Report on the Suspension of the Teva Marketing Authorisation for

Levothyroxine 100 microgram Tablets
(Teva UK Limited; PL 00289/0039)

Date: 22 April 2013

Medicines and Healthcare Products Regulatory Agency

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1 Lay Summary

Levothyroxine 100 microgram Tablets, marketed by Teva (marketing authorisation number PL 00289/0039) was first licensed in 1980. In September and October 2011, the MHRA noted an unexpected increase in reports from patients and healthcare professionals, some supported by results of blood tests, raising concerns that the Teva levothyroxine tablet might not be equivalent to or as effective as levothyroxine tablets from other manufacturers. The number of these reports was small when compared to the number of patients taking levothyroxine in the UK nevertheless these reports prompted the MHRA to investigate this further.

At around the same time that concerns arose with the Teva product, the MHRA was conducting a general review of quality and clinical considerations relating to levothyroxine products marketed in the UK. This was prompted by a low number of reports received over the years from healthcare professionals and patients raising concerns about potential inconsistencies in the quality and effectiveness of different makes of levothyroxine products. A report on the outcome of that review was published on the MHRA website on 07 January 2013. As part of that review, the MHRA generated tablet dissolution data in order to compare the rate and extent to which the drug substance (levothyroxine sodium) dissolves from all the available levothyroxine tablets marketed in the UK. While differences in dissolution data do not necessarily correlate with clinical differences, the extent of dissolution when determined by MHRA methodology was significantly lower for the Teva levothyroxine tablet when compared with the other UK levothyroxine tablets.

Between December 2011 and February 2012, further reports of non-equivalence of the Teva product with other brands were received. Some of these reports were supported by blood test results from a number of patients which showed that blood plasma levels of thyroid stimulating hormone (TSH), the marker used to assess control of the patient's thyroid disease, was not in

the target range.

In January 2012, the MHRA became aware that manufacture of this product was not in regulatory compliance with its marketing authorisation. As a result, the MHRA were no longer assured that all aspects of manufacture were appropriately controlled.

In February 2012, these concerns were put to the Commission on Human Medicines (CHM), an independent panel of experts who advise the licensing authority. The CHM advised that as a precautionary measure, the marketing authorisation for Teva Levothyroxine 100 microgram Tablets should be suspended. Suspension prevented the release of any new batches of tablets onto the UK market. The CHM also considered whether to advise immediate recall of all remaining Teva levothyroxine tablets from the market. As this action would have led to significant supply shortages that could cause unnecessary difficulties for the majority of patients that could continue taking Teva levothyroxine tablets, immediate recall of the product from the market was not recommended. Therefore recall of remaining Teva levothyroxine tablets was performed on 09 May 2012 once the MHRA was confident that there was sufficient supply of alternative products available to patients.

On the same day as the suspension of the marketing authorisation (16 Feb 2012), the CHM issued advice to prescribers stating that the majority of patients would not incur serious clinical consequences by continuing with their medication and changing to a different levothyroxine product at their next prescription, therefore it was not necessary for them to have an early appointment. However, specific advice was given for certain patient groups who might be particularly susceptible to changes in Thyroid Stimulating Hormone (TSH) and may require close monitoring. This included pregnant women, those with heart disease and patients receiving this product for thyroid cancer. Physicians were requested to contact these groups with an early appointment for a clinical review and blood test. Further notification of the issue

was also provided by way of an Agency publication known as the Drug Safety Update. The general public were informed by a press release and a “Question and Answer” document as published on the MHRA website. Together with the final advice from CHM, these are reproduced in annex 2 of this report.

A subsequent investigation identified potential root cause(s) for non-equivalence, stemming from changes to grade / source of formulation components. The marketing authorisation for Teva Levothyroxine 100 microgram Tablets remains suspended. Any reformulated Teva levothyroxine tablet range will be reviewed by CHM before it is re-introduced onto the UK market and if approved, the MHRA will publish an assessment report in the normal way.

2 Introduction

The Levothyroxine 100 microgram Tablet (PL 00289/0039) was first licensed in October 1980 to Approved Prescription Services Ltd (APS). The name of the marketing authorisation holder was subsequently changed to Teva UK Limited in September 2006. This marketing authorisation was suspended on 16 February 2012, following advice from the Commission on Human Medicines (CHM), an independent panel of experts that advise the licensing authority.

This report describes the circumstances leading up to the advice of the CHM, the suspension of this product, the communications issued with regard to the suspension and the outcome of MHRA investigations immediately following suspension.

Levothyroxine is an essential medicine for the treatment of underactive thyroid conditions and is very widely prescribed. In 2010, the MHRA estimates that approximately 1,300,000 people took levothyroxine in the UK. Levothyroxine tablets are mainly prescribed on a generic basis (i.e. by its chemical name rather than by a brand name). There are a number of marketing authorisation holders of levothyroxine products in the UK.

Over the past five years MHRA has received an increased number of reports from healthcare professionals and patients raising concerns about potential inconsistencies in the quality and effectiveness of different makes of levothyroxine products, and between different batches of the same product. Starting in January 2011, the MHRA commenced a general review of levothyroxine products in the UK. Levothyroxine products are known to be challenging to manufacture. A report on the difficulties associated with manufacture of levothyroxine tablets was published by the MHRA on 07 January 2013.

http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON222565

In September and October of 2011, there was an unexpected increase in reports from healthcare professionals and patients regarding the Teva Levothyroxine 100 microgram Tablet. The MHRA became concerned that this product might no longer be equivalent to other brands; further details are given in section 3 (Pharmacovigilance and Quality Complaints) of this report. The MHRA performed a comprehensive investigation of the relevant pharmaceutical aspects relating to the product specification, manufacturing process history and an investigation into potential root causes (section 4). The advice of the CHM and the communications following suspension are detailed in section 5 of this report.

A chronology of events and interventions is given in table 1 below:

Table 1 Chronology of events relevant to suspension of marketing authorisation of Teva Levothyroxine 100 microgram Tablets

30 Oct 1980	Marketing authorisation granted to APS Levothyroxine 50 microgram & 100 microgram Tablets.
12 July 1999	Addition of an alternative site of manufacture for the drug product.
01 Oct 2002	Dissolution method changed in line with updated methodology of the United States Pharmacopoeia (USP).
25 Sep 2006	Marketing Authorisations Holder names changed to Teva UK Limited by variation.
07 Jan 2009	MHRA acknowledges a minor (Type 1A) variation to change the method of manufacture. However, owing to stability concerns, the newly registered method of manufacture was not implemented. Teva then reverted to the previously registered method of manufacture; however the company did not submit a variation to reinstate this. As the method of manufacture was no longer registered, all subsequent batches of tablets ceased to be in regulatory compliance.
18 May 2010	Teva cease manufacture / marketing Levothyroxine 50 microgram & 100 microgram Tablets owing to concerns over its stability and failure to comply with specifications.
14 July 2010	Teva return levothyroxine 100 microgram Tablet to the market; the 50 microgram dosage strength remains withdrawn.
31 Oct 2011	MHRA raises with Teva the increase in reports received suggesting therapeutic non-equivalence, together with comparative dissolution data generated by the MHRA laboratories.
03 Feb 2012	MHRA raises with Teva receipt of further reports from patients / healthcare professionals, coupled with lack of assurance over consistency / controls for method of manufacture.
09 Feb 2012	Concerns regarding potential non-equivalence of Teva Levothyroxine 100 microgram Tablets reviewed by CHM at their meeting in February 2012.
16 Feb 2012	Suspension of marketing authorisation for Teva Levothyroxine 100 microgram Tablets preventing release of any new batches of tablets; release of CAS alerting all Healthcare Professionals and pharmacies, together with supporting website communications, all of which are detailed in section 6 of this report.
21-22 Feb 2012	MHRA conducts a targeted GMP (Good Manufacturing Practice) inspection of batch release site for Teva Levothyroxine 100 microgram tablets.
09 May 2012	Class 3 drug recall of remaining Teva Levothyroxine 100 microgram Tablets from wholesalers and pharmacies.

3 Pharmacovigilance and Quality Complaints – review of reports

3.1 Reporting of adverse events and potentially defective products in the UK

Reporting suspected defective medicines

Healthcare professionals or patients may report to the MHRA's Defective Medicines Reporting Centre any concerns that they have on the quality of their medicines. This may be done by completing the MHRA's Suspected Defect Reporting form which is available from the MHRA's website:

http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Reportingsuspecteddefectsinmedicines/Suspecteddefectonlineform/index.htm

The MHRA investigates reports and takes appropriate action.

Adverse Drug Reactions: The Yellow Card Scheme

The UK Yellow Card Scheme exists to collect and monitor information on suspected adverse drug reactions (ADRs) and also captures reports relating to loss of efficacy and concerns with the quality of medicines. The purpose of the Scheme is to provide an early warning that the safety of a product may require further investigation. The Scheme is run by MHRA and currently relies on voluntary reporting of suspected ADRs by health professionals and patients. There is also a legal obligation for pharmaceutical companies to report serious ADR reports to their drugs. Further information is available on the MHRA's website:

http://yellowcard.mhra.gov.uk/

It is recognised that there is under-reporting to the Yellow Card Scheme and this is particularly true for reports relating to lack of efficacy as patients may not appreciate these can be reported. While some patients and healthcare professionals do use the Yellow Card Scheme for that purpose, concerns regarding lack of efficacy for Teva levothyroxine tablets are likely to be under-reported in both the Yellow Card Scheme and in reports to the company.

ADR reporting is also problematic in a situation where the adverse event is not evident in the short term such as would be the case with levothyroxine, where the effects of taking a potentially deficient tablet may not manifest for several weeks due to the nature of the underlying condition. Despite these limitations, the value of the ADR reporting system is

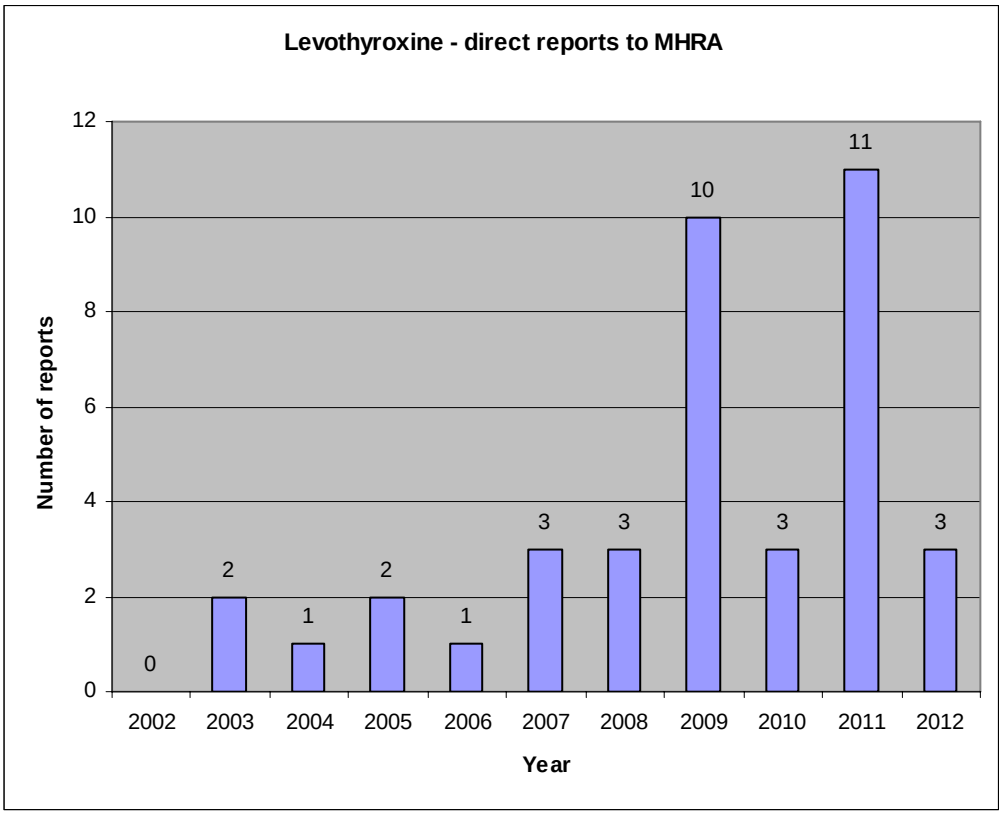
evident in that it did enable the MHRA to identify a peak in reporting for Teva levothyroxine tablets in the autumn of 2011.

3.2 Direct Reports to MHRA

Since 1990 to 03 February 2012, the MHRA has received approximately 45 reports that were referred to the Defective Medicines Report Centre, concerning all levothyroxine products that were marketed in the UK. These were received by a variety of routes: through the MHRA's information centre, directly to the Defective Medicine Report Centre (DMRC) and as Yellow Card reports. The number of reports remains small in comparison to the number of patients known to be taking levothyroxine, however increased reporting in autumn 2011 prompted a detailed review.

The frequency of defective medicine reports for the last ten years is depicted in Graph 1 below. This shows peaks in reporting in 2009 and 2011.

Graph 1 Number of reports received per year by the MHRA from Jan 2002 to 03 Feb 2012.



From 01 Jan 2010 to 03 February 2012, the majority of reports (13 out of 17) related to the Teva Levothyroxine 100 microgram Tablet and concerned apparent non-equivalence to other makes of levothyroxine. This was unexpected because the market share of Teva levothyroxine tablets was ~ 30-37% as estimated by Teva in 2011.

Prior to 2011, information on thyroid functions tests (clinical chemistry) was not available for the majority of reports. However, from 2011, the majority of reports of non-equivalence were accompanied by thyroid function data showing a correlation between patients changing to the Teva levothyroxine tablets and marked increase in thyroid stimulating hormone (TSH) and decrease in thyroxine (T4) levels, associated with a loss of control of hypothyroidism. The reports provided by dispensing GP practices in particular, show that raised TSH values were observed in clusters of patients once they were started on Teva levothyroxine tablets. These reports rarely described the clinical symptoms associated with raised TSH; however changes in TSH do not affect all patients in the same way.

In October 2011, Teva provided all product reports and ADR reports received since 2008 to the MHRA.

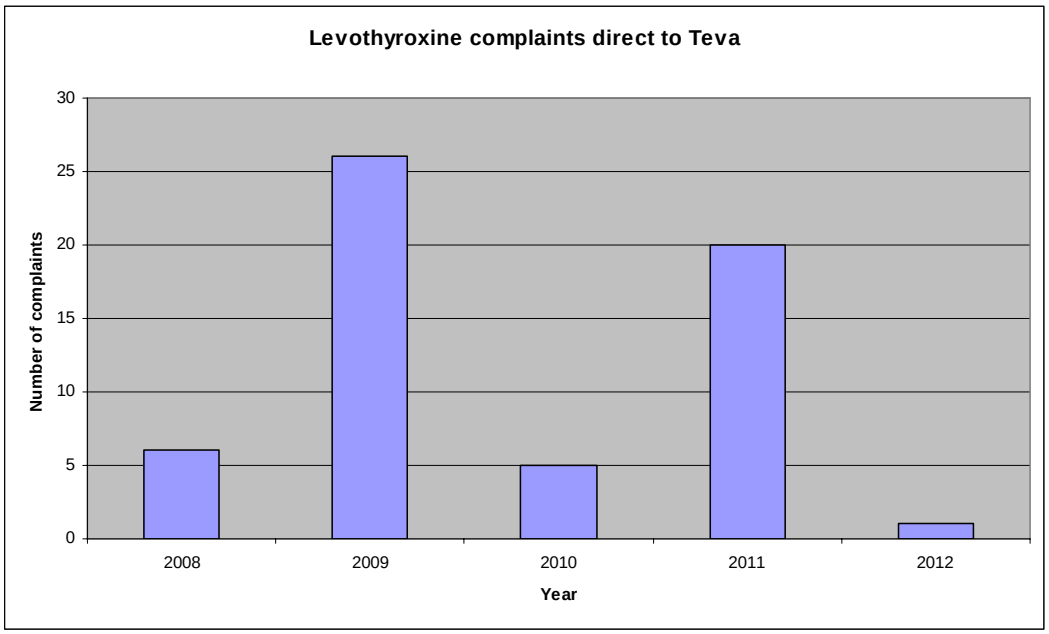
3.3 Direct Complaints to Teva

Complaints provided by Teva since 2008 also raised concerns regarding potential non-equivalence of Teva levothyroxine tablets; there were 58 complaints in total up to 26 Jan 2012, prompting 73 investigations. In a similar manner to reports received by the MHRA, these came from across the UK, concerned different tablet batches and originated from pharmacists, GP practices (including dispensing practices), primary care trusts and patients.

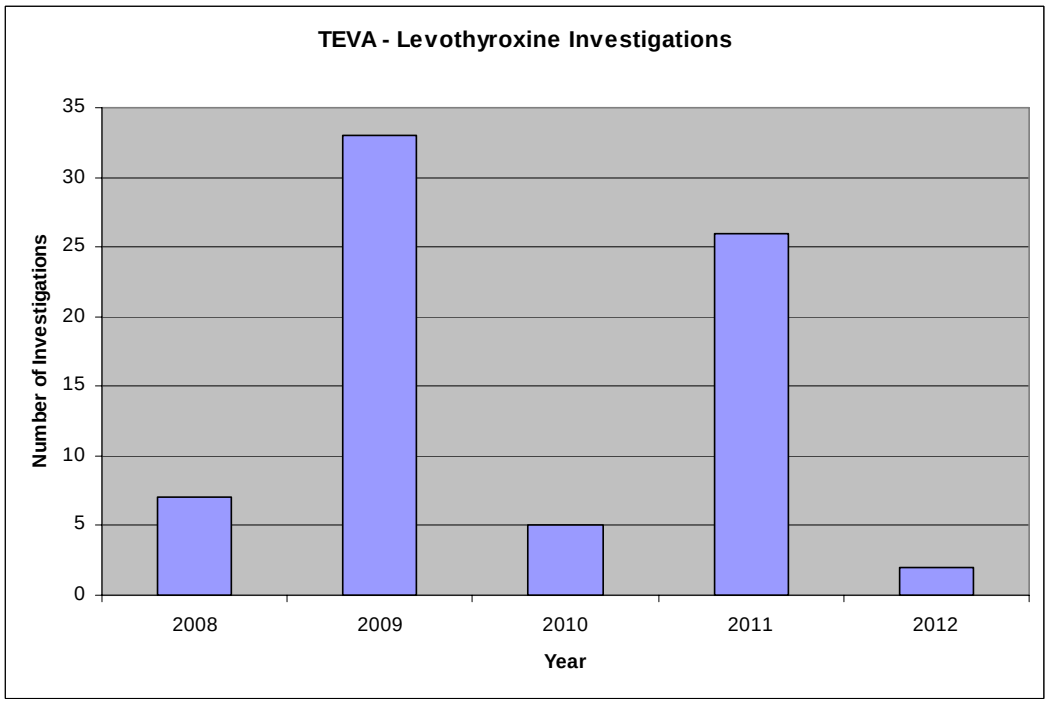
It should be noted that due to some complaints being reported to both the MHRA and Teva (duplicate reports), these will have been included in both the MHRA and the Teva figures. Therefore, the Teva incidence and the MHRA incidence figures will overlap. This duplication does not however detract from the signal in reporting incidence.

Graph 2 below shows the number of complaints received by Teva each year, from Jan 2008 to 26th Jan 2012. Graph 3 shows the number of investigations undertaken by Teva as a result of these complaints. These mirror the peaks in reporting to the MHRA in 2009 and 2011.

Graph 2 Teva: Number of complaints received per year (2008 to 26th January 2012) on Levothyroxine 100 microgram Tablets

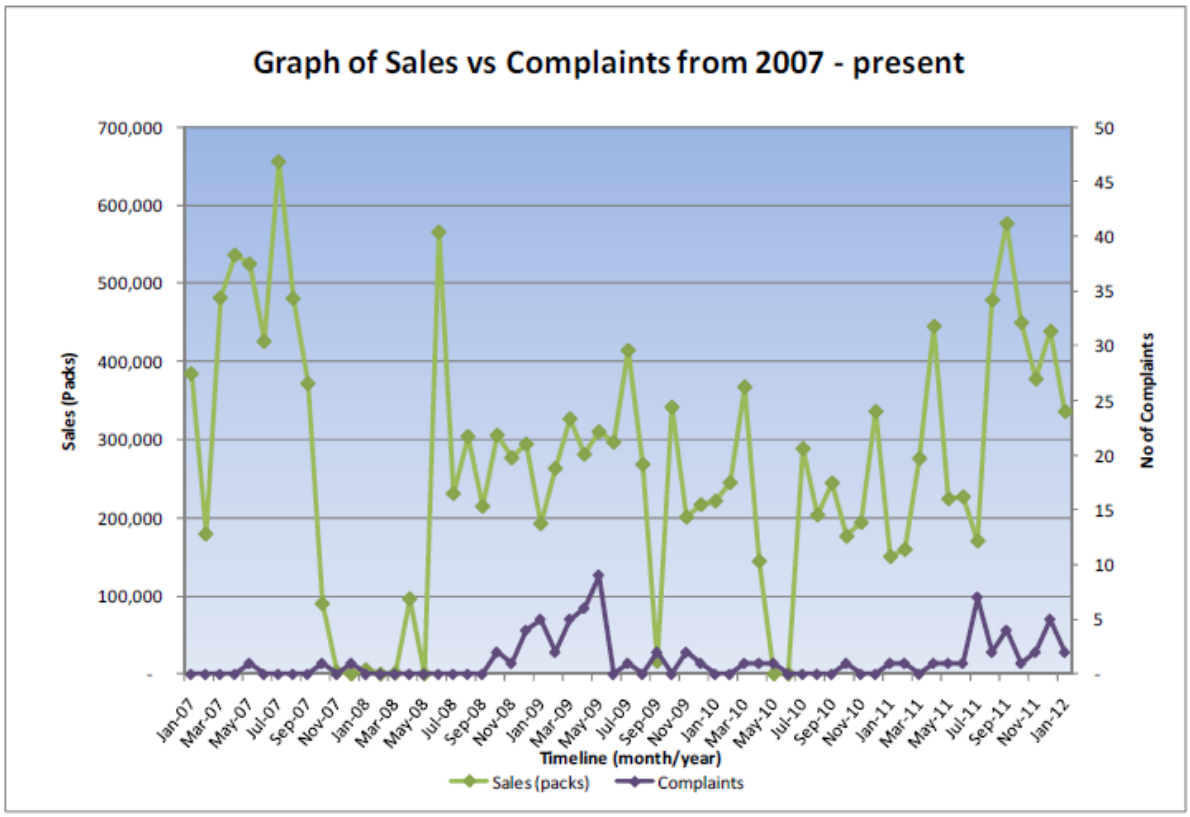


Graph 3 Teva: Number of investigations per year (2008 to 26th January 2012) on Levothyroxine 100 microgram Tablets



Graph 4 below, provided by Teva, shows how the number of complaints received per year compares with usage of their levothyroxine 100 microgram tablet over time. It is noteworthy that the peaks of reporting that occurred in 2009 and 2011 are not clearly mirrored by an increase in usage, suggesting that the increase in reporting was not simply the result of increased patient numbers.

Graph 4: Teva: Graph of sales versus complaints received from 2007 to January 2012



4 Quality aspects

An appropriate and comprehensive control specification is pivotal to assuring consistent manufacture and performance of all medicinal products. A review of key aspects of the manufacture and quality controls that are generally applicable to tablet products is provided in Annex 1.

In summary, the controls that ensure levothyroxine tablets are manufactured and released to an acceptable standard comprise a combination of:

- Provision and application of drug product specifications approved by the MHRA. As a minimum, this product is legally required to comply, when tested, with the British Pharmacopoeia (BP) Monograph for Levothyroxine Tablets.
- A legal requirement for the MAH to ensure that all batches released comply with the product specification, which is a responsibility of the Qualified Person (QP) of the manufacturing company.
- A legal requirement for the MAH to seek the approval of the MHRA for any substantive changes to the product formulation and/or manufacturing process as registered with the licensing authority.

Levothyroxine tablets are known to be sensitive to minor formulation and process changes. In January 2009, the MHRA acknowledged a variation notification to amend the manufacturing process of Teva Levothyroxine 100 microgram Tablets. However, owing to stability concerns, the company did not implement these changes and reverted to the previous method of manufacture without submitting a variation to reinstate this earlier process. As a result, after January 2009, manufacture of Teva levothyroxine tablets was no longer in regulatory compliance. Issues with regulatory compliance raised doubt about the consistency and control of manufacture in recent years. A regulatory review of the manufacturing process was presented to the CHM as well as a review of ADRs.

4.1 Teva levothyroxine 100 microgram tablet control specification

At the time that the marketing authorisation was suspended, the control specification for Teva Levothyroxine 100 microgram Tablets complied with the requirements of the British Pharmacopoeia (BP) monograph for Levothyroxine Tablets and included an additional control test for dissolution (release of levothyroxine from the tablet).

The relevance of key control tests applied to Teva's levothyroxine tablet is discussed below.

4.1.1 Assay (potency) limits

The content of levothyroxine drug substance contained within an average tablet is controlled by an allowed range for assay (the assay limits), expressed in terms of percent theoretical content of drug substance. The registered assay limits for the Teva levothyroxine product were 96 – 105% for release of batches to market with wider limits of 90 - 110% applicable throughout the shelf life (up to the expiry date).

The current BP Monograph for levothyroxine tablets requires limits over shelf-life of 90.0-105.0%. For the Teva product, the upper release limit of 105% meets the BP requirement and ensures compliance throughout shelf-life (since the content of levothyroxine cannot "increase" on storage). The lower specification limit of 90% over shelf-life is also in line with current BP requirements. Therefore, the content of drug substance in the Teva tablet, together with uniformity of content which is performed to compendial limits, are adequately controlled by the specification registered by Teva.

4.1.2 Dissolution tests and performance

Currently, the BP Monograph for levothyroxine tablets does not include a method and control limits for dissolution and therefore this is not a regulatory requirement. However, a discriminatory dissolution test and limits have been proposed following the recommendation of CHM and is anticipated to come into force as part of the BP Monograph for Levothyroxine Tablets from January 2014.

The control specification for the Teva levothyroxine 100 microgram tablet did contain a test and limit for dissolution performance which was included in the dossier at the time of initial authorisation. Since August 1990, this has been concordant with the monograph of the United States Pharmacopeia (USP), comprising dissolution in phosphate buffer, pH 7.4. Over time, the dissolution method applied to the Teva tablet specification was amended, in line with changes to the USP method as summarised in table 2 below.

Table 2 Dissolution tests and limits applied to control of the Teva Levothyroxine 100 microgram Tablet since 1998

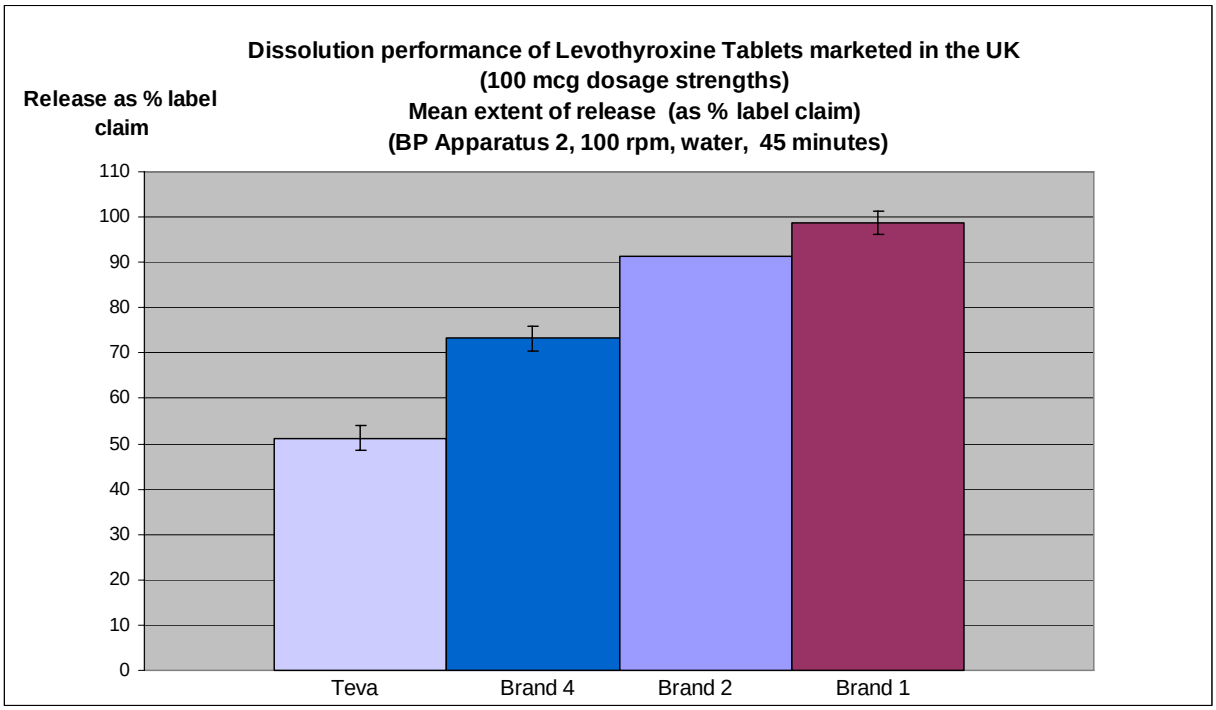
Date	Dissolution method details	Teva Control limits
1990 – Dec 2002	USP Monograph for Levothyroxine Tablets; USP 24 Medium: Phosphate buffer, pH 7.4 Conditions: Ph. Eur. Apparatus 2, 100 rpm	Not less than 70% at 30 minutes.
Dec 2002	USP Monograph for Levothyroxine Tablets; USP 24 Supplement 1 to current edition. Medium: 0.1M HCl containing 0.2% sodium dodecyl sulphate Conditions: Ph. Eur. Apparatus 2, 50 rpm	Not less than 80% at 30 minutes.

In August 2002, Teva filed a minor variation to change the dissolution method in line with the most recent edition of the USP monograph for Levothyroxine Tablets. This variation was authorised in October 2002.

Maintaining concordance with the most current version of the USP monograph was reasonable and justifiable and was approved by the MHRA. However subsequent published literature[1] [2] showed that the adoption by the USP of a dissolution medium containing the surfactant, sodium dodecyl sulphate, may have compromised its ability to detect the potential impact of changes to formulation or process upon the rate and extent of dissolution (discrimination). In hindsight and for this product, the sole use of the updated USP method may not necessarily have been capable of distinguishing between products which owing to differences in formulation and / or process may not have been compliant with the previous dissolution test and control limits.

As part of a wider review of levothyroxine products in 2011, MHRA analysts performed comparative dissolution analysis of all tablet products currently available in the UK. A range of dissolution conditions were evaluated before a discriminatory method was selected using water as dissolution medium, with BP Dissolution Apparatus 2 (100 rpm, 45 minutes). The batches listed below were obtained from community pharmacies; all met BP criteria of 90.0-105.0% for assay. The dissolution of the samples of UK levothyroxine products under these conditions are given in graph 5. Standard error bars are included where more than two batches were tested (for all products, n = 2 to 5 batches). These data demonstrate clear differences in extent of levothyroxine released between formulations, with relatively little inter-batch variability.

Graph 5 Comparison of dissolution (extent of release as % theoretical content) for Teva Levothyroxine 100 microgram Tablets vs. other UK Levothyroxine Tablets



Under these conditions, the extent of dissolution (levothyroxine released) for the Teva tablet is substantially lower than that obtained for all other manufacturers, however the clinical significance of this difference remains to be established.

Nevertheless, in light of reports received regarding potential non-equivalence, particularly those since Oct 2011, dissolution data for the Teva levothyroxine tablet gave cause for concern.

While higher than the Teva levothyroxine tablet, extent of release for Brand 4 was lower than that of Brands 1 and 2. On evaluation, there was no significant difference in terms of reports of potential inequivalence or any other adverse event for Brand 4.

These dissolution conditions form the basis of a new dissolution test that is proposed for inclusion in the British Pharmacopoeia monograph for Levothyroxine Tablets.

4.2 Composition, method and site of manufacture

Levothyroxine is prone to instability when formulated and the drug content in a tablet is extremely low. Therefore, there are significant challenges inherent in its formulation and manufacture which requires that these are very carefully controlled. Further information and literature references are given in the MHRA website publication “Levothyroxine tablet products: a review of clinical & quality considerations”.

The composition of the Teva Levothyroxine 100 microgram Tablet is listed below in table 3. The excipients (inactive ingredients) are typical of an immediate release tablet dosage form. The method of manufacture is also conventional, comprising wet granulation, drying, blending and tablet compression processes. No manufacturing in-process controls were registered with the MHRA, although it is expected that in-process controls were defined internally by Teva as part of routine batch manufacture. To meet current regulatory expectations, including the review of CHM conducted in March 2012, these would in future be required to be registered with the licensing authority.

Table 3 Composition of Teva Levothyroxine 100 microgram Tablets

Name of ingredient	Content per tablet (mg)	Function	Quality standards
Drug substance			
Levothyroxine sodium, anhydrous	0.100	Drug substance	BP
Excipients			
Magnesium stearate	**	Lubricant	BP
Maize starch	**	Bulking agent	EP
Lactose	**	Bulking agent	EP
Dextrin	**	Binder	BP
Granulation Solvent 1**	As required.***	Granulation solvent	BP
Granulation Solvent 2**	As required.***	Granulation solvent	In-house specification

** Confidential information
*** Granulation solvents are removed by evaporation during manufacture

From 1980 – 1999, Teva levothyroxine tablets were manufactured at the original site. In 1999, manufacture of the product was transferred to another manufacturing site, which in this report will be referred to as the replacement site.

4.2.1 Non-compliance with the registered manufacturing process

At the time of suspension of its marketing authorisation, the manufacturing process for Teva Levothyroxine 100 microgram Tablets was acknowledged by Teva to be out of compliance with the Marketing Authorisation.

A minor variation (Type 1A notification) that was acknowledged by the MHRA in January 2009 changed the method of manufacture at the replacement site. However product manufactured by this new method of manufacture proved to have significantly poorer assay stability, failing to comply with registered assay limits over the approved product shelf-life. As a consequence, Teva ensured that none of the batches manufactured by this amended process were released to market and discontinued the amended process.

Teva then reverted to the previously registered method of manufacture; however the company did not submit a variation to reinstate this. As this process was no longer registered, all batches of tablets released for marketing since 2009 ceased to be in regulatory compliance.

The company also implemented additional, seemingly minor, process, process control and excipient grade changes that were not reported to the MHRA by the submission of variations including a change to the source and grade of the tablet binder.

4.3 Potential root cause of non-equivalence of the Teva levothyroxine 100 microgram tablet

Subsequent to suspension of the marketing authorisation, investigations by the MHRA was performed to identify potential root cause(s) of non-equivalence. Based on a history of manufacturing changes, Teva agrees that the performance of Levothyroxine 50 & 100

microgram Tablet products have been shown to be sensitive to process and formulation changes. The Teva Levothyroxine 50 microgram Tablet has not been marketed since May 2010 owing to stability issues.

On 12 July 1999, a variation was approved enabling transfer of product manufacture from the original to the replacement site of manufacture. At this time, significant changes were made to the manufacturing process, including the composition of the granulation fluid and the principle of operation of the granulating equipment. This transfer was problematic; substantial difficulties arose during process validation studies and subsequent batches, with product failing to meet the specified minimum dissolution criteria by the dissolution method in place (USP 2004). This alerted Teva to problems with their product and process. Teva did not release to market any of the above batches which failed to comply with the product specification.

Variable dissolution performance was associated with minor changes in granulation conditions. Such sensitivity to relatively minor changes suggests that dissolution performance was strongly influenced by excipients included in the granulation step.

Two formulation changes have been identified that could have affected dissolution:

- Change in the title / grade of granulation solvent 1 in May 2002
  While grades of granulation solvent are closely related, these differ in quantitative composition. This change was also coupled with an increase in the relative proportions of granulation solvent 1 to granulation solvent 2 used for granulation.

- Change in source / grade of dextrin in Aug 2007 & Feb 2008:
  When the supplier signalled the discontinuation of the original source and grade of Dextrin BP, a number of alternative grades / sources were substituted. Each had noticeable effects upon ease of processing and on stability performance. The most recent grade / source of Dextrin BP has been in place since Feb 2008.

Of the above, dextrin has most potential to cause dissolution problems for the Teva levothyroxine tablet. It is known to gel on hydration and is used within this formulation as a binding agent (a material that helps wet particles to adhere during wet granulation and holds them in place once the granulation solvent has evaporated).

Control specifications (Monographs) for Dextrin BP are defined in the British and European Pharmacopoeias. While the specifications for dextrin correspond with these monographs, the drug product manufacturer specifications did not control functional characteristics such as viscosity, which may be relevant to the performance of the dosage form.

The variation provided to the MHRA in Dec 2002, supporting the change in dissolution methodology did not include an assessment of dissolution discrimination. In other words, it did not assess whether product that did not show satisfactory dissolution by the original method would also have failed by the new methodology. It is possible that the alternative grades of dextrin used in the manufacture of Teva levothyroxine tablets may have differed significantly in functional performance. This, either alone or in combination with other factors, may in turn, have impacted the extent of release under some dissolution conditions and possibly adversely impacted bioavailability.

To better assure the consistency and quality of levothyroxine products in the future, recommendations from a general review of levothyroxine products and endorsed in March 2012 by the Commission on Human Medicines, have been implemented. These include more stringent controls to quality, including the introduction of a discriminatory dissolution test in the BP Monograph and tighter regulatory controls.

5 MHRA regulatory actions and CHM advice

In early February 2012, in the light of further reports of non-equivalence supported by plasma TSH levels, aware that Teva was using an unauthorised manufacturing procedure and not reassured on the basis that the product continued to meet its shelf-life specification, the MHRA advised Teva that they believed that the product should be removed from the market as soon as the supply situation allowed. On 08 Feb 2012, Teva informed the MHRA of their decision to voluntarily cease further distribution of stock while they investigated the issues with the product.

5.1 Suspension of the marketing authorisation of the Teva Levothyroxine 100 microgram Tablet

The MHRA consulted with the CHM (an independent panel of experts that advise the licensing authority). On 09 February 2012, the CHM advised that the marketing authorisation for Teva Levothyroxine 100 microgram Tablets should be formally suspended due to potential safety concerns for this product and manufacturing issues. Acting on this advice, the MHRA suspended the marketing authorisation on 16 February 2012, pursuant to regulation 68(1) of, and paragraph 4(1) of Schedule 11 to, SI 2012/1916. The grounds of the suspension were lack of therapeutic effect (regulation 68(2)(c)) and breach of a term of the authorisation (regulation 68(4)(a)) – namely manufacture otherwise than in accordance with the notified description. The basis of the safety concerns are detailed below:

a. the defect reports submitted since 2009, including those supported by results of clinical chemistry which indicate that the generic Teva product cannot be used interchangeably with other levothyoxine products leading to loss of control of TSH levels;

b. the loss of control of TSH may have serious safety implications for certain subgroups of patients notably: those who are pregnant, especially in the first trimester of pregnancy, those under treatment with TSH suppressive doses of levothyroxine following treatment for thyroid cancer, and patients with heart disease ;

c. use of a non-discriminatory dissolution test which might not be able to discriminate between batches expected to have a different *in vitro* release rate profile; in conjunction with

d. manufacture of the medicinal product is not carried out in compliance with the particulars provided in support of the marketing authorisation.

The product lacked therapeutic efficacy, evidence of which had been submitted from healthcare professionals as defect reports supported by patients' blood levels of TSH becoming destabilised when changing to this product and the manufacture of the medicinal product was not carried out in compliance with the particulars provided pursuant to point (d) of Article 8(3) of Directive 2001/83.

Changes in TSH within the normal clinical range do not pose a risk to the health of the majority of patients. In certain subpopulations however, a more meticulous TSH control may prove critical. These include patients with heart disease and those with thyroid cancer who are on TSH-suppressive doses of levothyroxine due to tumour growth factor like properties of TSH. Loss of TSH control in patients with thyroid cancer is associated with a higher risk of cancer recurrence. Pregnant women (particularly in the first trimester) comprise another population at risk. Lack of efficacy of levothyroxine tablets during pregnancy could adversely affect the neuropsychological development and survival of the foetus. Lack of control of hypothyroidism in pregnant women may also be associated with hypertension and pre-eclampsia.

The above regulatory action formally prevented the release of further batches of tablets to the market while permitting Teva to undertake necessary investigations into the cause of the problem and remedial action.

5.2 CHM considerations regarding potential immediate recall of Teva levothyroxine tablets from the market

Consideration of an immediate recall of all existing stocks of Teva Levothyroxine 100 microgram Tablets from the market was discussed by the Commissioners at the CHM meeting of 09 February 2012. Immediate action would be considered appropriate if there were concerns that the product on the market may pose an immediate threat to safety of patients. Although the reports received between December 2011 and February 2012 were of concern, in the small number of reports that contain a description of patients' clinical status, serious adverse drug reactions had not been reported as a result of using the Teva product.

The CHM considered that there was no evidence that Teva levothyroxine tablets posed an immediate risk, but that it did have a distinctly different dissolution profile compared to levothyroxine tablets made by other manufacturers. This, together with non-compliance of the manufacturing process might be linked to the reports of lack of efficacy.

There were significant practical difficulties associated with an immediate product recall as, at that time, Teva was estimated to supply 30-37% of the market share of levothyroxine 100 microgram tablets. The Department of Health advised that an immediate recall would result in a large number of patients needing to have their treatment changed to another existing levothyroxine product. This resulting demand was likely to lead to a shortage of supply with some patients being unable to obtain levothyroxine 100 microgram tablets. The other manufacturers hold sufficient stock to supply the market in the short term but required between 4-6 weeks to increase future supplies. Hence if immediate recall was implemented,

there were significant risks that resultant supply shortages could lead to patients failing to receive their treatment.

The potential for over or under-dosing of levothyroxine that may occur as patients are switched between Teva levothyroxine tablets and those of other manufacturers was considered unlikely to lead to immediate serious clinical consequences for the majority of patients.

On balance a suspension of the marketing authorisation but without immediate recall was deemed the most appropriate course of action. This allowed gradual depletion of existing Teva stock over an estimated 3.5 weeks whilst other manufacturers increased production to fill the gap in the market. It also allowed time for GPs to arrange an appointment with patients to carry out additional monitoring if necessary.

Once sufficient supplies of levothyroxine tablets from alternative suppliers became available, the remaining stock of Teva Levothyroxine 100 microgram Tablets was recalled by means of a Class 3 drug alert on 9 May 2012. This was deemed to be practical and proportionate bearing in mind that there had been no changes in the CHM advice in the interim period.

6 Communication of CHM advice to healthcare professionals and the general public

Healthcare professionals were notified through a Dear Healthcare Professional communication, issued on 16 February 2012 through the Central Alerting System. In this, CHM advice to prescribers was that "the majority of patients will not incur serious clinical consequences by continuing with their medication and changing to a different levothyroxine product at their next prescription, therefore it is not necessary for them to have an early appointment".

Specific advice was given for certain patient groups who might be particularly susceptible to changes in TSH and may require close monitoring. This included pregnant women, those with heart disease and patients receiving this product for thyroid cancer. Physicians were requested to contact these groups to arrange an early appointment for a clinical review and blood test.

The full text of the Dear Healthcare Professional Communication can be found at:-

https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=101734

The general public was notified by means of a press release. The Agency also published a Question and Answer document at:

http://www.mhra.gov.uk/home/groups/comms-po/documents/news/con143690.pdf

7 Future MHRA action

Teva has expressed its intention to redevelop their levothyroxine tablet products and is aware that substantial data (including a clinical demonstration of bioequivalence and comprehensive dissolution data by discriminating methodology) will be required to demonstrate interchangeability with other UK marketed levothyroxine products. The advice of CHM will be

sought prior to any approval to return to market. If successful, the MHRA will publish a public assessment report on the reintroduction of the product.

Annex 1 – Background to Drug Product Control Specification and Tests

Drug product control specification

All licensed medicinal products are required to comply with a control specification, both at batch release and throughout their shelf-life. A specification comprises a list of tests, references to validated analytical procedures and acceptance criteria or limits. Specifications are established for active substances and for medicinal products and form part of the control strategy designed to ensure product quality and batch-to-batch consistency. It may be necessary to have tighter limits at the time of batch release to ensure that a batch of product remains in compliance with the shelf life specification throughout the approved period of use. Each batch of drug product must be tested and comply with its control specification prior to its release to market.

For many products that are prescribed on a generic basis, the British Pharmacopoeia (BP) includes monographs for medicinal products which define minimum control specifications. For a product that is marketed in the UK and the subject of a monograph in the British Pharmacopoeia, the finished product specification should take account of the requirements described in the monograph. Where a monograph might be insufficient to ensure the quality of the product, additional tests and limits should be included in the finished product specification.

Assay (content) limits

The content of drug substance contained within the average dosage unit is controlled by means of an allowed range expressed in terms of percent theoretical content of drug substance.

Dissolution test and limits

While the content of drug substance is important, in order for a drug substance to be absorbed from the gastro-intestinal tract, it must first be released from the dosage form and pass into solution. This process, known as “dissolution”, may be influenced not only by the fundamental physico-chemical properties of the drug substance, but also by physical factors such as its particle size distribution and surface area and by other constituents of the dosage form in which it is incorporated (its formulation as a tablet for example). Thus bioavailability will be dependent on the extent to which these factors affect the rate of dissolution of the drug substance. There are a number of methods described in the British Pharmacopoeia for examining dissolution testing in a laboratory setting, **although it is important to note that apparent differences in dissolution performance do not necessarily equate to differences in bioavailability or therapeutic effect.**

Qualified Person

A Qualified person (QP) is typically a registered pharmacist, biologist or chemist (or a person with another permitted academic qualification) who has several years experience working in pharmaceutical manufacturing operations, and has passed examinations attesting to his or her knowledge. Under European Union pharmaceutical legislation (Directive 2001/83/EC), all batches of medicinal product for human use must be certified by a QP as in accordance with the relevant requirements, prior to release to market.

Annex 2 – CHM Final Advice to the MHRA and Communications

Commission on Human Medicines		**FINAL ADVICE**
DATE OF MEETING	:	9th & 10th February 2012
REFERENCE NUMBER(S)	:	PL 00289/0039
COMPANY	:	Teva
PRODUCT	:	Levothyroxine 100 microgram Tablets
ACTIVE CONSTITUENT	:	Levothyroxine Sodium
THERAPEUTIC CLASS	:	ATC code H03AA01
KEY WORDS	:	

The Commission were requested to advise the Licensing Authority with regard to the following questions:

1. The Commission is asked to advise whether or not suspension of the marketing of Teva Levothyroxine 100mcg is justified under the urgent procedure on grounds of safety (a) with recall of marketed stock or (b) without recall of stock to facilitate management of supply; or

2. If not whether the Licensing Authority should consider suspension under the non-urgent procedure after the outcome of further planned investigations of manufacturing records : or

3. Whether the product can remain on the market with a longer term corrective action plan in place as (a) a generic product or (b) a branded product .

On the evidence before them, the Commission advised the Licensing Authority that suspension of the marketing authorisation of Teva Levothyroxine 100 mcg Tablets is justified under the urgent procedure on grounds of safety. These safety concerns arise from:

a. the defect reports submitted since 2009, including those supported by results of clinical chemistry which indicate that the generic Teva product cannot be used interchangeably with other levothyoxine products leading to loss of control of TSH levels;

b. the loss of control of TSH may have serious safety implications for certain subgroups of patients notably: those who are pregnant, especially in the first trimester of pregnancy, those under treatment with Thyroid Stimulating Hormone (TSH) suppressive doses of levothyroxine following treament for thyroid cancer, and patients with heart disease ;

c. use of a non-discriminatory dissolution test which might not be able to discriminate between batches expected to have a different in vitro release rate profile; in conjunction with

d. manufacture of the medicinal product is not carried out in compliance with the particulars provided in support of the marketing authorisation.

However, to facilitate management of supply, suspension without recall of stock was advised.

Safeguarding public health

Press Release

Date: Thursday 16 February 2012
Time: 16:15
Contact: Press Office 020 3080 7651
Out of hours 07770 446 189
press.office@mhra.gsi.gov.uk

MHRA suspends licence for Teva levothyroxine 100 microgram tablets

The Medicines and Healthcare products Regulatory Agency (MHRA) has suspended the licence of levothyroxine 100 microgram tablets, manufactured by Teva, for patients with hypothyroidism. This follows manufacturing difficulties and concerns that the product might not be interchangeable with other available levothyroxine 100 mcg tablets. This may lead to a loss of control of hypothyroidism when switching between products.

Only levothyroxine 100 mcg tablets supplied in the Teva and Numark brands are affected. As this medicine is a generic, alternative products are available and most patients are unlikely to notice any change if they are switched from the Teva product to another levothyroxine product. Teva levothyroxine 100 mcg tablets will cease to be available in the UK within the next few weeks as stocks are exhausted.

The decision to suspend follows a review by the Commission on Human Medicines (CHM), the MHRA's independent advisory body, of manufacturing issues and sporadic reports of loss of control of hypothyroidism when switching between products. As a precautionary measure, whilst investigations are ongoing, Teva has voluntarily ceased manufacture and distribution in line with the CHM recommendation.

The CHM review concluded that it might not be possible to switch use of the Teva product with other levothyroxine products, and that no further supplies of the product should be released for marketing until these issues are resolved.

Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

An executive agency of the Department of Health

If patients feel unwell taking the Teva levothyroxine tablets they should report them to their healthcare professional because adjustments to the dose of levothyroxine may be required.

The following patients may be particularly susceptible to changes in thyroid stimulating hormone (TSH) and may require close monitoring by their doctor: pregnant women, those with heart disease and those under treatment with levothyroxine following treatment for thyroid cancer. For those patients an early appointment with their doctor may be needed.

After dose adjustment of levothyroxine, consistent with usual practice, TSH should be retested after a period of six weeks to confirm blood levels are stabilised within the normal range as determined by their doctor.

Further information is published in a Q and A on the MHRA website: www.mhra.gov.uk

Ends

Notes to Editor

1. The MHRA and its independent advisory body the CHM (Commission on Human Medicines) considered all available data including: the reported defects; information relating to the manufacturing process; and the results of studies conducted by the MHRA's Medicines Testing Laboratory. CHM concluded that these data raised uncertainty as to whether Teva's product was interchangeable with other levothyroxine products.

2. The suspension will remain in place until Teva has completed its investigation and resolved the underlying issues.

3. The MHRA is the government agency responsible for ensuring that medicines and medical devices work, and are acceptably safe. No product is risk-free. Underpinning all our work lie robust and fact-based judgements to ensure that the benefits to patients and the public justify the risks. We keep watch over medicines and devices, and take any necessary action to protect the public promptly if there is a problem. We encourage everyone – the public and healthcare professionals as well as the industry – to tell us

about any problems with a medicine or medical device, so that we can investigate and take any necessary action. www.mhra.gov.uk

Teva levothyroxine questions and answers

1. Why are Teva levothyroxine 100mcg tablets being withdrawn?

MHRA has received sporadic reports from prescribers and patients, which have increased in Dec 2011 / Jan 2012, raising concerns about the interchangeability of this product with other makes of levothyroxine 100 mcg tablet.

Some patients have experienced a loss of control of thyroid stimulating hormone (TSH) levels when switching between Teva Levothyroxine tablets and other Levothyroxine products. The manufacturer, Teva, has also been experiencing difficulties in manufacturing this product. Results of tests conducted by the MHRA's Medicines Testing Laboratory, suggest that the TEVA product may differ from other products in the amount of levothyroxine that is released over time (dissolution). While it cannot conclusively be said that these issues prove Teva tablets are not interchangeable with other makes of levothyroxine 100 mcg tablets, the MHRA has taken prompt action as a precautionary measure. The MHRA has suspended the manufacture and distribution of Teva tablets having obtained advice from an independent panel of experts, the Commission on Human Medicines (CHM).

Many patients changing to or from the Teva product will not experience any changes in their symptoms. However, there are some patient groups where control of thyroid function is particularly important. These subgroups of patients are:-
Pregnant women, throughout pregnancy but especially in the first 3 months of pregnancy (first trimester)
Those with heart disease
Those under treatment with TSH suppressive doses of levothyroxine following treatment for thyroid cancer

Patients in these groups taking the Teva or Numark Levothyroxine 100 mcg Tablet product should make an early appointment with their doctor.

2. Which levothyroxine products are affected?

Only Levothyroxine 100 mcg tablets that are supplied in the Teva and Numark liveries are affected. The product will bear the Marketing Authorisation number, PL 00289/0039. Levothyroxine products from other manufacturers are unaffected by this suspension

3. Are the TEVA and Numark levothyroxine 100 mcg tablets identical?

Yes, they are identical apart from the packaging.

4. What other makes of levothyroxine 100mcg tablets are available?

A list of manufacturers and suppliers of Levothyroxine 100mcg Tablets is given below:

Product Licence (PL) Number as stated on the label and patient leaflet	Product Name/Brand as stated on the label and patient leaflet	Marketing Authorisation (MA) Holder	Distributed by
PL 00142/0105	THYROXINE TABLETS BP 100 MICROGRAMS	Actavis UK Limited	Almus, or Actavis, or Lloyds
PL 16201/0002	LEVOTHYROXINE 100micrograms Tablets	Forley Generics Limited	Forley Generics Limited
PL 10972/0032	ELTROXIN TABLETS 100MCG	Goldshield Group Limited	Goldshield Group Limited

5. Are all patients that are taking levothyroxine affected?

Patients who are taking tablets of 50 mcg or 25 mcg are not affected. Patients who are taking doses of 100mcg or more, are only affected if they are taking a Teva (or Numark) levothyroxine 100mcg tablet.

6. Why do the Teva 100mcg tablets continue to be available over the next few weeks?

Most patients taking Teva levothyroxine tablets will continue to feel well. Levothyroxine is an essential medicine and it is important that the suspension of the Teva product does not create a shortage with patients being unable to fulfil their prescription. It will take a few weeks before other suppliers have built up stocks of this medicine. .

7. Can I use up my existing Teva 100mcg tablets or should I ask my doctor to change them?

Most patients will not feel any different by continuing with their medication and changing to a different levothyroxine product at their next prescription. Blood test results will then allow any dose adjustment.

8. I have been taking Teva levothyroxine 100mcg tablets for some time. What advice can you give me? Will I be able to obtain further supplies?

Patients who have been taking Teva levothyroxine for some time would be stabilised on this product and feel well. However because of the concerns raised about the interchangeability of this product compared with other levothyroxine tablets, no further supplies of the product will be released for marketing and the tablets will not be available until these issues have been resolved.

Unless you are in the groups of patients described in Q&A no. 1, you should continue to take your Teva tablets and change to a different levothyroxine product at your next prescription. It should not be necessary to make an early appointment with your doctor. Most patients are unlikely to notice any change if they are switched from the Teva product to another Levothyroxine product, however if you start to feel unwell then you should see your doctor.

9. What should I do if I feel unwell when I change from Teva tablets to a different brand at my next prescription?

Most patients are unlikely to notice any change if they are switched from the Teva product to another levothyroxine product. However, if you start to feel unwell then you should see your doctor. You may not notice any changes for 4-6 weeks after switching to a different brand.

10. Will my levothyroxine dose need to be changed if I switch to or from the Teva make?

It is possible that your dose of levothyroxine will need adjustment. If you feel unwell, then you should see your doctor who will check whether a dose adjustment is needed. You may not notice any symptoms until within 4-6 weeks after changing from the Teva tablets to another make.

11. Where can I get more advice on this subject?

Patients should discuss any questions with their supervising healthcare professional.

Please also visit our website www.mhra.gov.uk

FAQs covering specific patient groups for whom control of thyroid function is particularly important.

Pregnancy

12. I am pregnant and I am taking thyroxine tablets. What shall I do?

Pregnant women with under-functioning thyroid are monitored with blood tests throughout pregnancy. Therefore, any need for adjustments to your daily dose of levothyroxine would have been recognised and addressed by your supervising healthcare professional. However, if you have recently been supplied with Teva levothyroxine 100mcg tablets, it is recommended that you make an early appointment (within a week) with your healthcare professional, so your thyroid status can be assessed. In the meantime, please continue to take your tablets as instructed by your doctor.

13. I am unsure whether I have taken these tablets in the past, would I have harmed myself or my baby?

Pregnant women with under-functioning thyroid are monitored with blood tests throughout pregnancy. Therefore, any need for adjustments to your daily dose of levothyroxine would have been recognised and addressed by your supervising healthcare professional. If in doubt, please see your healthcare professional.

Cardiac disease

14. I have heart disease (including angina, previous heart attack, previous stroke, previous heart surgery, palpitations or irregular heart rhythm, problems with circulation in extremities) and take Teva levothyroxine 100mcg tablets. Will I be affected?

Patients taking these tablets for some time will have been stabilised on them with blood tests. However if you have any deterioration in angina, breathlessness or palpitations, then you should make an early appointment with your healthcare professional for a clinical review and blood test. Your thyroid status should be carefully monitored once your doctor puts you on a different make of levothyroxine.

Thyroid cancer

15. I have had previous treatment for thyroid cancer and now take Teva levothyroxine 100mcg tablets. What should I do?

If you are taking Teva levothyroxine 100mcg tablets, please make an early appointment with your supervising healthcare professional for an assessment of the effectiveness of treatment. In the meantime, please continue to take your tablets as instructed by your doctor.

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