**Submission for the Reclassification of hyoscine butylbromide**

**20 mg tablets (10 pack)**

**AFT Pharmaceuticals Ltd.**

**to**

**Medicines Classification Committee (MCC)**

**For the 50th Meeting**

**EXECUTIVE SUMMARY**

This application seeks the reclassification of 20 mg (per tablet or capsule) solid oral dose form containing hyoscine butylbromide as a single active ingredient in packs of 10 tablets from Prescription to Restricted (Pharmacist-Only Medicine). Hyoscine butylbromide 10 mg tablets are approved in NZ for the treatment of muscle spasm of the gastrointestinal tract at 20 mg per dose.

Hyoscine butylbromide is a quarternary ammonium compound that has poor oral absorption (8%) and low systemic bioavailability (>1%), although hyoscine butylbromide and its metabolites have been shown to have anti-spasmodic activity when administered orally. Side effects due to hyoscine butylbromide are uncommon because of this low absorption and bioavailability. Due to the quaternary ammonium structure, hyoscine butylbromide does not cross the blood-brain barrier and is thus not associated with CNS side effects that are occasionally seen with other hyoscine compounds.

Hyoscine butylbromide has been available since 1969 in NZ in tablets containing 10 mg of active (Buscopan 10 mg film coated tablet). A generic product (Gastro-Soothe 10 mg film coated tablet) became available in NZ as a restricted (Pharmacist-Only Medicine) in 2006. There are currently no 20 mg hyoscine butylbromide tablets available in NZ.

Australia currently has two brands of hyoscine butylbromide 20 mg film coated tablets (10 packs) approved as pharmacy only medicines: Buscopan Forte (Boehringer Ingelheim Pty Ltd), approved in 2011 and Cipla Stomach Ease (Cipla Australia Pty Ltd) approved in May 2013.

There do not appear to be any currently available 20 mg hyoscine butylbromide tablets available in the UK. Hyoscine butylbromide (known as butylscopolamine in the US), is not listed in the NDC, but rather a derivative (methscopolamine bromide) is listed as a human prescription drug.

Hyoscine butylbromide 20 mg (Gastro-Soothe Forte) is expected to be more convenient for the patient as only one tablet will need to be taken at each dosing time instead of two 10 mg tablets. As the pack size of hyoscine butylbromide 20 mg tablets is limited to 10 tablets per pack, this pack contains the same total amount of active as hyoscine butylbromide 10 mg 20 tablet packs (Buscopan and Gastro-Soothe). Thus, there should not be any issues with this pack size that are not already covered by the 20 pack of 10 mg hyoscine butylbromide tablets, thus should be consistent with the restricted (Pharmacist-Only Medicine) classification.

**PART A**

1. **International Non-Proprietary Name (or British Approved Name or US Adopted Name) of the medicine**

Hyoscine butylbromide (BAN) or Butylscopolamine (UAN).

2. **Proprietary Name(s)**

Gastro-Soothe Forte®

(hyoscine butylbromide 20 mg)

3. **Name of Company Requesting Reclassification**

AFT Pharmaceuticals Ltd

Level 1

129 Hurstmere Road

Takapuna

Auckland

NEW ZEALAND

4. **Dose Form(s) and Strength(s) for which a change is sought**

20 mg tablets

5. **Pack Size and Other Qualifications**

20 mg tablets of hyoscine butylbromide in blister foil packaging available in packs of 10, packed into a carton.

6. **Indications for which change is sought**

Hyoscine butylbromide is indicated for the relief of muscle spasm of the gastrointestinal tract.

7. **Present classification of medicine**

Prescription medicine.

8. **Classification sought**

Restricted (Pharmacist-Only Medicine).

9. **Classification status in other countries (especially Australia, UK, USA, Canada)**

Hyoscine butylbromide preparations are currently available in 41 countries worldwide (Martindale)

Hyoscine butylbromide 20 mg tablets are scheduled in the United Kingdom, United States of America, Australia and Canada as follows:

Australia: Pharmacy Only Medicine (S2)\*1

Canada: 20 mg tablets not listed.

United Kingdom: 20 mg tablets not listed.

United States of America: Hyoscine butylbromide not listed – derivative methscopolamine bromide listed as prescription only.

\*1 When included as the only therapeutically active substance, in divided preparations for oral use, containing 20 mg or less of hyoscine butylbromide per dosage unit in a pack containing 200 mg or less of hyoscine butylbromide.

Hyoscine butylbromide was first registered in Germany in 1951 and became commercially available in 1952. Since then, it has become a widely available medication worldwide, both as a prescription drug and an OTC medicine in several countries (Tytgat 2007). Countries where hyoscine butylbromide is registered as an OTC product (Tytgat 2007) include:

* Belgium
* Germany
* Italy
* Luxembourg
* The Netherlands
* Spain
* Switzerland
* UK
* Argentina
* Colombia
* Brazil
* Mexico
* Venezuela
* Japan
* South Korea
* Australia
* South Africa

10. **Extent of usage in NZ and elsewhere**

Hyoscine butylbromide 20 mg tablets (Gastro-Soothe Forte) are a new product intended for registration, and as such consent to distribute has not yet been given in NZ.

A competitor’s product (Buscopan Forte 20 mg hyoscine butylbromide tablets) is available in Australia.

Sales data (for both 10 mg and 20 mg hyoscine butylbromide tablets) for the past financial (2012) year in Australia and New Zealand is as on the following pages.

**AUSTRALIA**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| A 3A ANTISPASMOTIC/ANTICHOLINE | |  |  | **Pharmacy Sales (2012)** | **Hospital Sales (2012)** |
| **Manufacturer** | **Brand** | **Strength** | **Pack**  **size** | **Unit Sales** | **Unit Sales** |
| **BOEHRINGER**  **INGELHM** | **BUSCOPAN** |  |  | **834,400** | **14,800** |
|  | BUSCOPAN FORTE TABS | 20.0 MG | 10 tabs | 357,900 | 500 |
|  | BUSCOPAN TABS | 10 MG | 20 tabs | 464,000 | 11,500 |
|  | BUSCOPAN TABS | 10 MG | 100 tabs | 12,500 | 2,800 |
| **ASPEN** | **CHEMIST OWN STOMACH & PAIN** |  |  | **37,500** | **30** |
|  | CHEMIST OWN STOMACH & PAIN TABS | 10 MG | 20 tabs | 37,500 | 30 |
| **KEY PHARMA** | **STOMEX** |  |  | **24,000** | **-** |
|  | STOMEX TABS | 20.0 MG | 10 tabs | 24,000 |
| **AMCAL** | **AMCAL STOMACH & PAIN** |  |  | **22,700** | **-** |
|  | AMCAL STOMACH & PAIN RELIEF TABS | 10 MG | 20 tabs | 22,700 |
| **GUARDIAN** | **GUADRIAN STOMACH & PAIN** |  |  | **7,800** | **-** |
|  | GUADRIAN STOMACH & PAIN RELIEF TABS | 10 MG | 20 tabs | 7,800 |
| **PHARMACOR LIMITED** | **STOMACH EASE** |  |  | **6,100** | **18,700** |
|  | STOMACH EASE TABS | 10.0 MG | 20 tabs | 6,100 | 18,700 |
| **VALEANT** | **SETACOL** |  |  | **1,500** | **3,700** |
|  | SETACOL TABS | 10.0 MG | 20 tabs | 1,500 | 3,700 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Total AU Market** | |  | | |
| **Strength** | | **Volume (packs)** | | |
| 10 MG (20s) | | 573,530 | | |
| 10 MG (100s) | | 15,300 | | |
| 20 MG (10s) | | 382,400 | | |
| Extra product in Aus (multiple ingredients) | | |  | **Pack Size** | | **Unit Sales** | **Unit Sales** |
| **PFIZER** | **DONNATAB** | |  |  | | **97,000** | **300** |
|  | DONNATAB TABS | | Hyoscine hydrobromide 6.5 microgram + Hyoscyamine sulfate 103.7 microgram + Atropine sulfate 19.4 microgram | 25 tabs | | 51,000 | 200 |
|  | DONNATAB TABS | | 50 tabs | | 46,000 | 100 |

**NEW ZEALAND**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| A 3A ANTISPASMOTIC/ANTICHOLINE | | |  |  | | **Pharmacy Sales (2012)** | | **Hospital Sales (2012)** | |
| **Manufacturer** | **Brand** | | **Strength** | **Pack size** | | **Unit Sales** | | | **Unit Sales** |
|
| **AFT** | **AFT GASTROSOOTHE** | |  |  | | **234,900** | | | **5,540** |
|  | AFT GASTROSOOTHE TABS | | 10.0 MG | 20tabs (OTC) | | 12,000 | | | 40 |
|  | AFT GASTROSOOTHE TABS | | 10.0 MG | 20tabs\*\* | | 222,900 | | | 5,500 |
| **BOEHRINGER INGELHM** | **BUSCOPAN** | |  |  | | **500** | | | **-** |
|  | BUSCOPAN Tabs | | 10.0 MG | 100 tabs | | 500 | | | No sales |
| \*\*I think this one is on tender | | |  |  | |  |  | | |  | |  |  | |  | |  | | |  |
| **Relevant notes - NZ** | |  | | |  | | | | | |  |  | |  | |  | |  |  | |
| There is a new medicine application submitted to Medsafe for Stomach Soothe Tabs (Hyoscine butylbromide 10mg) by Arrow Pharma - submitted on 26/03/2013 | | | | | | | | | | | | | | | | | | |  | |
| No other registered products | | | | |  | | | | | |  |  | |  | |  | |  |  | |

|  |  |
| --- | --- |
| **Total NZ Market** |  |
| **Strength** | **Volume (packs)** |
| 10mg (20 tabs) | 240,440 |
| 10mg (100 tabs) | 500 |

11. **Labelling and/or Draft Labelling for the proposed new presentations**

(See attached draft artwork in Appendix 1).

12. **Proposed warning statements if applicable**

(See attached artwork in Appendix 1).

13. **Other products containing the same active ingredients which would be affected by the change.**

To the best of our knowledge, no 20 mg hyoscine butylbromide tablets are currently available in New Zealand thus no other product should be affected.

**PART B.**

1. **Statement of the benefits to both the consumer and to the public expected from the proposed change**

Abdominal cramping, that is not associated with organic, infectious or parasitic illnesses, are frequently encountered in Western adult populations with an estimated occurrence of up to about 30% (Tytgat 2007).

A multinational survey examined the incidence of abdominal cramping and pain in nine different countries including Belgium, Germany, Italy, UK, Japan, USA, Argentina, Brazil and Mexico (Quigley et al 2006). This survey showed wide variation in the prevalence of abdominal cramping ranging from 10% in Japan to 46% in Mexico. The Latin American countries had the highest prevalence of abdominal cramping and pain compared with Japan as the reference country. Quigley et al (2006) also found that the prevalence of abdominal cramping and pain was higher than men in all countries, except Germany.

Abdominal cramping and pain is not life-threatening, but it has a significant impact on the patient’s quality of life and subsequent socioeconomic consequences (Maxion-Bergemann et al 2006, Simrén et al 2004). Current treatment of abdominal cramping and pain focuses on relieving symptoms; diet, lifestyle and behavioural changes are often recommended as an adjunct to pharmacotherapy (Tytgat 2007). Medications used to treat abdominal cramping and pain include; antispasmodics (muscle relaxants), analgesics, antacids, antidiarrhoeals, laxatives and anti-gas products. Choice of medication is largely dependent on what symptoms are dominant or the most irritating (Tytgat 2007).

Hyoscine butylbromide is an efficacious, widely used antispasmodic medication for treating the symptoms of abdominal cramping and pain (Tytgat 2007).

*Mode of Action of Hyoscine Butylbromide*

Hyoscine butylbromide is an anticholinergic with high affinity for GI tract smooth muscle cell muscarinic receptors. The anticholinergic properties give rise to spasmolytic (muscle relaxing) action on the smooth muscle of the gastrointestinal, biliary and urinary tracts (Tytgat 2007). As a quaternary ammonium derivative, hyoscine butylbromide does not enter the central nervous system. Therefore, anticholinergic side effects at the central nervous system do not occur. Peripheral anticholinergic effects also result from binding of hyoscine butylbromide to nicotinic receptors also occurs in the visceral wall of the GI tract, creating a ganglion-blocking effect (due to the quaternary ammonium structure), as well as from anti-muscarinic activity (Tytgat 2007).

As a quaternary ammonium compound, hyoscine butylbromide is highly polar and

hence only partially absorbed following oral (8%) administration (Samuels 2009). Systemic

availability has been found to be less than 1% (estimated from renal excretion), with plasma concentrations often below the limit of detection (Tytgat 2007). Nevertheless, despite the briefly measurable low blood levels, hyoscine butylbromide and/or its metabolites have been observed at the sites of action (Samuels 2009) and the high tissue affinity of hyoscine butylbromide for muscarinic receptors means that it remains available at the site of action and generates a local muscle relaxant effect (Tytgat 2007).

The half-life of the terminal elimination phase t1/2γ is approximately 5 hours. The total

clearance is 1.2 l/min, of which approximately half is excreted unchanged renally. The main metabolic pathway is hydrolytic cleavage of the ester bond (Tytgat 2007). The main metabolites found in urine bind poorly to the muscarinic receptor, and are not thought to contribute to the therapeutic effect of hyoscine butylbromide. Elimination of hyoscine butylbromide after oral administration is mostly via faecal excretion and a small urinary excretion component. Hyoscine butylbromide does not pass the blood-brain barrier and plasma protein binding is low. Cmax has been observed to be 5 ng/mL (Tytgat 2007).

The change of scheduling proposed is expected to make it easier for the consumer, likely improving patient compliance as the dosing is effectively the same as for the currently available 10 mg tablets - they would only need to take **one** tablet up to four times daily, rather than the current **two** hyoscine butylbromide 10 mg tablets up to four times daily (up to 80 mg per day). There are no currently available 20 mg hyoscine butylbromide tablets on the market in New Zealand.

The Pharmacist-Only classification provides a health professional consultation to help rule out more serious causes of muscle spasm of the gastrointestinal tract, such as renal colic or gastroenteritis, which may be masked by the anticholinergic and antimuscarinic action of hyoscine butylbromide on the GI tract.

**2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated**

Diagnosis of muscle spasm of the GI tract in the first instance ***may*** be required to be by a doctor as abdominal muscle spasm (cramping) or abdominal pain can be from a variety of causes such as renal colic, irritable bowel syndrome, colitis and gastroenteritis. However, this will largely depend on the symptoms present. If unsure, or a more serious cause is suspected, the pharmacist may refer the patient to their doctor.

**3. Relevant comparative data for like compounds**

Meta-analyses performed indicate that differences between hyoscine butylbromide and other antispasmodics are likely to be small and therefore not clinically relevant (Lesbros-Pantoflickova et al 2004, Poynard et al 2001, Tygat 2007). Tygat (2007) also stated that there was no data to support difference in tolerability between hyoscine butylbromide and other antispasmodic agents, however as hyoscine butylbromide is a locally acting medication with poor systemic bioavailability and because it does not cross the blood-brain barrier, one would expect hyoscine butylbromide to be associated with a lower frequency of CNS and/or anticholinergic adverse events compared to readily systemically available smooth-muscle relaxants or those medicines that do cross the blood-brain barrier.

**4. Local data or special considerations relating to New Zealand**

AFT Pharmaceuticals Ltd (NZ) has identified no local data or special considerations with regard to GASTRO-SOOTHE FORTE® (hyoscine butylbromide 20 mg tablets) which could be regarded as being specific to New Zealand.

**5. Interactions with other medicines**

The effects of antimuscarinics may be enhanced by concomitant use of other medications that have antimuscarinic effects such as amantadine, phenothiazine antipsychotics, some antihistamines, quinidine, disopyramide and tricyclic antidepressants. Inhibition by MAOIs of medication-metabolising enzymes may potentially enhance the effects of antimuscarinics. The effect of antimuscarinic activity of reducing gastric motility may affect the absorption of other medications. Concomitant treatment with metoclopramide, cisapride and domperidone may result in dimunition of the effects of both drugs on the gastrointestinal tract. Antimuscarinic medications and parasympathomimetics may counteract the others effect (Martindale).

Hyoscine butylbromide can increase the tachycardic effect of β-adrenoreceptors (β-blockers).

Stockley’s Drug Interactions reports that “no adverse interaction usually appears to occur with hyoscine (scopolamine) and alcohol, although hyoscine hydrobromide presents more of a theroretical risk than hyoscine butylbromide”.

**6. Contraindications and Precautions**

This medication is contra-indicated in myasthenia gravis, megacolon and in patients who have demonstrated prior sensitivity to the product.

Because of the potential risk of anticholinergic complications, hyoscine butylbromide tablets should be administered with caution in patients susceptible to narrow angle glaucoma, intestinal or urinary outlet obstruction and those inclined to tachyarrhythmia.

Elevation of intraocular pressure may be produced by the administration of anticholinergics such as hyoscine butylbromide in patients with undiagnosed and therefore untreated narrow angle glaucoma.

*Pregnancy and Lactation*

Long experience has shown no evidence of ill effects during human pregnancy. Preclinical studies in rats and rabbits did not show either embryotoxic or teratogenic effects. Hyoscine butylbromide is classified with medications that have been taken by only a limited number of pregnant women but without an increase to the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. However, the usual precautions regarding the use of drugs at this time, especially during the first trimester, should be observed. Safety during lactation has not yet been established; however, adverse effects on the new born have not been reported.

*Effects on Ability to Drive and Use Machines*

In rare cases hyoscine butylbromide may cause drowsiness, if affected, patients should not drive or operate machinery.

**7. Possible resistance**

Not applicable.

**8. Adverse Events**

Anticholinergic side effects including xerostomia, dyshidrosis, tachycardia, visual accommodation disturbances, and potentially urinary retention may occur but are generally mild and self-limiting.

There have been rare reports of dizziness, drop in blood pressure, and flushing.

Hypersensitivity reactions including skin reactions, dyspnoea, anaphylactoid reactions and anaphylactic shock have been reported very rarely.

Elevation of intraocular pressure may be produced by the administration of anticholinergics in patients with undiagnosed and therefore untreated narrow angle glaucoma.

In rare cases hyoscine butylbromide may cause drowsiness, if affected, patients should not drive or operate machinery.

In addition, oral absorption and systemic bioavailability are low (8% and >1% respectively), so side effects resulting from oral administration of hyoscine butylbromide are much less common with at the normal dose than with the equivalent dose given intravenously (Samuels 2009). Most common side effects associated with this medication are mild and resolve spontaneously (Samuels 2009).

**9. Potential for abuse or misuse**

Hyoscine has previously been used by criminals to incapacitate and produce anterograde amnesia in their victims in crimes such as drug-facilitated rape (‘date rape’), robbery, and kidnapping. However, the quaternary derivative used in GASTRO-SOOTHE® and GASTRO-SOOTHE FORTE® (hyoscine butylbromide) is poorly absorbed after oral administration (8%) with a very low systemic bioavailability of less than 1% (Samuels 2009, Tytgat 2007). As stated in Martindale, hyoscine butylbromide is a quaternary derivative and as such, it does not readily cross the blood brain barrier so effects on the CNS due to hyoscine butylbromide are rare.

**CONCLUSION**

We believe that the rescheduling of hyoscine butylbromide at these strengths in the respective pack sizes will not impose any safety risks to the New Zealand population as the total amount of active being sold per pack is the same as in the 10 mg 20 packs and control over the medicine is maintained as the pharmacist can refer the individual to their doctor to establish clinical need (i.e. someone requiring this medicine for the first time with symptoms that are potentially due to another underlying disorder or illness). However, for those that have previously used this medication, rescheduling it to be the same as for the 10 mg packs is expected to be more convenient for the consumer and improved patient compliance.

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