg  
loratadine 10mg  
placebo  
alcohol  
combination of alcohol with each treatment

Times of tests : 1.5 to 5.5 hours post ingestion

Outcomes: driving  
EEG  
critical tracking  
choice reaction time  
response competition  
divided attention task  
subjective feelings

Results: driving – significantly impaired standard deviation of lateral position and speed with cetirizine but not with loratadine  
- alcohol caused more deviation of lateral position than cetirizine and no deviation in speed at all  
EEG – small trends to change by cetirizine but not by loratadine  
critical tracking – not impaired with cetirizine or loratadine, impaired by alcohol  
choice reaction time – impaired by cetirizine but not by loratadine, impaired by alcohol  
response competition - not impaired with cetirizine or loratadine, impaired with alcohol  
divided attention task – impaired by cetirizine but not by loratadine, impaired with alcohol  
subjective feelings – no significant difference

Critical appraisal:  
- well designed study  
- author interprets the findings as only mild impairment, which is not likely to affect driving
  - *Patat et al. (1995)*

Methods: n=18, healthy individuals, randomised, double blind, cross over, repeated dosing

Comparators: mizolastine 10mg od  
cetirizine 10mg od  
placebo  
combination of alcohol with each of the treatments

Times of tests : 1.5 to 7.5 hours post ingestion

Outcomes: driving  
critical flicker fusion  
divided attention task  
tracking

Results: driving – no impairment by cetirizine or mizolastine in lateral deviation and braking reaction, significant impairment with alcohol  
critical flicker fusion – no impairment by cetirizine or mizolastine  
divided attention – both cetirizine and mizolastine impaired performance 6hours post ingestion  
tracking – sustained impairment ( 1.5h to 7.5h) after cetirizine and impairment at 7.5h after mizolastine

Critical appraisal: This study was designed to investigate mizolastine. There is no true positive control for cetirizine. Impairment with cetirizine was shown on two sensitive tests.

- *Rihoux et al. (1990)*

Methods: n=7, healthy individuals, randomised, double blind, cross over, single dosing

Comparators : cetirizine 2.5mg, 5mg, 10mg  
loratadine 10mg, 20mg, 40mg  
placebo

Times of tests : 0 to 8 hours post ingestion

Outcome: visual analogue scale of sedation

Results : Subjective sedation was induced with 40mg of loratadine only.

Critical appraisal: - no objective tests.  
- no positive control.  
- the design of this study is not satisfactory.

- *Rihoux et al. (1987)*

Methods: n=18, healthy individuals, randomised, double blind, cross over, single dosing

Comparators: terfenadine 60mg , 180mg  
cetirizine 10mg  
placebo

Time of tests : 0 to 24 hours post ingestion

Outcome: visual analogue scale of sedation

Results: no significant differences

Critical appraisal : - no positive control  
- no objective tests  
- methodology not satisfactory

- *Coulie et al (1991)*

Methods: n=12, healthy individuals, randomised, double blind, cross over, single dosing

Comparators: cetirizine 10mg  
oxatomide 30mg  
ketotifen 1mg  
placebo

Times after tests : 0 to 12h post ingestion  
Outcomes: visual analogue scale of sedation  
Results: Cetirizine was not different from placebo in causing subjective sedation, while ketotifen and oxatomide were.  
Critical appraisal : No objective tests and therefore no conclusion can be drawn about cetirizine's sedating properties.

- *Sannita et al. (1996)*

Methods: n=8, healthy individuals, randomised, double blind, crossover, single dosing  
Comparators : cetirizine 10mg, 20mg  
chlorpheniramine 4mg  
placebo  
Times of tests : 1 to 6 hours post ingestion  
Outcomes: EEG  
visual analogue test  
memory tests  
Results: EEG – change in power with cetirizine 20mg and with chlorpheniramine  
memory tests – no change with any treatment  
visual analogue test – no change with any treatment  
Critical appraisal : - reasonable study design  
- the clinical significance of the EEG changes is somewhat unclear.

- *Gengo (1987)* - study consisted of two parts

1) Methods: n=12, atopic individuals, randomised, double blind, cross over, single dosing  
Comparators: hydroxyzine 25mg  
cetirizine 10mg, 20mg  
placebo  
Times of tests : 0 to 36 hours post ingestion  
Outcome: critical flicker fusion  
Stroop word scale  
visual analogue scale  
Results: all tests – cetirizine caused no impairment while hydroxyzine did  
Critical appraisal : reasonably well designed study  
2) Methods: n=15, healthy individuals, randomised, double blind, cross over, single dose  
Comparators: cetirizine 5mg, 10mg, 20mg  
diphenhydramine 50 mg  
placebo  
Times of tests : 0 to 24 hours post ingestion  
Outcomes: digit symbol substitution  
trails B maze tracking  
driving  
visual analogue scale  
Results: preliminary analysis  
driving – reaction time significantly prolonged by

diphenhydramine but not by cetirizine  
visual analogue scale – mild drowsiness after cetirizine  
20mg, marked drowsiness after  
diphenhydramine

Critical appraisal : - incomplete results at time of reporting  
- needs to be viewed with caution

- *Simons et al. (1995)*

Methods: n=20, healthy individuals, randomised, double blind, cross  
over, single dosing  
Comparators: cetirizine 10mg  
hydroxyzine 50mg  
diphenhydramine 50mg  
placebo  
Times of tests : 0 – 2.5 hours post dose  
Outcomes: P 300 latency  
subjective somnolence  
Results: P 300 and subjective  
somnolence – no significant impairment with cetirizine  
impairment with hydroxyzine

Critical appraisal : reasonably well designed study

Conclusion:

Results of the studies done with single dosing regimens as well as with repeated doses have been reported as being contradicting.

A thorough literature review showed, that well designed studies demonstrated either no impairment of objective parameters of CNS function at all or showed mild impairment at higher doses on sensitive tests, such as the sleep latency, tracking speed, critical fusion, divided attention. In only one of the well designed studies there was evidence of minor impairment in the driving test, though the author agrees, that the practical relevance is questionable.

One or two small studies with methodological problems showed impairment with cetirizine without a dose response relationship. Little weight should be attached to these studies.

Although a few of the well designed trials show that cetirizine is not completely devoid of CNS effects, these effects are minor and of questionable practical relevance and cetirizine 10 mg daily could still be considered non sedating.

Recommendation: Cetirizine should be classified as a non sedating antihistamine.

## 11) Ketotifen

Proprietary preparations:

- Asmafen- 1mg/5ml syrup, dose 1mg bid, max 2mg bid

Summary of the relevant trials:

- *Simons et al. (1996)* compared the CNS effects of single doses of six H1 antagonists on 15 healthy subjects. Measures of sedation were the P300 latency test and a subjective somnolence score. In rank order from least to greatest effect on the P 300 latency (i.e. least to greatest sedation), the medications were : terfenadine 60mg, placebo, cetirizine 10mg, ketotifen 2mg, loratadine 10 mg, astemizole 10mg and diphenhydramine . Only diphenhydramine increased the P 300 latency significantly compared to baseline and placebo. Subjective somnolence was significantly greater than baseline and placebo after cetirizine, ketotifen and diphenhydramine. The conclusion was that effects on cognitive function differ from the effect of inducing subjective somnolence.
- *Coulie (1991)* found that ketotifen causes subjective sedation, but used no objective tests to measure CNS impairment ( see same study listed under cetirizine as well).

Conclusions:

Although very few clinical studies have investigated ketotifen's sedative properties, in clinical practice it is widely recognised, that ketotifen causes sedation.

Recommendation: It should be classified as a sedating antihistamine.

## 12) Levocabastine

Preparations:

- Livostin 0.5mg/ml eyedrops or nasal spray, dose 1 drop each eye max qid or two puffs each nostril bid

Relevant trials include:

- *Arriaga and Rombaut (1990)* did a randomised, double blind cross over study on 12 healthy volunteers receiving levocabastine eye drops (0.5 mg/ml) 2 drops per eye qid or placebo for one week. CNS effects were measured with the help of two objective tests (critical flicker fusion test and choice reaction time test) and one subjective test (visual analogue scale of sedation ). No significant treatment effects could be detected, therefore the conclusion was, that repeated instillations of levocabastine eye drops are devoid of sedative effects.
- *Rombaut et al (1991)* did another randomised, double blind, double dummy, placebo controlled crossover study on 12 healthy female volunteers. Comparison was made between single doses of (levocabastine eye drops two drops per eye plus nasal spray 0.5 mg/ml two sprays per nostril), (levocabastine eye drops plus nasal spray 2mg/ml), (oral placebo plus placebo eye drops and nose spray) and (oral triprolidine 10 mg as a verum). Cognitive and psychomotor tests were performed before and 40, 75, 150 and 300 min after administration of a single dose. Results of the critical flicker fusion, choice reaction time, simulated car tracking test, Sternberg memory scanning task , word recognition task showed no difference between placebo and either concentration of levocabastine, whereas the triprolidine group performed significantly worse than placebo on most objective tests. Subjective measures included the Line analogue rating scale with no more sedation reported for levocabastine versus placebo. The triprolidine group reported a significant increase in sedation, especially after 75 min following administration. The conclusion was that single doses of levocabastine eyedrops and nasal spray in the above doses are devoid of sedative effects.

### Conclusions:

Topical levocabastine has been shown to be devoid of sedative effects.

Recommendation: It should be classified as a non sedating antihistamine.

### **13) Loratadine**

#### Proprietary/ OTC preparations:

- Claratyne- 10mg tablets, dose 10mg once daily

#### OTC preparations:

- Clarinase- 10mg per tablet, dose 10mg od
- Claratyne decongestant- 5mg per tablet, dose 1 tablet bid
- Demazin non-drowsy- 5mg per tablet, dose 1 tablet bid

#### Examples of the relevant trials:

- *Valk et al (1997)* performed a randomised double blind three way cross over study whereby 18 men received either loratadine 10mg, triprolidine 5mg or placebo. Objective (vigilance, complex tasks) and subjective tests, tailored to the specific tasks of aircrew were applied under hypobaric conditions. Loratadine and placebo did not cause any impairment of alertness or performance from 1-6 hr after ingestion, whereas triprolidine did. The authors concluded that a single dose of loratadine 10mg is unlikely to affect flying performance.
- *Simons et al. (1996)* compared the CNS effects of single doses of six H1 antagonists on 15 healthy subjects. Measures of sedation were the P 300 latency test and a subjective somnolence score. In rank order from least to greatest effect on the P 300 latency (i.e. least to greatest sedation), the medications were : terfenadine 60mg, placebo, cetirizine 10mg, ketotifen 2mg, loratadine 10 mg, astemizole 10mg and diphenhydramine . Only diphenhydramine increased the P 300 latency significantly compared to baseline and placebo.
- *Ramaekers et al (1992)* studied the effects of single doses of loratadine 10 mg and cetirizine 10 mg on driving with and without alcohol (dose adjusted per lean body mass). Sixteen healthy volunteers took part in a 6 way, double blind, cross over, placebo controlled study. Performance was measured with psychometric tests, road driving and EEG. Alcohol significantly affected almost every performance measure and altered the EEG spectrum. Loratadine had no significant effect on any performance parameter.
- *Hindmarch et al. (1999)* performed a double blind, placebo controlled cross over study with 24 healthy volunteers. The comparators included single doses of fexofenadine 80mg, 120mg and 180mg, loratadine 10mg, promethazine 30mg and placebo. The test battery included critical flicker fusion (CFF), choice reaction time (CRT) and assessment of subjective sedation (LARS). Activity levels were monitored with wrist actigraphs. Fexofenadine at all doses tested was not statistically different from placebo in any of the tests used and loratadine did not cause any significant impairment of cognitive function. Significant impairments were found following promethazine.
- *Bradley et al. (1987)* studied the effects of loratadine 10mg, 20mg and 40mg compared to triprolidine 10mg (but not to placebo), on visuomotor coordination, dynamic visual acuity, short term memory, digit symbol substitution and on subjective assessments of mood up to 6 hours after ingestion. While triprolidine

impaired the performance on all tasks, loratadine 10 and 20 mg caused no impairment. Loratadine 40mg caused impairments on the digit substitution test, dynamic visual acuity and memory. The authors conclude that loratadine at 10 mg is unlikely to cause impairment in performance.

- *Roth et al. (1987)* compared the sedative effects of loratadine 10 and 40mg with those of diphenhydramine 50mg tid and placebo for 2 days each in a double blind crossover study involving 16 healthy adults. Mean latency to sleep was reduced significantly with diphenhydramine compared with placebo, whereas neither loratadine dose reduced sleep latency. Reaction time, vigilance, digit symbol substitution and other tasks demonstrated a significant impairment after diphenhydramine compared to both loratadine doses. The authors concluded that loratadine 10 and 40mg did not have clinically significant CNS activity.

#### Conclusions:

Loratadine has been marketed as a non sedating H1 antagonist.

Single administration of loratadine has been consistently shown to have no significant sedative effects at the daily recommended dose of 10mg. Higher doses may cause clinically significant impairment of CNS function.

The sedative effect of repeated doses of loratadine has not been sufficiently investigated.

Recommendation: It should be classified as a non sedating antihistamine.

## ADDITIONAL SAFETY ISSUES

### **1. Abuse**

We examined the literature on abuse of these medicines.

#### Abuse potential

Intake of toxic amounts of a substance usually occurs either with the intent of deliberate self harm or of achieving a desired side effect, such as sedation. In the latter situation patients may believe, that preparations that are available over the counter, are completely devoid of adverse effects, or – that ingestion of larger doses is safe. Less commonly ingestion of toxic amounts occurs accidentally.

At doses approaching toxic amounts, antihistamines are hallucinogenic and can cause seizures. Although less popular than other substances, antihistamines have been used to produce deliberate intoxication.

- In 1968 Nigro et al reported about a young girl suffering from acute psychosis following ingestion of 500 mg of diphenhydramine.
- In 1982 Leighton reported about a 27 year old male with a long history of Actifed (a preparation containing pseudoephedrine hydrochloride and triprolidine hydrochloride) abuse suffering from acute psychosis after doubling the dose to two bottles per day.
- In 1985 Kofoed reported about a 56 year old man presenting with drowsiness, anorexia, nausea, hallucinations following regular ingestion of a bottle of OTC liquid each night for a month as a night sedation. The liquid contained antihistaminic and anticholinergic agents plus alcohol and paracetamol.

- There is a number of reports in the literature about dependence on cough preparations (Perera 1997, Bedi 1991, Borde 1988) and abuse of sedating antihistamines (Barsoum 2000, Roberts 1999, Dinndorf 1998 etc.).
- Diphenhydramine and pheniramine are well recognised in the literature as drugs of abuse (Buckley 1994, Dinndorf 1998). Adverse effects such as seizures have been reported in 30% of the admissions for pheniramine overdose and 1.3% of the admissions for overdose with other antihistamines (Buckley 1994).
- Accidental and deliberate ingestion of toxic doses of cetirizine, fexofenadine and loratadine have not been reported to cause either significant adverse effects or any fatalities (Mason 1999, Philpot 2000, Buckley 1994, Hansen 1998)

### Incidence of abuse

While there are surveys that capture what proportion of particular groups use antihistamines and there are data on admissions for overdoses and adverse effects, there are no data available on the incidence of antihistamine abuse in the community.

- In a survey of 3476 adolescents from public high schools Johnson et al (1971) found that about 70% have at some stage in their life used antihistamines and antihistamine containing cold remedies and that about 10% were using the above 8 times per year or more.
- In a survey of 600 young adults between 18 and 21 years about their total drug use Vener et al (1982) found, that antihistamines ranked as a second most commonly used prescription drug utilised by both sexes (3.2% of all participants). Additionally 16% of all participants were taking cold remedies and/or antihistamines as over-the-counter preparations.

These studies tell us nothing about the frequency of abuse.

### Abuse of newer antihistamines

The non sedating antihistamines are likely to be abused less frequently than sedating antihistamines. The data on this issue are very limited.

- Buckley et al (1994) reported on all cases of antihistamine poisoning admitted to Newcastle Hospital Waratah NSW over 6 years. Out of the 118 admissions pheniramine accounted for 34% and promethazine for 28% of all cases respectively. Non sedating antihistamines accounted for only 2.4% of admissions and if the respective market shares are taken into account, this percentage diminishes further.

## **2. Inappropriate use**

Inappropriate use refers to the use of a medicine for the wrong indication. In the case of sedating antihistamines this usually occurs with the aim to achieve paediatric sedation.

- An extensive survey by the Dangar Research Group (1995) prepared for PHARM Australia investigates the behaviour of mothers administering sedating antihistamines to their children. Beyond the two recognised indications (symptoms of cold/flu and allergic conditions), mothers who administer a sedating antihistamine to their children do this in 16% of the cases, because the child has difficulty sleeping and in further 16% of the cases because the mother herself is not coping. This proportion rises to 32%, if the age group is narrowed down to 2 years and under. Special concerns raised in the survey include the lack of real concern for use of

OTC medications generally (52%), the perceived safety of OTC medications (70%), the complacent approach to dosing (10%) and the potential for regular misuse. Further results of note were that 12% of GPs were reported to prescribe antihistamines for sedation of children and that only 30% of mothers read the labels of OTC medications to find out whether they are suitable for children.

In every day life the distinction between abuse and inappropriate use of a substance can become blurred.

## CONCLUSIONS

Reasons for changing the classification of sedating antihistamines from Pharmacy-Only to Restricted Medicine would include concerns about:

- Safety
- Potential for abuse
- Inappropriate use

Newer antihistamines in the manufacturers' recommended doses are less likely to slow neurotransmission, cause somnolence or impair psychomotor performance than the first generation ones. However there is great variability in their ability to produce adverse CNS effects.

Only a few, such as fexofenadine, loratadine and levocabastine seem to be consistently free from these effects at manufacturers' recommended doses. The results of the cetirizine trials raise the question about an appropriate cut-off point for safety when testing sedative effects of antihistamines. Presently there is no consensus whether impairments on very sensitive laboratory tests translate into impairment of practical functions. As the majority of the well designed studies on cetirizine showed no significant impairment both on driving and on very sensitive parameters, we would classify cetirizine as a non sedating antihistamine. It is important to recognise that there may be occasional individuals who experience sedation with these medicines but that most individuals will tolerate these medicines with no adverse effects. We would not envisage any problems with these antihistamines (i.e. fexofenadine, loratadine, levocabastine and cetirizine) remaining as Pharmacy Only Medicines

We believe that all other antihistamines should become Restricted Medicines, because of their propensity to cause sedation. It is important that the patient be warned that these medicines can cause sedation and that care should be exercised with driving and the use of heavy machinery. As has been noted already the use of sedating antihistamines is associated with an increased risk of motor vehicle accidents. Although these medicines carry a warning to this effect on the package, one cannot rely on patients to read this. We believe, that if there is a requirement for the pharmacist to counsel the patient about the risks of these medicines, the patient is more likely to heed this advice.

We would argue that compound preparations should be Restricted Medicines if they contain a dose of a sedating antihistamine known to cause CNS impairment. Where, however, the compound preparation contains a low dose of a sedating antihistamine, it is probably more appropriate that the preparation is a Pharmacy Only Medicine.

The sedative effect of the sedating antihistamines is likely to wear off with repetitive use. However this should not be used as an argument for these medicines not being a Restricted Medicine since sedating antihistamines are commonly taken as a one off dose.

Sedating antihistamines and especially compound preparations containing the same may be abused. This is recognised in clinical practice and described in the literature and should argue in favour of classifying them as Restricted Medicines. There is no evidence in the literature that non sedating antihistamines are being abused for achieving pleasant sensations. This may reflect their lack of central effects. There is a small incidence of non sedating antihistamines being misused for suicide attempts, but there are no reports about fatalities.

With regard to inappropriate use there is the issue of antihistamine preparations being used as a sedative in young children.

Consideration should be given to the suggestion that antihistamines that are likely to be used in children under the age of two should carry warnings about the possibility of serious adverse effects. Unfortunately there are limited data in this area but the possibility that these medicines may increase the risk of SIDS in infants cannot be excluded.

There is no evidence that problems with sedating antihistamines have become more frequent in recent years. Nevertheless we believe that it does not weaken the case for them being restricted because of concerns about safety.

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