Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 2 – December 2016

Chronic obstructive pulmonary disease (COPD) – update on tiotropium inhalers

There have been several developments with tiotropium inhalers recently. Following the expiry of tiotropium's UK patent, the first lower cost 'equivalent' to Spiriva Handihaler has just been launched by Teva under the brand name **Braltus**. Also, the price of Spiriva Respimat (tiotropium aqueous solution for inhalation) dropped substantially earlier this year. As such, there may be opportunities for cost savings, which, given the high levels of tiotropium prescribing, may be substantial. Below we provide prescribers and medicines optimisation teams with a quick update on Braltus, which we hope may be useful for local discussions.

Whilst drug acquisition costs and savings are provided for information below, there are many other factors to consider with regards to inhaler choice. As per the comments in the latest update to the GOLD COPD guideline, the choice of inhaler device has to be individually tailored and will depend, most importantly, on the person's ability to use the device and their preference.

Update on Braltus

General product Information:

- Braltus was assessed by the UK's Medicines and Healthcare products Regulatory Agency (MHRA). The Public Assessment Report summarises the MHRA's evaluation of Braltus.
- Braltus is available as a single strength dry powder inhaler: tiotropium (Braltus) 10 microgram per delivered dose inhalation powder, hard capsule.
- It is important to note that Braltus has been named according to the dose of tiotropium that is '***delivered***' (i.e. the dose that leaves the mouthpiece), whereas the reference product Spiriva Handihaler (tiotropium 18 microgram powder for inhalation capsules) is named according to the '***pre-metered***' dose of tiotropium. The pre-metered dose for Braltus is 13 micrograms. **However, both products provide the same '*delivered*' 10 microgram dose of tiotropium.**
- Dosing regimens are the same for both products (inhalation of the contents of one capsule, once daily), using the products' respective delivery devices, which, in the case of Braltus, is the Zonda device.
- The therapeutic indications for Braltus and Spiriva Handihaler are identical, with both licensed as maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD). (*Note - tiotropium is also indicated as an add-on maintenance treatment in asthma, however, this applies only to the Spiriva Respimat aerosol inhaler – neither Spiriva Handihaler or Braltus are licensed for use in asthma*.)
- Based on the information provided in the Summaries of Product Characteristics (SPCs), the administration methods for the Braltus and Spiriva dry powder inhalers appear similar. Administration instructions in the patient information leaflets for Braltus and Spiriva Handihaler also broadly correspond. However, there are some differences in the appearance of the two products. The Braltus Zonda device is a different shape and has different livery (*green cap and body, and white push button*) to Spiriva Handihaler. Also, Braltus capsules are provided in a bottle with a safety ring, whereas Spiriva capsules are packaged in blister packs. Braltus capsules are colourless and transparent, which the manufacturer suggests may assist with confirmation that a dose has been delivered. In contrast, Spiriva Handihaler capsules are light green and marked with the company's logo and product code.
- For Spiriva, there is an option to prescribe only the refill capsules for use with an existing Handihaler device (*n.b the device should be cleaned by the patient each month, and discarded after 12 months*). For Braltus, a new Zonda device is provided with each prescription.
- Both medicines contain the same excipient: lactose monohydrate, which contains milk protein. Each Braltus capsule contains 18 mg of lactose monohydrate, whereas a Spiriva capsule contains 5.5 mg.
- For Braltus, the shelf life of the unopened product is 2 years, the same as for Spiriva Handihaler. Shelf-life is 60 days once the Braltus 30-capsule bottle is opened and 30 days for a 15-capsule bottle. Shelf-life for Spiriva capsules is 9 days after opening of a blister.
- The SPC for Braltus states do not refrigerate or freeze, or store above 25°C, which is in line with advice for Spiriva Handihaler (do not store above 25°C; do not freeze).

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Clinical programme for Braltus:

Approvals for generic drugs are generally based on 'abridged' clinical programmes that demonstrate bioequivalence to the originator (reference) product in pharmacokinetic (PK) studies. These studies are normally carried out in healthy volunteers to reduce variability; such studies are also considered acceptable by the European Medicines Agency to compare the lung deposition of different inhaled products.

The MHRA's assessment report indicates there were two 'pivotal' PK studies for Braltus. In the first study, tiotropium was administered at the approved 'delivered' 10 microgram dose. However, the plasma concentrations reached at this dose were too low to accurately measure.

The second PK study, which has also recently been published, employed a randomised, three-treatment period crossover design (n = 30) and used a double dose (20 micrograms) of tiotropium delivered from Braltus and Spiriva inhalers. To demonstrate bioequivalence, the 90% Confidence Intervals (CIs) of the ratios of key PK parameters for the test and reference products have to lie within 80-125%, which is the standard accepted range for bioequivalence studies. Both primary PK parameters for Braltus (*Cmax, AUC[0-t]*) were within this range.

Main bioequivalence study PK findings for Braltus:*

PK Parameter	Ratio: Braltus/Spiriva (%)	90% Confidence Interval+
AUC (0-t)	106.35	101.3 – 111.6
Cmax	96.45	87.3-106.6

**from Braltus Public Assessment Report. +Accepted 90% CI limits to demonstrate bioequivalence are 80-125%*

Four non-serious adverse events occurred during this study but resolved. The results of clinical examinations and laboratory screening gave no indication of adverse events or adverse drug reactions.

Other studies discussed in the assessment report compared the inhalation profiles of the two devices using placebo capsules, when used by patients with COPD and healthy volunteers who had been trained using the respective patient information leaflets. The peak inhalation flow rates through the two devices were similar; flow rates of 30-60 L/min were seen in patients with COPD, and these rates were considered suitable to achieve dose emission of the dry powder. *In vitro* studies provided evidence for the similarity of the particle size distribution, delivered dose and fine particle dose between the two devices over a range of inhalation flow rates.

Risk minimisation and other prescribing considerations:

- Guidance has been produced to minimise prescribing and administration errors due to differences between Braltus and Spiriva Handihaler (*see risk materials on emc website*). Key points are:
  - that the delivered doses of the medicines are the same, and if a patient is being switched from Spiriva Handihaler to Braltus, it is important to tell the patient and/or carer that the dosing schedule should remain as one capsule, once daily and that both products deliver equivalent doses. No dose adjustment is necessary.
  - it should also be highlighted that only the Zonda inhaler should be used with Braltus capsules.
- Brand name prescribing of inhalers is recommended to help avoid confusion about which device a pharmacist should dispense. This is especially important given the recent launch of branded generic inhalers, such as AirFluSal, DuoResp and Sirdupla. Whilst prescribing by brand is advised, generic substitution shouldn't occur in the case of Spiriva Handihaler and Braltus, due to the differences in pre-metered doses of the products (18 micrograms and 13 micrograms, respectively).
- As a reminder, in 2015 the MHRA issued a drug safety update for tiotropium, advising healthcare professionals to take the risk of cardiovascular side effects into account when prescribing tiotropium delivered via Respimat or Handihaler to patients with certain cardiac conditions, who were excluded from clinical trials of tiotropium (See update for full advice). These trials included the TIOSPIR, safety study, which compared the safety of tiotropium delivered via the Respimat and Handihaler devices. No significant difference was found in the risk of death, including death due to cardiovascular events and incidences of major cardiovascular adverse events, between tiotropium delivered via Respimat and Handihaler devices.

Economic considerations:

- 30-day treatment costs for tiotropium inhalers are provided in the table (prices are taken from MIMS.co.uk [Dec-16]; if discount agreements are in place locally, costs may vary)
- The Braltus dry powder inhaler therefore costs approximately £8-£9 less per 30 days' treatment compared with Spiriva Handihaler and Spiriva refills.
- Our analysis of PACT data estimates an annual saving for CCGs in England (combined) of around **£19 million** based on 50% of Spiriva Handihalers and refills being prescribed as Braltus.

30 day treatment costs: tiotropium inhalers (MIMS.co.uk; Dec-16)

Spiriva Handihaler (device and 30 capsules)	£34.87
Spiriva Handihaler (refill - 30 capsules)	£33.50
Braltus (device and 30 capsules)	£25.80
Spiriva Respimat (device and cartridge [60 puffs = 30 daily doses])	£23.00

- In the summer, the price of Spiriva Respimat (tiotropium solution for inhalation) dropped substantially, from £33.50 to £23.00 per device. It is currently the lowest cost long-acting muscarinic antagonist inhaler on the market (MIMS, Dec-16) and savings may be greater if Spiriva Respimat is prescribed in place of tiotropium dry powder inhalers.
- As with any inhaler change, careful consideration should be given to training the patient (and/or carer). In the case of changing from a Handihaler to a Respimat device, this would involve familiarisation with a different (aerosol) drug delivery system.