

5 May 2007

Hon Jim Anderton MP  
Associate Minister of Health  
Parliament Buildings  
WELLINGTON

Dear Minister

### **Further EACD Advice on Benzylpiperazine (BZP) and related substances**

The EACD met on 3 May 2007 and considered further information on Benzylpiperazine (BZP) that has become available since our last meeting in November 2006. Three members of the Committee were not present: Dr Tim Maling, Dr Stewart Jessamine, and Assistant Commissioner Gavin Jones (NZ Police). Detective Superintendent Win Van der Velde, Police National Crime Manager attended in place of Assistant Commissioner Jones.

The Committee considered the following papers and information during its discussion on BZP.

- An overview paper compiled by the Ministry of Health's National Drug Policy Team summarising and commenting on the additional information.
- Two independent peer reviews of each of the following reports:
  - Report by Sheridan and Butler from the University of Auckland School of Pharmacy titled "Legal party pills and their use by young people: summary report of findings".
  - Draft report dated 24 November 2006 titled "The benzylpiperazine (BZP) / trifluoromethylphenylpiperazine (TFMPP) and alcohol safety survey by Thompson et al at the Medical Research Institute of New Zealand
- The response by the authors of the above studies to the peer reviewers' comments.
- A paper published in the New Zealand Medical Journal in February 2007 by Theron and colleagues titled 'Benzylpiperazine-based party pills' impact on the Auckland City Hospital Emergency Department Overdose Database (2002-2004) compared with ecstasy (MDMA or methylene dioxymethamphetamine), gamma hydroxybutyrate (GHB), amphetamines, cocaine and alcohol'.
- Results of testing by ESR of one party pill product (Torque).
- A paper published in the Lancet in April 2007 by Wood and colleagues titled 'Collapse, reported seizure – and an unexpected pill', and an accompanying editorial by Staack titled 'Piperazine designer drugs of abuse'.
- A report provided by the Social Tonics Association of New Zealand on a 2007 Consumer Link survey titled 'Comparative risks of legal party pills, alcohol and illegal drugs'.
- A report analysing the submissions elicited during the consultation process on the EACD's December 2006 advice to you on BZP and related substances.

- A paper dated 21 March 2007 titled 'Report on the Proposal to Reclassify Benzylpiperazine (BZP)' by A/Professor Michael Dawson and Dr Alex Wodak on behalf of accessUTS for Chen Palmer Barrister and Solicitors, Wellington.

The ESR Drugs Group April 2007 report and summary analysis of BZP and trifluoromethylphenylpiperazine (TFMPP) in tablets submitted to ESR from 1 June 2006 to 30 April 2007 were tabled and also briefly discussed.

The EACD considered each of the documents in turn. The peer review reports elicited important points about both the studies, which the Committee carefully considered in reassessing its earlier conclusions and recommendations. A summary of the Committee's discussion will be included in the final minutes of the 3 May 2007 meeting.

The Committee was aware that some submissions on our earlier advice raised concerns, which were summarised in the analysis of the submissions, and we discussed these at the meeting. Our response is noted below each point.

Concerns were expressed that the EACD:

- relied on unpublished and un-replicated research/reports that had not been subject to a robust peer review process

Response: Some of the research was unpublished. The key unpublished reports have now been independently peer reviewed and these, along with the authors' response, were considered by the EACD at its 3 May 2007 meeting.

- had not defined moderate risk and has not undertaken a formal risk assessment

Response: In judging the level of risk as moderate – that is 'medium' and neither excessive nor minimal – the EACD made a careful and thorough assessment of BZP against the criteria outlined in the Misuse of Drugs Act 1975 (MODA) as it is required to do. This included consideration of all the information available to it at the time, as well as comparison with other substances already classified under the MODA.

- was asked only to evaluate harm not potential benefits

Response: The EACD is required to explicitly consider therapeutic benefit and its advice noted, "There are perceived beneficial effects (e.g. wakefulness and increased sociability)." There are currently no approved therapeutic uses for BZP.

- had not evaluated other harm minimisation options such as tighter regulation

Response: The current Schedule of restricted substances in the Misuse of Drugs Amendment Act 2005 and attendant regulatory powers arose from the initial advice on BZP by the EACD. The EACD advice of December 2006 refers several times to the option of tighter regulation, including the statement that "there are potential advantages in retaining BZP as a restricted substance, as the Misuse of Drugs Amendment Act 2005 has provisions allowing a range of restrictions to be put in place".

- relied on information from two sources (letter from the National Poisons Centre and report from the MRINZ) that are subject to serious challenge

Response: The EACD advice was based on an assessment of all the information available to it, without placing undue emphasis on any particular study. The Committee identified a number of issues with the National Poisons Centre study when it considered that study at its December 2006 meeting, and reported these back to the authors. The MRINZ study has now been independently peer reviewed, and the EACD considered these reviews and the authors' response at the 3 May 2007 meeting.

- formed conclusions from results of recent studies in which there has been inaccuracies as well as misinterpretation and misrepresentation of the facts

Response: This is a matter of opinion. Reports on original research by MRINZ and the University of Auckland have now been independently peer reviewed.

- relied on research where the researchers could be viewed as having been compromised by the need to bid for funds or having a conflict of interest because of funding source

Response: This implies that the researchers who undertook Ministry of Health-funded research 'massaged' their results to fit with what they considered the Ministry (or Minister) wanted to hear. The EACD considers that this suggestion is not credible as the reputation of researchers and their ability to publish in high quality journals rests on their scientific independence.

Following this discussion, the Committee then reconsidered the assessment of BZP undertaken at its 29 November 2006 meeting against the criteria set out in section 4B of the MODA. Based on the new information, the Committee made some modifications to its earlier assessment. The full assessment follows: statements that are crossed out appeared in the 29 November assessment but have been replaced, removed or modified in this assessment; new or replacement statements are in **bold** (excluding headings).

**a. *The likelihood or evidence of drug abuse, including such matters as the prevalence of the drug, levels of consumption, drug seizures trends, and the potential appeal to vulnerable populations.***

- BZP is widely available, accessible and actively marketed.
- BZP is widely used: around 20% of people aged 13 to 45 have ever used party pills containing BZP, including nearly 50% of males aged 20 to 24. Around 15% of people aged 13 to 45 admit to using party pills in the past year.
- BZP is almost invariably used with alcohol.
- BZP is also included in some preparations intended for daily use such as dieting agents.
- Public perception is that party pills are being targeted to individuals under-18 year of age. Evidence also shows that under-18 year olds are using BZP.

- Drug seizures are not relevant in this case, although the EACD is aware that Australian jurisdictions are seizing BZP that has been ordered over the internet and shipped from New Zealand.

**b. *The specific effects of the drug, including pharmacological, psychoactive, and toxicological effects***

- BZP is an amphetamine-like substance with significant stimulant effects. The EACD is of the opinion that the current evidence suggests that BZP's potency is approximately one tenth that of the equivalent weight of dexamphetamine.
- Compared with other substances currently controlled under the MODA, the pharmacological, psychoactive and toxicological profile of BZP indicates that the risk associated with BZP use is lower than that of methamphetamine, and broadly similar to that of ephedrine.
- There are perceived beneficial effects (e.g. wakefulness and increased sociability).
- **One controlled clinical trial of BZP showed that it improved short-term performance on a driving simulator.**
- Adverse effects are common, in particular insomnia, headaches, flushes, nausea and vomiting, and some of these may be a result of piperazines other than BZP e.g. TFMPP. Seizures have been reported, including at apparently low doses.
- **One controlled clinical trial suggested that BZP blood levels reach a peak several hours after ingestion**
- ~~Studies show a relatively slow onset of effect, which can lead users to take repeat or high doses to gain a more rapid effect.~~
- BZP is excreted relatively slowly, which produces a prolonged duration of effect that possibly contributes to **some of the side effects such as prolonged insomnia.** ~~the pronounced "come down" effect.~~
- The effects of chronic use are unknown.
- ~~A controlled trial demonstrated frequent and severe adverse effects from BZP and TFMPP.~~
- **One controlled clinical trial to assess the effect on driving performance of BZP alone and in combination with alcohol was stopped early due to the frequency and nature of side effects experienced by participants assigned to take BZP/TFMPP (with or without alcohol). All participants had previously taken BZP-containing party pills. Side effects described by the participants as severe in nature were experienced by 7 of 17 of the participants assigned to take BZP/TFMPP, and none of the 18 participants assigned to placebo. Other factors may have influenced or explained the nature and severity of the side effects, including: that the trial was conducted during the day and in a laboratory situation; the relatively high dose of BZP used, and; the requirement that participants were fasting and abstinent of caffeine and tobacco (and may have been experiencing withdrawal symptoms).**
- There is potential for severe toxicity in some individuals, which has been reported after ~~relatively~~ **apparently** low doses.

- BZP is often taken with alcohol and other drugs, making toxicological effects difficult to predict.
- **There is potential for users to inadvertently take a toxic dose – a dose that causes significant side effects – due to a wide range in the level of BZP in different preparations.**

**c. *The risks, if any, to public health***

- Although there are no formal reports, there is potential for harm to others e.g. the effects of rebound fatigue or acute intoxication on driving performance or operation of machinery
- There is concern that BZP use has been ‘normalised’, potentially creating or contributing to an increased risk of a culture of drug use that may encourage individuals to participate in other substance use.
- It is possible that some users who would otherwise use more harmful drugs especially methamphetamine are using BZP as a legal (and safer) alternative.
- As with alcohol and other psychoactive drugs, there is the potential to affect neurodevelopment in adolescents.
- There is a suggestion of links with New Zealand’s culture of risky alcohol consumption
- Evidence shows very low levels of intravenous BZP use presently, hence there is a low risk of blood-borne communicable diseases associated with its use. The availability of raw BZP powder and the potential to extract BZP powder from capsules creates a potential risk of increased intravenous use.
- There is a public perception that the legal status implies that BZP has been through a robust regulatory process and is thus considered ‘safe’, even though the products are not subject to any form of safety or quality review before they enter the market.
- There is no evidence of aggressive behaviour, sexual assault or date rape type behaviours.
- ~~There have been no recorded deaths solely as a result of BZP use. Use of BZP is associated with a high rate of adverse effects: severe adverse effects occur unpredictably and have been reported at relatively low doses.~~
- **Use of BZP is associated with a high rate of adverse effects; many of these are relatively minor in nature and appear to deter many occasional users from becoming regular users.**
- **Severe adverse effects appear to be uncommon but occur unpredictably and have been reported at apparently low doses.**

**d. *The therapeutic value of the drug, if any***

- No evidence in any robust scientific studies to date has shown that BZP has any therapeutic use in humans.
- At least one product containing BZP is actively marketed in pharmacies as an aid to weight loss. Some anecdotal evidence of contribution to weight

loss, which would fit with its status as a stimulant, **and self treatment of social anxiety.**

***e. The potential for use of the drug to cause death***

- There is no evidence to date of any deaths in New Zealand or internationally caused solely by BZP consumption.
- ~~However,~~ Toxic effects, **including hyponatraemia and especially BZP-related grand mal seizures, that have been described even at relatively low doses, while very rare,** have the potential to lead to death.
- The potential to cause death is increased from the way in which BZP is frequently used with other substances, **especially alcohol, (e.g. alcohol)** and in high doses. **High rates of concurrent substance use occur despite warnings on BZP-containing products and manufacturers' websites not to mix with alcohol and other drugs.**

***f. The ability of the drug to create physical or psychological dependence***

- Some evidence suggests that BZP has the ability to create dependence **in a very small proportion of users.**

***g. The international classification and experience of the drug in other jurisdictions***

- BZP is not classified in any international drugs treaties.
- The United Nations Office on Drugs and Crime International Narcotics Control Board has previously written to New Zealand requesting information on our experience with BZP and intentions regarding possible controls.
- Australia and the USA have made BZP illegal, although on the basis of little or no experience with the drug. **The UK has recently determined that the sale of BZP domestically falls under existing legislative provisions to regulate medicines.**
- There is a growing international perception of New Zealand being a primary BZP supplier, which has the potential to impact on New Zealand's international reputation.

***h. Any other matters for consideration that the Minister may consider relevant***

- A key concern is the widespread availability of BZP with few restrictions on and how BZP can be sold and by whom.
- Most party pills also include TFMPP, which may be responsible for some of the adverse effects. Other piperazines, about which there is no safety information, are now being included in some party pills.
- A possible mechanism for reducing demand and funding regulatory and enforcement activities could be subjecting party pills to taxation other than GST e.g. an excise tax.

- Should BZP be made illegal, this may discourage people who continue to use it from seeking medical attention if they experience adverse effects.
- A key policy issue that needs an explicit decision is whether New Zealand wishes to have a legal market for psychoactive drugs.
- **There is some evidence of an apparent reduction in use of BZP over the last 6 months, including a reduced rate of BZP-related presentations to the Christchurch Hospital emergency department, which has a high level of awareness of this substance.**
- **The ESR Drugs Group data suggest a ‘blurring’ of the legal and illegal drug market, with tablets and capsules containing BZP and a range of illegal substances now appearing. However, there is no evidence to date that illegal substances have been included in any BZP-containing party pills being marketed and sold by ‘legitimate’ businesses e.g. specialist shops.**
- **There is a possibility that, should BZP be classified as a Class C substance, manufacturers of BZP-containing products will turn their efforts to producing new substances that are not covered by any existing or new legislative provisions.**

The Committee reaffirms the following key points contained in its December 2006 advice to you.

- There are potential advantages in retaining BZP as a restricted substance, as the Misuse of Drugs Amendment Act 2005 has provisions allowing a range of restrictions to be put in place.
- While scheduling BZP as a controlled substance under the MODA will lead to the removal of existing party pills from the legal market, the change in legal status is no guarantee that the availability and use of BZP will decrease. However, the Committee points to the recent experience with GHB (Fantasy), where scheduling of the substance has led to a significant decrease in its use. In addition, the widely-described negative effects of BZP use (such as insomnia, headaches and nausea) suggest that this is not likely to be a drug that people will actively seek if it is less available, more expensive and carries risks associated with illicit status.
- In theory, a regime could be put in place to control, *inter alia*, the availability, advertising and supply of BZP, which would address some of the concerns about its current availability and use. However, in practice this will require the establishment of a significant administrative and enforcement capacity, for example as there is for pharmaceuticals and for the legal drugs tobacco and alcohol.

In particular, the Committee wishes to strongly re-emphasise the following point:

“While it is the EACD’s view that the research has now demonstrated that BZP does pose a moderate risk of harm, newer substances may be shown to pose a low risk of harm but still be worthy of restrictions. The Committee’s view is that the implementation of restrictions should place the burden of proof on the person supplying the substance to demonstrate the safety of a new psychoactive substance.”

In the Committee's view, placing responsibility for proving safety on those supplying these substances in New Zealand is key to progress efforts to take a measured and evidence-based approach to drug classification and, importantly, reducing drug-related harm. This would require legislative change separate from any decision about scheduling BZP.

Having discussed the new information available, the Committee reconsidered the recommendations contained in its December 2006 advice to you. As in our earlier discussion, there were different views among Committee members as to the potential risk of harm posed by BZP. Two Committee members considered that BZP poses a low risk of harm. A further Committee member considered that BZP poses a low-to-moderate risk of harm. Five Committee members present at this meeting held the view that BZP poses a moderate risk of harm. The two Committee members unable to attend this meeting and who attended the November 2006 meeting held the view at that time that BZP poses at least a moderate risk of harm.

Therefore, the majority view of the EACD is that BZP poses a moderate risk of harm, and on this basis the Committee continues to recommend that:

- 1. BZP be classified under Schedule 3 Part 1 (Class C1) of the Misuse of Drugs Act 1975**
- 2. the classification as a Class C1 drug covers all known analogues and derivatives of benzylpiperazine and phenylpiperazine that have no known therapeutic use**
- 3. BZP be removed from Schedule 4 of the Misuse of Drugs Amendment Act 2005 in order that it no longer be a Restricted Substance**

All Committee members support the earlier recommendation that:

- 4. work continue to further develop the regulatory framework and enforcement capacity that would support the Restricted Substances provisions of the Misuse of Drugs Amendment Act 2005.**

The Committee re-emphasises that it is important that additional regulations supporting the provisions of the Misuse of Drugs Amendment Act 2005 are adequately supported. For example, a licensing regime might be required, which will require administration and enforcement capacity.

Yours sincerely

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**Chair, Expert Advisory Committee on Drugs.**