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26th January 2016

Dear Sir/Madam,

In light of the forthcoming general discussion on 26 January 2016 (18:00 – 20:00) of the standing committee on health, welfare and sport, on drug shortages in general and shortage of Thyrax in particular – please find below the position of Aspen Pharma Trading Limited (APTL), the marketing authorisation holder of Thyrax in the Netherlands:

APTL has problems with supply of Thyrax duotabs. The supply interruption is as a result of multiple technical requirements impacting availability

- Merck divested Thyrax to Aspen in January 2014
- Post marketing authorisation transfer, the implementation of a previously approved variation of bottle packing to blister packaging was undertaken via the original site of manufacture.
- Following the implementation of this change there was an increase in adverse events experienced by patients
- Consultation regarding these adverse events has been undertaken with the MEB and Lareb. These consultations have resulted in the MEB requiring Aspen to develop new discriminatory product test methods and implement tighter control specifications for Thyrax.
- Simultaneously, in alignment with agreed terms of agreement with MSD, Aspen was obligated to transfer the product to its site Aspen Bad Oldesloe in Germany. Aspen Bad Oldesloe is the approved manufacturer of Eltroxin and has extensive experience with the levothyroxine molecule.
- Given that Thyrax's historical formulation was registered on the basis of the historical test method and specifications, those new requirements have limited the chances of success of the technical transfer.
- The differences in the stability results obtained from the two sites of manufacture together with the need for more discriminatory test methods and tighter control specifications have meant that to date the transferred product cannot be placed on the market.
- Development of the new discriminatory test methods and application of the tighter specifications is ongoing and has been given priority.
- There is no evidence yet generated to show that the original MSD manufactured product will meet the new requirements and accordingly reformulation may be required.

- Aspen has continuously engaged all stakeholders and in this regard has had multiple written and face to face communications with MEB and Lareb throughout the process.

In conclusion

Thyrax is an old lactose based formulation developed and launched in the 1980's. The site transfer which Aspen was obligated to initiate to one of its sites which has extensive knowledge on the levothyroxine molecules, has now been impacted by the new requirements requested by the MEB. These have limited the chance of a successful transfer.

- The MEB has requested that Aspen consider

    - An observational study analysing AEs in a random chosen cohort of patients using levothyroxine (including all brands) could be considered. Occurrence of any AEs /symptoms of hypo/ hyperthyroidism should be investigated in relation to TSH and free T4 serum levels and other relevant laboratory values, levothyroxine dose, duration of use, levothyroxine formulation and brand.
    - It was agreed following subsequent follow up correspondence that this would not be required

- The MEB have required that Aspen develop and apply to the transferred product.
    - An update should include tightening of the release and shelf-life limits for assay and/or dissolution to a more appropriate, justified level and adjustment of the dissolution method and its acceptance criteria to achieve suitable discriminative power.

    - A method with sufficient in vivo relevance and/or the most discriminatory conditions from a QC perspective should be selected and a justification should be provided, taking into account the three applied test conditions.

MEB also stated that the ongoing dissolution and specification issue would need resolution before the transfer could be approved.

Significant work is required to ensure that the Thyrax product can sustainably be manufactured and supplied in accordance with the MEB requirements. In reality, as stated earlier the chance of success and even success timeously was not possible.

Throughout the process Aspen has engaged with key stakeholders in the best interest of the patient. In addition Aspen has prioritised production and ensured the availability of Eltroxin to meet the increased demand in the Netherlands.

The ongoing increase of regulatory and GMP requirements will continue to challenge products developed many years ago and situations such as this will arise.

Aspen, as evidenced by a detailed chronology of events has done everything reasonably possible to avert this issue and at all times has acted in the best interest of the patient. The reality of the additional MEB requirements have minimised this probability of success and definitely made success not possible in the timelines. Aspen can confirm that the switch of patients from Thyrax to Eltroxin or Thyrax to another brand will negatively affect Aspen's revenue. The shortage of Thyrax, as shown above is purely a technical issue.

It can be concluded that the shortage of Thyrax is no way a consequence of Aspen's negligence or wilful misconduct.

Aspen empathises with the patients impacted by this matter.

Penalising the pharma industry for stock outs caused by events such as the above which are outside of the control of the pharma industry through liability could potentially negatively impact the overall product portfolio made available in the Netherlands

David Flynn

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Mr. David Flynn
Executive: Group Pharmaceutical Affairs