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The Secretory
Medicines Classification Committee
Medsafe, Wellington

22 December 2020

RE: Recommendation made at the 65th meeting of the Medicines Classification Committee

Dear Committee Members,

Thank you for the opportunity to provide feedback on the recommendations made at the 65th meeting of the Medicines Classification Committee held on 27 October 2020.

AFT Pharmaceuticals Ltd. object the recommendation that:

The current classification for hyoscine butylbromide should remain unchanged.

The decision letter describes the following considerations:

1. The Committee briefly discussed the proposal and were satisfied with the overall safety profile of hyoscine butyl bromide. However, concerns were raised over the undesirable effects such as hallucination and induced delirium.
2. The Committee note there is a potential for unintended misuse of liquid form hyoscine butylbromide in paediatric patients and an increased risk to elderly patients with reduced renal function.
3. The Committee concluded the potential harm outweighs the suggested benefit a liquid dose form would provide. The Committee noted that the available tablets are very small and do not perceive swallowing as an issue, therefore a liquid dose form has few advantages over the tablet.

AFT would like to request Medsafe to consider our explanation on each of these points as mentioned below:

Point 1: The Committee briefly discussed the proposal and were satisfied with the overall safety profile of hyoscine butyl bromide. However, concerns were raised over the undesirable effects such as hallucination and induced delirium.

We acknowledge the Committee's satisfaction with the overall safety profile of hyoscine butyl bromide. Regarding concerns over the undesirable effects such as hallucination and induced delirium, AFT would like to point out the fact that these undesirable effects are experienced following parenteral administration of Hyoscine butylbromide and are rare. Medsafe's datasheet for Buscopan tablets and injection[1] reads:

Very rarely in the national post marketing surveillance data base, there have been isolated reports following parenteral administration of coma, hallucinations, dystonia, confusion, agitation and dizziness from which the patient recovered after drug withdrawal and appropriate treatment.

On the other hand, the datasheet[1] also reads:

Anticholinergic side effects of BUSCOPAN and BUSCOPAN FORTE are generally mild and self-limited.

Hence, the side effects which may be associated with the oral liquid formulation are the same as those experienced after taking tablets, and these are mild and self-limited.

Point 2: The Committee note there is a potential for unintended misuse of liquid form hyoscine butylbromide in paediatric patients and an increased risk to elderly patients with reduced renal function.

The classification requested for Hyoscine butylbromide oral liquid formulation is Restricted (Pharmacist Only) Medicine. Since this product will be "Pharmacist Only" medicine, there is no risk of a person buying the product without a clear knowledge of his indications and the effectiveness of this product to treat his/ her indications. Hence there is no potential of misuse due to "mistaken" buying of this product for some other indication.

a. Risk of misuse in paediatrics: The dosage instructions[1] for Hysocine butylbromide tablets is "Adults and children over 6 years: 2 BUSCOPAN 10 mg tablets (20 mg) four times a day". The proposed product, Hyosince butylbromide oral liquid will also have the same dosing instructions. Hence, there is no risk of misuse in infants or children below 6 years of age. Regarding dosing in children above 6 years of age, a dose of 20 mg is recommended to be administered at one time. The concentration of the proposed product is 1 mg/mL. This corresponds to a dose of 20 mL. This quantity (20 mL) is a substantial amount and the risk of dosing error is very low. Further, the dose of 20 mL will be repeated after 4-6 hours and a maximum dose of 80 mg (80 mL) can be taken by the child in one day. Hence, in worst case, a slight dosing error of 1 or 2 mL should not be significant.

b. Risk of misuse in elderly patients with reduced renal function: Following oral administration, hyoscine butylbromide remains available at the site of action in the intestine and exerts a local spasmolytic effect. The bioavailability of hyoscine butylbromide, estimated from renal excretion, was generally <1%[2]. Studies in man show that only 2 to 5% of radioactive doses is eliminated renally after oral, and 0.7 to 1.6% after rectal administration. The urinary excretion of hyoscine butylbromide is less than 0.1% of the dose. Approximately 90% of recovered radioactivity can be found in the faeces after oral administration[1]. Hence, it can be concluded that hyoscine butylbromide is not significantly absorbed into systemic circulation and not primarily excreted by kidneys. Therefore, it should not pose any problems in renally compromised patients.

   After intravenous administration too, clinical studies with radiolabeled hyoscine butylbromide show that 42 to 61% of the radioactive dose is excreted renally and 28.3 to 37% faecally. The portion of unchanged active ingredient excreted in the urine is approximately 50%. The metabolites excreted via the renal route bind poorly to the muscarinic receptors and are therefore not considered to contribute to the effect of the hyoscine butylbromide[1]. Further the Wellington ICU Drug Manual[3] also states that no dosage adjustment is required for Hyoscine butylbromide injection in renally impaired patients.

   Hence, it can be concluded that oral formulations of hyoscine butylbromide do not pose any problem (and do not require any dose adjustment) in renally impaired patients.

Point 3: The Committee concluded the potential harm outweighs the suggested benefit a liquid dose form would provide. The Committee noted that the available tablets are very small and do not perceive swallowing as an issue, therefore a liquid dose form has few advantages over the tablet.

AFT acknowledges the committee's comment that the available tablets are small and do not perceive any swallowing problems. However, the product is indicated for symptomatic treatment and hence it will always be better if the dose can be titrated better. The CMI of Buscopan tablets[4] states "If you no longer have any stomach pain it is not necessary to finish taking all the tablets in the pack". This means if the patient is experiencing improvement, he does not need to stick to the 10 mg or 20 mg dose which the tablets offer. The liquid product being available as 1 mg/mL offers the flexibility of 1 mg dose with every 1 mL. This is, in turn, largely beneficial for patients and healthcare professionals as the dose can be titrated as per individual need.

References

1. New Zealand Data Sheet: Buscopan & Buscopan Forte - Hyoscine butylbromide. Accessed: 18 December 2020; Available from: https://www.medsafe.govt.nz/profs/Datasheet/b/Buscopantabinj.pdf.
2. Tytgat, G.N., Hyoscine butylbromide: a review of its use in the treatment of abdominal cramping and pain. Drugs, 2007. 67(9): p. 1343-57. doi: 10.2165/00003495-200767090-00007.
3. Wellington ICU Drug Manual: Hyoscine Butylbromide IV, PO, IM, SC. Accessed: 18 December 2020; Available from: https://drug.wellingtonicu.com/F-K/H/Hyoscine%20Butylbromide/.
4. New Zealand Consumer Medicine Information: Buscopan Tablets. Accessed: 18 December 2020; Available from: https://www.medsafe.govt.nz/Consumers/CMI/b/buscopantab.pdf.

Sincerely yours,

Regulatory Affairs Associate