Administration and Pharmacokinetics of Levothyroxine

Hans-Peter Lipp

Lifelong treatment with LT4, guided by levels of thyrotropin, is the mainstay of management of hypothyroidism. The bioavailability of LT4 is about 70% following an oral dose, with absorption occurring mainly in the ileum and jejunum. Maximum plasma concentrations of LT4 are achieved about 3 h after an oral dose in patients with hypothyroidism. The long terminal half-life of orally administered LT4, about 7.5 days, is consistent with once-daily dosing. Pregnancy, several medical conditions (especially) those affecting the gut, and a number of drugs, supplements, or foodstuffs can reduce the absorption and absolute bioavailability of LT4, or can alter the secretion of TSH, with detrimental consequences for long-term control of thyroid function. Poor adherence to LT4 therapy is also a common challenge. The introduction of novel formulations of LT4, with more precise delivery of the active ingredient and higher levels of bioequivalence with existing products will facilitate accurate titration of LT4 for patients with hypothyroidism.

1 Introduction

Oral administration of levothyroxine (LT4), which targets the circulating level of thyrotropin (thyroid-stimulating hormone, TSH) to within a predefined reference range, is the mainstay of treatment of hypothyroidism [1–3]. This chapter summarises the administration, absorption, distribution, metabolism, and elimination of LT4. In addition, it addresses the therapeutic significance of pharmacologic and other factors that can alter exposure to LT4, and of changing regulatory requirements concerning the manufacture of LT4 tablets.

H.-P. Lipp (✉)
University Hospital Tübingen, Tübingen, Germany
e-mail: Hans-Peter.Lipp@med.uni-tuebingen.de

2 Absorption, Distribution, Metabolism, and Elimination of Levothyroxine

2.1 Absorption and Distribution

In general, about 70–80% of an oral dose of LT4 is absorbed from the intestine [4], which may involve transport of the LT4 molecule on the Organic Acid Transporting Polypeptide 2B1 (OATP2B1) transporter [5]. One study did not find significant differences in absorption of LT4 between subjects with and without hypothyroidism, whereas another study demonstrated higher bioavailability of LT4 in subjects with hypothyroidism or hyperthyroidism, compared with euthyroid subjects [6]. It has been shown that about half of an oral dose of the hormone was absorbed in the jejunum and ileum following administration of radiolabelled LT4 [7]. A modest reduction in LT4 absorption was noted in elderly subjects (>70 years), compared with younger adults [8]. In routine clinical practice, titration of the LT4 dose in an elderly patient to an appropriate age-specific reference range would account for this effect of age on LT4 absorption (see chapter, “Levothyroxine in the Older Patient”, of this book) [9]. Unlike T4, T3 is essentially completely absorbed (100%) from the intestine following an oral dose [10].

Fig. 1 shows the plasma concentration-time curve from a pharmacokinetic evaluation of two formulations of LT4 in healthy subjects [11]. The time to maximal plasma concentration ($T_{\max}$) of LT4 has been reported as 3 h in subjects with primary

Fig. 1 Plasma concentration-time curves from a comparison of an existing LT4 tablet formulation with a new LT4 tablet formulation designed to meet new regulatory requirements for the manufacture of such products. (Reproduced with permission from Ref. [11])

hypothyroidism and 2 h in euthyroid controls [12]. Concomitant food intake reduces the bioavailability of LT4, hence the labelling requirement to take LT4 tablets on an empty stomach, e.g. 30 min before breakfast, or 3 h after the evening meal [12, 13]. In plasma, LT4 is highly bound to plasma proteins (>99.9%) and distributes within a volume equal approximately to the human body’s total extracellular space (about 11–15 L) [14, 15].

2.2 Metabolism and Elimination

The main route of metabolism of LT4, and the route most relevant to its physiological actions, is conversion to T3 and deactivation, mediated by three peripheral deiodinases (Table 1) [16, 17]. Briefly, deiodinases D1 and D2 can mediate the conversion of T4 to T3, enhancing the availability of T3 to local tissues. Accordingly, LT4 may be considered to act largely as a prodrug for delivery of T3 to peripheral tissues. D2 is more important than D1 for generating T3; D1 is especially important for clearing the inactive thyroid hormone metabolite, reverse T3 (rT3), from the system via conversion to a further inactive deiodinated thyroid hormone metabolite. The main function of deiodinase D3 is the degradation of thyroid hormones. Polymorphisms of deiodinases may inhibit the conversion of LT4 to T3 in the periphery and have been proposed to explain an incomplete effect of exogenous LT4 treatment in resolving symptoms of hypothyroidism in some patients [18].

Multiple metabolites of thyroid hormones exist, and some of these may have intriguing biological actions that are the focus of current research [19–21]. Pathways for biotransformation of LT4 include decarboxylation and oxidative deamination, which results in, e.g. 3-iodothyroacetic acid. The biological activity of metabolites of LT4 remains to be established; 3-iodothyroacetic acid, for example, has been shown to induce antidepressant effects, and to promote itching and discomfort, in animal models [21].

Table 1 Metabolism of levothyroxine by peripheral deiodinases

	Deiodinase D1	Deiodinase D2	Deiodinase D3
Mainly expressed in	Liver, kidney, thyroid	Brain, pituitary, skeletal muscle, heart	Widely expressed
Principal reaction	T4 → T3	T4 → T3	T4 → rT3
Other important reactions	T4 → rT3 T3 or rT3 → T2	rT3 → T2	T3 → T2
Summary of physiological importance	<ul style="list-style-type: none">• Important source of plasma T3• Recovery of iodine from inactive thyroid hormone metabolites	<ul style="list-style-type: none">• Regulation of local cellular T3 levels• Maintaining pituitary/hypothalamic feedback for thyroid hormone production	<ul style="list-style-type: none">• Regulation of local cellular D3 levels, independent of local T3 or T4 levels• Degradation of thyroid hormones

T4 thyroxine, T3 triiodothyronine, rT3 reverse triiodothyronine, T2 3,3'-diiodothyronine. Compiled from information presented in Refs. [16, 17]

The elimination half-life of LT4 after oral dosing averages 7.5 days in patients with hypothyroidism, consistent with once-daily dosing [14]. A slightly lower elimination half-life was reported in euthyroid subjects (average 6.2 days) [14]. Interestingly, the elimination half-life of T3 is much lower (1–1.4 days, on average) [14], which may complicate future attempts to deliver LT4–T3 combination therapies [22].

3 Factors That May Alter Exposure to an Oral Dose of Levothyroxine

3.1 Factors That May Reduce Exposure to Levothyroxine

3.1.1 Diurnal Variation

Taking LT4 at bedtime (e.g. 3 h after the evening meal) rather than in the morning modestly but significantly increased LT4 levels and reduced TSH levels in the blood [23]. Consequently, it has been proposed to move the routine administration of LT4 from morning to evening, especially as a range of secondary measures (creatinine, lipids, body mass index, heart rate, quality of life) were unchanged between morning and bedtime administration. However, the usually recommended time of intake of LT4 remains in the morning (but at least 30 min before consumption of tea, coffee, or breakfast).

3.1.2 Malabsorption of, and Suboptimal Adherence to, Levothyroxine

Numerous factors may inhibit the absorption of LT4 into the bloodstream, including pre-existing intestinal disorders (e.g. celiac disease, prior gut resection or some forms of bariatric surgery), or concomitant intakes of certain supplements that contain metal ions (e.g. antacids, calcium, iron), drugs (e.g. laxatives, sevelamer, proton pump inhibitors), or soya protein [24–29]. The solubility of LT4 increases as pH decreases [30]. Proton pump inhibitors reduce the acidity (and increase the pH) of the stomach, and thus may reduce the bioavailability of LT4 by about 40% [29]; conversely, co-administration of ascorbic acid (vitamin C) reduces gastric pH and increases the absorption of LT4 [29, 30].

Malabsorption of LT4 results in lower than expected blood levels of LT4 and higher than expected levels of TSH, sometimes even in the setting of high doses of exogenous LT4. Alternative formulations to the usual tablet may be considered for patients with documented LT4 malabsorption [27, 31]. In cases where suboptimal adherence to LT4 therapy is suspected [32], the LT4 absorption test, where thyroid hormone levels are measured after a supervised dose of LT4, can be useful in distinguishing non-adherence of LT4 from genuine cases of malabsorption of LT4 [33].

Intramuscular LT4 treatment has been proposed for patients with severe intestinal malabsorption of LT4 though this approach remains within the research domain at present [34].

3.2 *Factors That May Alter the Measured Level of Thyrotropin*

A series of other factors influences the TSH test result, and therefore have clinical implications for the administration of LT4. This has been reviewed elsewhere [27], and is summarised briefly as follows:

Pregnancy	The requirement for, and production of, thyroid hormones increase markedly during pregnancy, with a consequent fall in TSH levels. Current guidelines recommend use of locally derived, trimester-specific reference ranges for testing thyroid function in pregnant women [35].
Drugs	Substances that alter the level of TSH will impact on the required dosage of LT4, as the TSH level is used to guide therapy. Several medications have the potential to decrease the TSH result, including dopamine antagonists, glucocorticoids, alemtuzumab, proton pump inhibitors, interferon-alpha, and metformin. Other drugs may increase or decrease the TSH test result, including lithium or amiodarone [27, 36–40].
Biorhythms	TSH secretion follows a diurnal variation, with the lowest value recorded around the middle of the day [41]. A circannual variation in TSH has also been observed in a large database study, with lower values during the summer [42], although the functional significance of this observation remains uncertain [43].
Demographics	TSH levels increase with age and are higher in women vs. men [43, 44]. Ethnicity also influences thyroid hormone levels [43, 44], which adds weight to the importance of using relevant reference populations for determining “normal” TSH results.
Smoking	TSH levels may be lower in smokers vs. non-smokers [45].
Obesity	Obesity is often considered to be a consequence (or a symptom) of hypothyroidism [1]. However, TSH levels correlate positively with BMI, consistent with a mechanism in which increased leptin secretion in obese subjects may drive increased secretion of TSH [46, 47]. The relationships between obesity, the TSH level, and the LT4 requirement are therefore complex.
Interference with TSH assays	Different commercial TSH assays may have different ability to recognise “macro-TSH”, which is TSH attached to IgG autoantibodies [48]. Macro-TSH is secreted variably between individuals with hypothyroidism. Other substances in the patient’s circulation may interfere directly with the operation of the TSH test, such as autoantibodies to LT4, rheumatoid factors (IgM antibodies directed against human IgG), and heterophilic antibodies (particularly human anti-mouse IgG antibodies [HAMA]), leading to variable test results [49].

4 Levothyroxine Tablets in a Changing Regulatory Environment

The manufacture of pharmaceutical products is subject to regulatory supervision to ensure maintained, high quality and consistency of successive batches; in particular, new formulations of currently available LT4 products must be bioequivalent to the existing formulation [50]. A small change in the level of T4 in the bloodstream will result in a much larger relative change in TSH secretion [28]. Accordingly, LT4 is regarded as a “narrow therapeutic index” drug in Europe (similar terms are used in other countries). According to the standard criteria for bioequivalence between an equivalent oral dose of two pharmaceutical preparations, the 90% confidence intervals (90%CI) for the geometric mean ratio of the area under the concentration-time curve (AUC) and the peak plasma concentration ($C_{\max}$) must be contained between 80% and 125% [51, 52]. For most narrow therapeutic index drugs, including LT4, current specifications now require that the 90% CI for the geometric mean ratio of the AUC and $C_{\max}$ values must lie between 90% and 111%, for the products to be considered to be bioequivalent [51, 52]. Updated regulations in several countries now also require the actual LT4 content of LT4 tablets to lie between 90% or 95% (depending on the country) and 105% of the amount declared on the package, throughout the shelf life of the product [53–55].

A randomised clinical trial compared the clinical pharmacokinetics of a new formulation of LT4 that meets these updated, narrowed requirements for bioequivalence with the previous formulation, in 216 healthy subjects [11, 56]. Fig. 1 showed that the plasma concentration-time curves and $C_{\max}$ values of the two formulations were essentially identical [11]. A formal evaluation of bioequivalence showed that the new formulation with improved specifications met the updated, stricter criteria for bioequivalence for a new formulation of a narrow therapeutic index drug (Fig. 2).

Fig. 2 Formal demonstration of bioequivalence according to updated regulatory criteria between the new and former LT4 tablet formulations shown in Fig. 1. (Reproduced with permission from Ref. [56])

5 Conclusions

LT4 is absorbed well and quickly from the gastrointestinal tract after oral administration. Once-daily dosing is feasible, based on its long half-life. Several medical conditions, particularly those affecting the gut, a number of drugs, pregnancy, and ingestion of supplements or food can interfere with the absorption of LT4 or the corresponding TSH test. As a consequence, care must be taken to identify and exclude these factors, as well as suboptimal adherence to therapy, when a patient presents with symptoms of hypothyroidism in spite of LT4 prescriptions. The introduction of novel formulations of LT4, with improved drug stability over time, more precise delivery of the active ingredient, and higher levels of bioequivalence compared with existing products promises to simplify accurate titration of LT4 for patients with hypothyroidism.

References

1. Okosieme O, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. *Clin Endocrinol (Oxf)*. 2016;84:799–808.
2. National Institute for Health and Care Excellence. Clinical knowledge summaries. Hypothyroidism. Last revised in June 2018. Available at <https://cks.nice.org.uk/hypothyroidism>. Last accessed Jul 2019.
3. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. *Thyroid*. 2014;24:1670–751.
4. Read DG, Hays MT, Hershman JM. Absorption of oral thyroxine in hypothyroid and normal man. *J Clin Endocrinol Metab*. 1970;30:798–9.
5. Meyer Zu Schwabedissen HE, Ferreira C, Schaefer AM, et al. Thyroid hormones are transport substrates and transcriptional regulators of organic anion transporting polypeptide 2B1. *Mol Pharmacol*. 2018;94:700–12.
6. Hasselström K, Siersbaek-Nielsen K, Lumholtz IB, Faber J, Kirkegaard C, Friis T. The bioavailability of thyroxine and 3,5,3'-triiodothyronine in normal subjects and in hyper- and hypothyroid patients. *Acta Endocrinol (Copenh)*. 1985;110:483–6.
7. Hays MT. Localization of human thyroxine absorption. *Thyroid*. 1991;1:241–8.
8. Hays MT, Nielsen KR. Human thyroxine absorption: age effects and methodological analyses. *Thyroid*. 1994;4:55–64.
9. Leng O, Razvi S. Hypothyroidism in the older population. *Thyroid Res*. 2019;12:2.
10. Hays MT. Absorption of triiodothyronine in man. *J Clin Endocrinol Metab*. 1970;30:675–6.
11. Gottwald-Hostalek U, Uhl W, Wolna P, Kahaly GJ. New levothyroxine formulation meeting 95–105% specification over the whole shelf-life: results from two pharmacokinetic trials. *Curr Med Res Opin*. 2017;33:169–74.
12. Benvenga S, Bartolone L, Squadrito S, Lo Giudice F, Trimarchi F. Delayed intestinal absorption of levothyroxine. *Thyroid*. 1995;5:249–53.
13. Wenzel KW, Kirschsieder HE. Aspects of the absorption of oral L-thyroxine in normal man. *Metabolism*. 1977;26:1–8.
14. Nicoloff JT, Low JC, Dussault JH, Fisher DA. Simultaneous measurement of thyroxine and triiodothyronine peripheral turnover kinetics in man. *J Clin Invest*. 1972;51:473–83.

15. Colucci P, Yue CS, Ducharme M, Benvenega S. A review of the pharmacokinetics of levothyroxine for the treatment of hypothyroidism. *Eur Endocrinol*. 2013;9:40–7.
16. Peeters RP, Visser TJ. Metabolism of thyroid hormone. *Endotext* [Internet]. Available at <https://www.ncbi.nlm.nih.gov/books/NBK285545>. Accessed Jul 2020.
17. Bianco AC, da Conceição RR. The deiodinase trio and thyroid hormone signaling. *Methods Mol Biol*. 1801;2018:67–83.
18. Bianco AC, Kim BS. Pathophysiological relevance of deiodinase polymorphism. *Curr Opin Endocrinol Diabetes Obes*. 2018;25:341–6.
19. Köhrle J. The colorful diversity of thyroid hormone metabolites. *Eur Thyroid J*. 2019;8:115–29.
20. Louzada RA, Carvalho DP. Similarities and differences in the peripheral actions of thyroid hormones and their metabolites. *Front Endocrinol (Lausanne)*. 2018;9:394.
21. Landucci E, Laurino A, Cinci L, Gencarelli M, Raimondi L. Thyroid hormone, thyroid hormone metabolites and mast cells: a less explored issue. *Front Cell Neurosci*. 2019;13:79.
22. Kansagra SM, McCudden CR, Willis MS. The challenges and complexities of thyroid hormone replacement. *Lab Med*. 2010;41:338–48.
23. Bolk N, Visser TJ, Nijman J, Jongste JJ, Tijssen JG, Berghout A. Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. *Arch Intern Med*. 2010;170:1996–2003.
24. Mersebach H, Rasmussen AK, Kirkegaard L, Feldt-Rasmussen U. Intestinal adsorption of levothyroxine by antacids and laxatives: case stories and in vitro experiments. *Pharmacol Toxicol*. 1999;84:107–9.
25. Sathyapalan T, Manuchehri AM, Thatcher NJ, et al. The effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: a randomized, double-blind, crossover study. *J Clin Endocrinol Metab*. 2011;96:1442–9.
26. Fain K, Rojas AP, Peiris AN. Hypothyroidism following gastric sleeve surgery resolved by ingesting crushed thyroxine tablets. *Proc (Bayl Univ Med Cent)*. 2019;33:38–9. eCollection Jan 2020.
27. Castellana M, Castellana C, Giovannella L, Trimboli P. Prevalence of gastrointestinal disorders having an impact on tablet levothyroxine absorption: should this formulation still be considered as the first-line therapy? *Endocrine*. 2020;67:281–90.
28. Razvi S, Bhana S, Mrabeti S. Challenges in interpreting thyroid stimulating hormone results in the diagnosis of thyroid dysfunction. *J Thyroid Res*. 2019;2019:4106816.
29. Skelin M, Lucijanić T, Amidžić Klarić D, et al. Factors affecting gastrointestinal absorption of levothyroxine: a review. *Clin Ther*. 2017;39:378–403.
30. Virili C, Antonelli A, Santaguida MG, Benvenega S, Centanni M. Gastrointestinal malabsorption of thyroxine. *Endocr Rev*. 2019;40:118–36.
31. Virili C, Trimboli P, Centanni M. Novel thyroxine formulations: a further step toward precision medicine. *Endocrine*. 2019;66:87–94.
32. Kumar R, Shaukat F. Adherence to levothyroxine tablet in patients with hypothyroidism. *Cureus*. 2019;11:e4624.
33. Gonzales KM, Stan MN, Morris JC 3rd, Bernet V, Castro MR. The levothyroxine absorption test: a four-year experience (2015–2018) at The Mayo Clinic. *Thyroid*. 2019;29:1734–42.
34. Garayalde Gamboa MLÁ, Saban M, Curriá MI. Treatment with intramuscular levothyroxine in refractory hypothyroidism. *Eur Thyroid J*. 2019;8:319–23.
35. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27:315–89.
36. Faix JD, Thienpoint LM. American Association of Clinical Chemists. Thyroid-stimulating hormone. Why efforts to harmonize testing are critical to patient care. *Clinical Laboratory News*. 2013. Available at <https://www.aacc.org/publications/cln/articles/2013/may/tsh-harmonization>. Accessed Jul 2019.

37. Koulouri O, Moran C, Halsall D, Chatterjee K, Gurnell M. Pitfalls in the measurement and interpretation of thyroid function tests. *Best Pract Res Clin Endocrinol Metab.* 2013;27:745–62.
38. Cappelli C, Rotondi M, Pirola I, et al. TSH-lowering effect of metformin in type 2 diabetic patients. Differences between euthyroid, untreated hypothyroid, and euthyroid on L-T4 therapy. *Diabetes Care.* 2009;32:1589–90.
39. Lupoli R, Di Minno A, Tortora A, Ambrosino P, Lupoli GA, Di Minno MN. Effects of treatment with metformin on TSH levels: a meta-analysis of literature studies. *J Clin Endocrinol Metab.* 2014;99:E143–8.
40. McMillan M, Rotenberg KS, Vora K, et al. Comorbidities, concomitant medications, and diet as factors affecting levothyroxine therapy: results of the CONTROL Surveillance Project. *Drugs R D.* 2016;16:53–68.
41. Warade J, Pandey A. Diurnal variation of TSH: factor affecting interpretation of test. *J Pharm Biomed Sci.* 2014;4:776–80.
42. Yoshihara A, Noh JY, Watanabe N, et al. Seasonal changes in serum thyrotropin concentrations observed from big data obtained during six consecutive years from 2010 to 2015 at a single hospital in Japan. *Thyroid.* 2018;28:429–36.
43. Ehrenkranz J, Bach PR, Snow GL, et al. Circadian and circannual rhythms in thyroid hormones: determining the TSH and free T4 reference intervals based upon time of day, age, and sex. *Thyroid.* 2015;25:954–61.
44. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab.* 2002;87:489–99.
45. Kim SJ, Kim MJ, Yoon SG, et al. Impact of smoking on thyroid gland: dose-related effect of urinary cotinine levels on thyroid function and thyroid autoimmunity. *Sci Rep.* 2019;9:4213.
46. Sanyal D, Raychaudhuri M. Hypothyroidism and obesity: an intriguing link. *Indian J Endocrinol Metab.* 2016;20:554–7.
47. Biondi B. Thyroid and obesity: an intriguing relationship. *J Clin Endocrinol Metab.* 2010;95:3614–7.
48. Hattori N, Ishihara T, Shimatsu A. Variability in the detection of macro TSH in different immunoassay systems. *Eur J Endocrinol.* 2016;174:9–15.
49. Després N, Grant AM. Antibody interference in thyroid assays: a potential for clinical misinformation. *Clin Chem.* 1998;44:440–54.
50. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP). Note for guidance on the investigation of bioavailability and bioequivalence. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003519.pdf. Accessed Jul 2020.
51. European Medicines Agency. Committee For Medicinal Products for Human Use (CHMP). Guideline on the investigation of bioequivalence. Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1, Jan 2010. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed Jul 2020.
52. Davit B, Braddy AC, Conner DP, Yu LX. International guidelines for bioequivalence of systemically available orally administered generic drug products: a survey of similarities and differences. *AAPS J.* 2013;15:974–90.
53. Medicines and Health Regulatory Authority. Levothyroxine tablet products: a review of clinical & quality considerations. 7 Jan 2013. Available at [http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessages/con222566.pdf](http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafety/messages/con222566.pdf). Accessed Jul 2020.
54. Agence Française de Sécurité Sanitaire des Produits de Santé 2012. Commission Nationale de Pharmacovigilance. Compte rendu de la réunion du mardi 27 Mars 2012. Available at https://ansm.sante.fr/var/ansm_site/storage/original/application/4e4d2a70e5ddd6b150fe87360d6b13dd.pdf. Accessed Jul 2020.

55. The United States Pharmacopeial Convention. 2009. Current USP monograph of levothyroxine sodium tablets (published in Revision Bulletin, Official 1 Feb 2010). Available at https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/levothyroxineSodiumTablets.pdf. Accessed Jul 2020.
56. Lipp HP, Hostalek U. A new formulation of levothyroxine engineered to meet new specification standards. *Curr Med Res Opin.* 2019;35:147–50.

Open Access This chapter is licensed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.