

COMMISSION ON HUMAN MEDICINES**Working Group on Harm Reduction & Nicotine Replacement Therapy**

Extract from the minutes of the meeting held on **Wednesday 14th October 2009 at 10.00am** in the 19th Floor Conference Rooms, Market Towers.

COMMISSION ON HUMAN MEDICINES**Working Group on Harm Reduction & Nicotine Replacement Therapy****1. Apologies and Announcements**

- 1.1** The Chair reminded those present that the papers and proceedings are confidential and should not be disclosed.
- 1.2** The Chair reminded members to declare their personal specific, personal non-specific, non-personal specific and non-personal non-specific interests in the agenda items.

2. Background

- 2.1** The Chairman went through the Terms of Reference of the Working Group (WG). These were :
 - to consider the evidence of safety and efficacy of a harm reduction element as part of the indication for the Nicorette inhalator
 - to advise on whether indications including harm reduction are appropriate for other forms of NRT
 - to advise on changes to product information that would maximise the benefits and minimise the risks of NRT in relation to active and passive smoking
 - to advise on communication of relevant information to health care professionals and the general public.
 - 2.2** MHRA presented an overview of licensed products that were on the UK market and ran through the approved indications, which included temporary abstinence and use in pregnant women and other vulnerable populations.
- 3. MA 15513/0179 Nicorette/ Boots Johnson & Johnson/Boots
NicAssist 10mg
Inhalator (nicotine)**

- 3.2** The MHRA presented to the WG the application for a harm reduction indication for the Nicorette Inhalator product. The proposed indication is: “Nicorette Inhalator relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence. It is indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them. Nicorette Inhalator is indicated in pregnant and lactating women making a quit attempt.”
- 3.3** The WG noted that in addition to the currently authorized indications (abrupt quit attempt; cut down to quit), the proposed indication included temporary abstinence (as is already authorised for some other forms of NRT) and reduction in smoking without an intention to quit and without restriction of duration.
- 3.4** The MHRA summarised the data in the paper to support efficacy both in relation to the specific product and published data in relation to NRT. This included data from 2 placebo-controlled studies, which showed the Nicorette inhalator to be effective in relieving cravings and withdrawal symptoms during nicotine abstinence, and efficacy was also shown for abrupt cessation in those motivated to quit. In addition, there were 2 pivotal studies resulting in efficacy (as measured by subsequent quit rates) for the inhalator in smokers who cut down but were not motivated to make an abrupt quit attempt. Published data for other forms of NRT also supported this finding.
- 3.5** The available data on safety were summarised and although limited in terms of long term duration, did not indicate an increased risk of adverse events over time. There was no evidence from the available data of an association with cardiovascular disease or other serious adverse events with long term use of NRT.
- 3.6** The Agency proposed that the marketing authorisation (MA) holder should provide acceptable advertising and product launch programme as well as an acceptable monitoring programme to address areas of concern identified.

4. Consideration of use of Nicorette inhalator in pregnancy

- 4.1** The WG gave initial consideration to the inclusion of use in pregnancy in the harm reduction indication. The WG noted that there was a substantial body of evidence which showed the negative effects of tobacco smoke on growth and lung function in the foetus, particularly in late pregnancy. Early intervention in pregnancy was therefore important and even cessation for a short period would be beneficial. There was a time limited opportunity for a successful quit attempt and very real consequences of a failed quit attempt. It was important for early interactions with General Practice to encourage a quit attempt, supported by NRT if necessary.
- 4.2** The WG advised that NRT use in pregnancy must be better than continuing to smoke and that its use in pregnancy should be indicated in Section 4.1 of the Summary of Product Characteristics (SPC). The Patient Information Leaflet (PIL) was an important vehicle for ensuring women understood the risk benefit context and that the ideal would be to stop smoking without the help of NRT. The WG advised that the proposed SPC wording in relation to pregnancy could be improved and clarified.

5. Consideration of the evidence of the safety and efficacy of a harm reduction element as part of the indication for Nicorette Inhalator

- 5.1** In addition to the data submitted with the application the WG also received tabled information and comments. The WG considered the data provided in relation to efficacy and agreed that Nicorette Inhalator had been shown to relieve cravings and withdrawal symptoms, improve the likelihood of a successful abrupt quit attempt and reduce the amount smoked in those not immediately motivated to quit. Due to the demonstrated efficacy from relief of cravings and withdrawal symptoms, the efficacy for temporary abstinence was considered satisfactory.
- 5.2** The WG considered the data provided in relation to safety. It was noted that there was a well established favourable risk benefit for Nicorette inhalator in the current indication, however if the extended indication was approved individuals may use the product long term. From the data available for patients without pre-existing cardiovascular disease there was little evidence that nicotine was a risk factor for this, however, the WG highlighted the absence of long term safety data in patients with cardiovascular disease.
- 5.3** The WG noted that there was no evidence of an increase in cardiovascular or Myocardial Infarction (MI) events or in deaths related to NRT use. Although not submitted with the application, the WG noted that the SCENIHR report Health Effects of Smokeless tobacco Products (February 2008) was highly relevant. This study evaluated, among other products, SNUS (a moist snuff from Sweden). The study did not show an increased risk of cardiovascular disease, nor an increased risk of MI. When MI did occur in the study, however, it was more likely to be fatal. The study showed a small increase in the risk of pancreatic cancer. The WG concluded that there was a spectrum of evidence which supported the safety of NRT in long term use and that the Swedish data supported this conclusion.
- 5.4** The WG also considered the safety of concomitant use of NRT and smoking. There was evidence of an increase in blood nicotine levels compared to smoking alone but this was balanced against the lower intake of other toxins contained in tobacco smoke, such as carbon monoxide. There was some evidence to suggest smokers regulated their own nicotine levels, just as they do when smoking tobacco alone. The WG therefore concluded that the overall effect of reducing the consumption of smoked tobacco was beneficial.
- 5.5** The WG considered that due to the local irritation that was often experienced with the Nicorette Inhalator product, abuse/dependence was unlikely to occur and even if abuse/dependence did occur it was likely to be considerably less harmful than smoking.
- 5.6** The WG considered a number of points of concern that had been identified in the assessment report relating to possible indefinite use of NRT and concurrent use with smoking.

5.7 i) Evidence of health benefits of cutting down smoking, as opposed to quitting completely, has yet to be established

The WG noted that no evidence of health benefits of cutting down smoking, as opposed to quitting had been submitted as part of the variation application. They also acknowledged that, although there were some data it was limited. It was stated that a systematic review (Pisinger & Godtfreson, Nicotine & Tobacco Research 2007;6:631-46) suggested that a substantial reduction in smoking improved several cardiovascular risk factors, and respiratory symptoms. Overall it was agreed that there was some evidence that cutting down reduced the risks associated with smoking and that this was likely to be helped by use of NRT as this would reduce compensatory smoking. The wider benefit to society of smokers cutting down was also an important factor, in relation to the known harms of secondary or passive smoking.

5.8 ii) Will cutting down undermine a future quit attempt?

The WG agreed that there was a lack of data as to whether cutting down could undermine a future quit attempt, although noted that the available evidence pointed towards a reduction in smoking being beneficial to future quit attempts. The WG noted that new Quality and Outcome Framework (QOF) targets resulted in GP practices being rewarded according to how many patients they helped to quit smoking, rather than those cutting down. It was noted, however, that there was a NICE consultation on QOF targets at the time the WG met.

5.9 iii) The established tendency of ‘compensatory smoking’ when smokers cut down the number of cigarettes smoked but get relatively more nicotine by smoking more intensely and or/using higher nicotine content cigarettes

The WG agreed that available data showed that there might be an increase in blood nicotine levels as a result of ‘compensatory smoking’ when smokers cut down but that this needed to be balanced against the reduced overall smoke intake.

5.10 iv) Promotion of relapse among quitters and increased initiation of smoking by suggesting that low-rate smoking is relatively safe

The WG agreed that this was a theoretical concern with some surveys having shown that a very small number of ex-smokers might subsequently choose to use nicotine containing products long term.

5.11 v) The theoretical risks of long-term NRT use (including activation of tumour producing genes and cardiovascular toxicity)

The WG agreed that there was no evidence that nicotine encouraged tumour growth. Circumstantial evidence had been observed in animals, however, the Swedish study involving SNUS use provided evidence of long term safety and did not show any evidence of oral cancer. In addition, although not particularly robust, the available evidence did not indicate that the long-term use of NRT is associated with cardiovascular illness or other serious side effects.

5.12 The WG noted that in cases where there was a lack of long term safety data this would be addressed in a risk management plan.

5.13 The WG advised that the MA holder should be asked to provide a robust risk management plan that would satisfactorily address the outstanding issues including:

- Further investigation of the impact of the harm reduction indication on quit rate at a population level
- Re-assurance on the safety of long-term use – particularly cardiovascular safety in those with underlying cardiovascular disease
- Possible promotion of relapse among quitters by suggesting that low-rate smoking is relatively safe
- Possible increased initiation of smoking by suggesting that smoking can be done in a somewhat safe manner.

6. Extension of the harm reduction indication for other forms of Nicotine Replacement Therapy

6.1 The WG discussed whether a harm reduction indication would be appropriate for other forms of NRT and agreed that the available evidence supported a common approach to all currently licensed NRT products, with common core indications for all products. The WG noted that dose, speed of delivery and concentration of nicotine and other components of tobacco smoke impacted on addiction whereas nicotine alone was less addictive and the risk of primary addiction was thought to be low. There may be a spectrum of risk of addiction with the nasal spray products at the higher end and patches at the lesser end, but any such risk needed to be balanced against the risk of tobacco addiction. There was some evidence to suggest blood nicotine levels were slightly higher when a patch was used concurrently with smoking than when NRT gum was used concurrently with smoking. The WG noted that the patch was the most commonly used product and that anecdotal evidence suggested smokers already used them to cut down the amount they smoked. The WG advised that it would be helpful to agree core elements of an NRT SPC and MHRA said they would take this forward to ensure consistency.

7. Changes to product information to maximise the benefits and minimise the risks of NRT in relation to active and passive smoking

7.1 The WG advised that the product information should have more emphasis and clarity on the positive indication for use in pregnancy and advice about the benefits of concurrent use of NRT whilst continuing to smoke. Messages about the harms of smoking for pregnant and breast feeding women were needed and the message that NRT is better than smoking needed to be strengthened. This provided an opportunity to communicate the message that it was not nicotine that was the most harmful component of smoking tobacco. It was agreed that the PIL should be considered by members of the Patient Information Expert Advisory Group (EAG). The Group advised that use of headlines in NRT PILs would be an important means of communicating key messages.

7.2 The WG advised that the SPC wording of warnings relating to other at risk populations, such as those with cardiovascular disease and diabetes etc should be reviewed to ensure they would not discourage people in these groups from using NRT.

8. Communication of relevant information to health care professionals and the general public

8.1 The WG was briefed on how their advice would be conveyed to the CHM, whose advice would be taken into account by the Licensing Authority (LA) in reaching a decision. The need for strict confidentiality to be observed by all present was again stressed in that the decision of the LA would have implications for the regulation of other products, which would need to be thought through and considered in the context of the wider DH Strategy.

8.2 Assisting smokers to quit was one of the goals of the DH strategy, together with preventing young smokers starting and reducing harms to wider society. In this context, the harm reduction approach fitted well with wider Government strategy.

8.3 MHRA said that the WG had provided helpful advice on the key headline messages including around the dangers of smoking and taking control of smoking, however, there would be opportunity for further discussion with the WG depending on the outcome of CHM discussion and the Licensing Authority decision. It was likely that complex messages would need to be communicated and advice from the Patient Information EAG would be important in moving forward. DH said they would be looking at how messages were communicated with hard to reach groups. The British Heart Foundation said they had a portfolio of information and educational materials about smoking that would be helpful. The WG commented that public communications would also need to address some of the reasons smokers use for continuing to smoke, such as stress and preventing weight gain.

8.4 As part of the application, J&J had provided early sight of their advertising ‘concepts’. The WG suggested that more work was necessary on the images and the concepts, including covering the issues relating to pregnancy in one or more examples.

9. Other issues relating to the licensing of nicotine containing products

9.1 It was noted that companies were trying to develop innovative NRT products with new formulations and delivery systems and advised that MHRA should consider how this might be facilitated. MHRA confirmed the Agency’s commitment to supporting innovation and highlighted the availability of scientific advice meetings which were recommended as early as possible in product development in order to be maximally useful.

9.1 The WG advised that it was important that the approach to innovative products was flexible and supportive and that the licensing requirements were clearly and effectively communicated.

10. Any other business**10.1 None.**

Members are reminded that the content of papers and proceedings of the meeting are to be treated as 'Restricted - Commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice.