Case Report

LEVOTHYROXINE MALABSORPTION INDUCED BY DIABETIC GASTROPARESIS EXACERBATED DURING PREGNANCIES: EFFECT OF INTRAMUSCULAR LEVOTHYROXINE INJECTIONS AND LEVOTHYROXINE SOFT GEL CAPSULES

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ABSTRACT

Objective: We report a case of severe hypothyroidism with levothyroxine (LT4) malabsorption induced by diabetic gastroparesis. This was exacerbated during the patient's 2 pregnancies. Management was improved by intramuscular (IM) LT4) injections and LT4 soft gel capsules.

Methods: Case report with literature review.

Results: A 23-year-old Hispanic female with type 1 diabetes (DM) and hypothyroidism developed diabetic gastroparesis with unpredictable responses to LT4. She had 2 pregnancies during which her oral LT4 was switched to weekly IM injections of LT4 that maintained her euthyroid state. An LT4 absorption test with 1,000 mcg LT4 revealed reduced LT4 absorption. A gastric emptying scan showed delayed emptying, and endoscopy demonstrated a large amount of residual food in the patient's stomach after an overnight fast. Weekly IM injections of LT4 and LT4 soft gel capsules maintained her euthyroid state after her last pregnancy with a follow-up longer than 1-year. A repeat LT4 absorption test with a 1,000-mcg LT4 soft gel capsule preparation demonstrated improved absorption compared to the initial LT4 absorption test.

Conclusion: This may be the first patient described in the literature in whom diabetic gastroparesis was associated with impaired oral LT4 absorption and exacerbation during pregnancies. Our experience with this patient suggests that rational management of this problem may include IM LT4 injections or oral LT4 soft gel capsule administration. **(AACE Clinical Case Rep. 2015;1:e73-e78)**

Abbreviations:
CHF = congestive heart failure; **DM** = diabetes mellitus; **IM** = intramuscular; **LT4** = levothyroxine; **T4** = thyroxine; **TFTs** = thyroid function tests; **TSH** = thyroid-stimulating hormone

INTRODUCTION

Gastroparesis is defined as delayed gastric emptying in the absence of mechanical obstruction (1). In a community study, the prevalence rates of gastroparesis were 4.8% and 1% in patients with type 1 diabetes mellitus (DM) and type 2 DM, respectively (2). Much higher prevalence rates of delayed gastric emptying, ranging from 25 to 55% in type 1 DM and as high as 30% in type 2 DM have also been reported (1). The features of gastroparesis are complex and include abnormal gastric motor function, impaired glycemic control, extrinsic and intrinsic neuropathy, abnormalities of interstitial cells of Cajal, loss of neuronal nitric oxide synthase, and possibly, myopathy (3).

Approximately 15 to 21% of patients with type 1 DM test positive for thyroid autoantibodies (4,5), and this may be pertinent as hypothyroidism itself is associated with impaired gastrointestinal motility. In this report, we describe a patient with type 1 DM and hypothyroidism who developed gastroparesis with impaired absorption of oral levothyroxine (LT4). This may be the first patient described in the literature with LT4 malabsorption caused by diabetic gastroparesis in whom thyroid hormone deficiency was exacerbated by pregnancies.

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CASE REPORT

A 23-year-old Hispanic female with hypothyroidism (Hashimoto thyroiditis) and type 1 DM (onset at 7 and 11 years old, respectively) was referred to our medical institution in 2004 after experiencing frequent episodes of diabetic ketoacidosis. During her follow-up, she was given different doses of oral LT4 tablet with variable control of her thyroid status (Period 1). Subsequently (Period 2), it was considered necessary to switch to intramuscular (IM) LT4 on the 2 occasions when she was pregnant. She also received IM LT4 after her second pregnancy (Period 3). Finally (Period 4), she was prescribed a soft gel capsule LT4 preparation.

Period 1: At the time of her presentation in 2004, her initial thyroid function tests (TFTs) consisted of a serum thyroid-stimulating hormone (TSH) level of 97 μU/mL (normal range 0.34-5.6 μU/mL) and a serum free thyroxine (T4) of 0.96 ng/dL (normal range 0.58-1.64 ng/dL) at a time that she was taking LT4 tablet, 75 mcg daily. Subsequently, her LT4 tablet dose was increased to 150 mcg daily (Table 1). In 2004, the patient was noted to have symptoms of gastroparesis, which was confirmed by a gastric emptying scan in November 2004. From January 2004 to July 2009, her serum TSH was usually elevated on doses of LT4 tablet ranging from 75 to 250 mcg daily (Fig. 1). Initially, poor medication compliance was suspected but was ruled out by contacting the pharmacy and confirming medication intake with the patient's mother at each visit and performing pill counts. However, the patient remained hypothyroid while taking a higher LT4 tablet dose of 250 mcg with a TSH of 111 μU/mL (Table 1). The patient was screened for conditions associated with LT4, including celiac disease, by testing for antibodies against gliadin immunoglobulin A and G and tissue transglutaminase) (Table 2). A test for TSH-binding inhibitory immunoglobulin was negative.

Period 2: The patient became pregnant for the first time in late 2008. Her symptoms of hypothyroidism worsened, and there was a rapid rise of serum TSH to 66 μU/mL despite improved glycemic control (Table 1). Weekly IM injections of 1,000 mcg LT4 were initiated with an LT4 tablet 200 mcg daily. The patient's TFTs improved, and she was maintained in euthyroid state on a combination of oral LT4 tablet (150-200 mcg daily) with and a weekly LT4 IM injection (1,000-1,200 mcg) (Table 1). After an uneventful delivery of a premature but otherwise healthy infant in July of 2009, her IM LT4 injections were discontinued, and she was placed on oral LT4 tables. In August 2009, the

Table 1
Variable TSH and Thyroid Hormone Levels in Response to LT4 given PO as Tablets or Capsules (Tirosint®) or IM

Laboratory Results	6/04	1/05	4/05	5/08	2/09*	3/09*	6/09*	9/09	12/09*	12/09*	4/11	5/11	5/13	8/13	9/13	12/13	4/14
Treatment Stage[b]	1	1	1	1	2	2	2		2	2		3	4	4	4	4	4
Body Weight (kg)	42.7	44	42	52.7	**59**	**63.6**	**68.6**	62.7	**62.7**	**57.3**	63	58	57	55.5	57.6	63.6	63
A1c (%)	12.4	15.2	15.1	7.8	**6.8**	**6.4**	**7.1**	7.0	**8.0**	**8.0**	9.9%	11.5	11.2	11.5	11.1	8.5	11.6
TSH (0.35-5.6 μIU/L)	97.4	77	111	16.93	**66**	**6.02**	**1.43**	2.53	**140.9**	**4.57**	>500	1.95	0.03	0.2	0.11	1.85	0.44
Free T4 (0.58-1.64 ng/dL)	0.96	0.63	0.46	0.58	**0.58**	**0.84**	**1.45**	0.98	**0.56**	**1.12**	0.65	2.11	1.53	1.41	1.32	0.88	1.05
LT4 PO daily dosage (mcg)	75	150	250	100	**200**		**150**	300	**350**	**150**	375						
LT4 IM weekly dosage (mcg)						**1000**	**1200**			**1200**		1000					
L-T4 soft capsule daily (mcg)													300	250	250	200	200

Abbreviations: A1c = glycated hemoglobin; IM = intramuscular; LT4 = levothyroxine; PO = per oral; TSH = thyroid-stimulating hormone.
[a] The shaded areas represent pregnant periods.
[b] Period 1 (2004-2008): The patient was given various doses of oral L-T4 with variable response to L-T4.
Period 2 (late 2008-2010): The patient was given IM L-T4 doses during her 2 pregnancies.
Period 3 (2010-2012): The patient was given IM L-T4 doses postpartum.
Period 4 (2013-present): The patient received L-T4 soft capsules (Tirosint®).

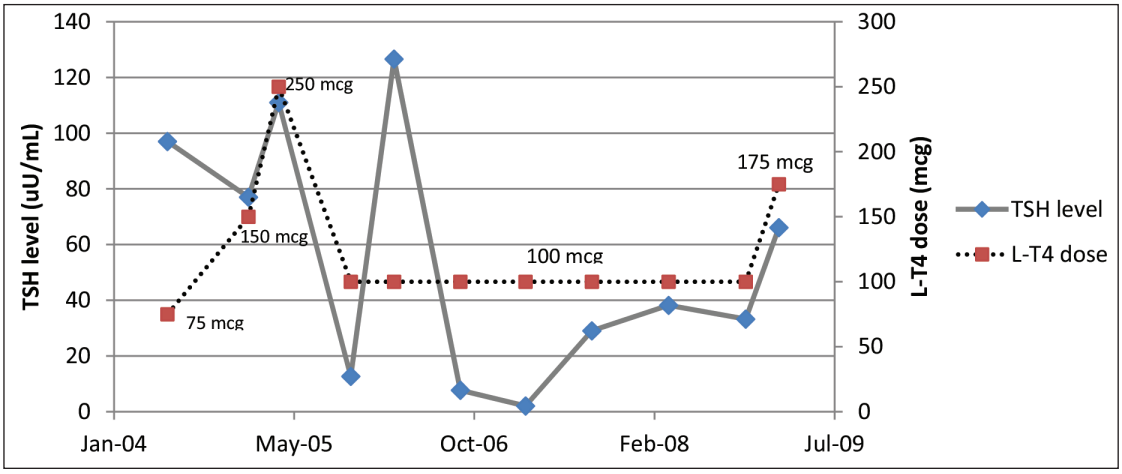

Fig. 1. Our patient's variable serum TSH and free T4 levels with different levothyroxine doses. *T4* = thyroxine; *TSH* = thyroid-stimulating hormone.

patient was euthyroid with a TSH level of 1.62 μU/mL on LT4 tablet (300 mcg daily). In November 2009, her LT4 tablet was increased to 350 mcg for a TSH level of 2.53 μU/mL. The patient remained euthyroid while taking oral LT4 tablet (350 mcg daily). In December 2009, the patient became hypothyroid again with a sudden increase of serum TSH to 140 μU/mL on LT4 tablet (350 mcg) when she became pregnant for the second time.

After the pregnancy was diagnosed, she was started on LT4 tablet (200 mcg daily) and weekly LT4 IM injection (1,200 mcg). On this treatment, the serum TSH remained between 4.57 and 31 μU/mL for the remainder of her pregnancy. She had an uneventful delivery of a healthy child in June 2010.

Period 3: Weekly IM LT4 injections were discontinued after her second pregnancy. The patient's TSH ranged from 0.14 to 31.5 μU/mL, and her LT4 tablet dose varied from 300 to 400 mcg between June and November 2010. On January 3, 2011, the patient's TSH level increased to 286 μU/mL with a T4 level of 0.85 mg/dL while on LT4 tablet (350 mcg daily). The reason for this increase was not clear. An LT4 absorption test was performed on January 20, 2010 by giving the patient a single 1,000 mcg LT4 tablet. Her morning baseline of TSH on the day of the test was 4.88 μU/mL, and her free T4 level was 0.99 mg/dL. As shown in Figure 2, the patient's serum free T4 level did not rise over the expected level of 1.71 mg/dL at 2 hours or during the remaining test period (Fig. 2). According to the criteria described in the literature (6), the 2-hour serum free T4 peak commonly rises above the expected upper limit of reference range (more than 1.71 mcg/dL or 22 pmol/L). This is an abnormal response, consistent with LT4 tablet malabsorption not pseudomalabsorption. In April 2011, endoscopy after an overnight fast showed a large amount

Table 2
Conditions and Medications that Affect LT4 Absorption and Our Patient's Results[a]

Conditions and Drugs	Screened result in our patient
Gastrointestinal diseases Celiac disease, Lactose intolerance, Inflammatory bowel disease, Chronic Gastritis of the stomach body, *Giardia lamblia* (parasitic infection)	Absent
Previous gastrointestinal surgery	Absent
Decreased T4 absorption Cholestyramine, Colesevelam, Proton Pump Inhibitor, Aluminum hydroxide containing antacids, Ferrous sulphate Sucralfate, Sevelamer hydrochloride, Calcium carbonate, Raloxifene, Orlistat	Absent
High Dietary Fiber and Simultaneous Food intake	Absent
Pregnancy	Present
CHF	Present

Abbreviations: CHF = congestive heart failure; LT4 = levothyroxine; T4 = thyroxine.
[a] Adapted from (8,9)

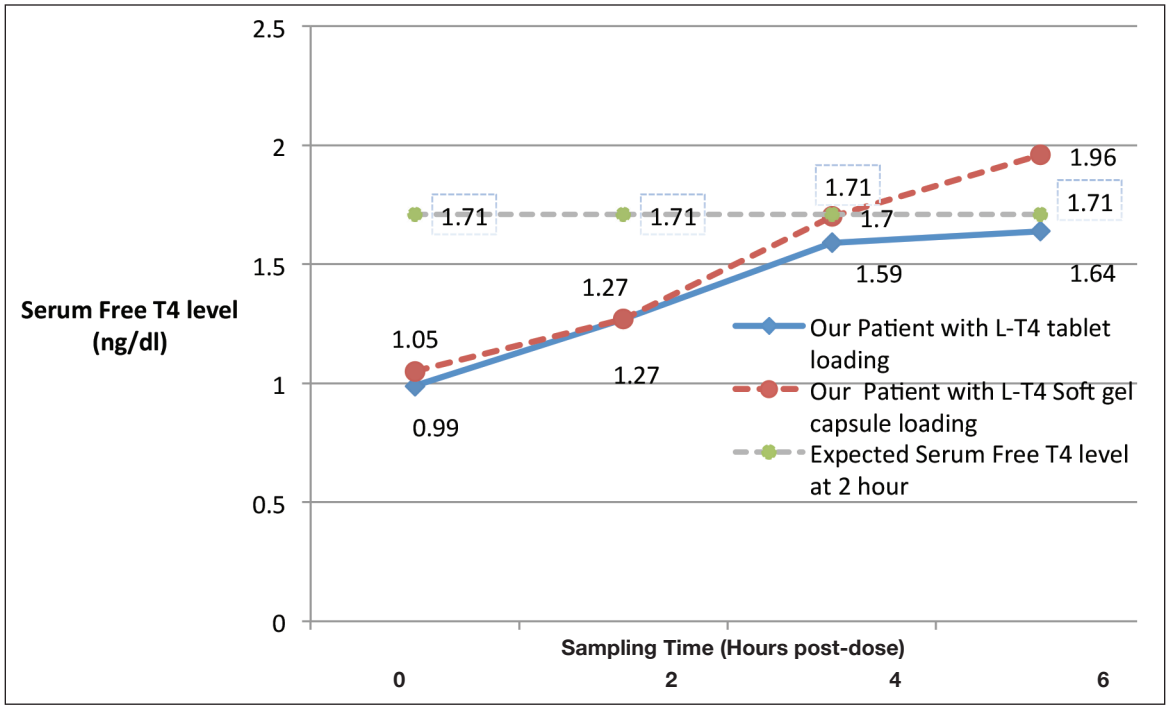

Fig. 2. Our patient's LT4 absorption test results with 1,000 mcg (LT4 tablet and soft gel capsule preparations) and the expected normal serum free T4 level after 2 hours reported in the literature (6).

of residual food in the stomach, confirming severe gastroparesis. A reliable gastric (*Helicobacter pylori*) or duodenal biopsy (celiac sprue) could not be performed because of residual food in the stomach. The patient was also hypothyroid during her endoscopy.

Period 3: In April 2011, the patient's serum TSH was noted to be over 500 μU/mL with a free T4 level of 0.65 mg/dL while taking LT4 tablet (375 mcg daily). Her maximum daily dose of LT4 tablet had been 400 mcg daily since her second child was born. The patient was again started on IM LT4 at a dose of 1,000 mcg weekly. On this regimen, the serum TSH declined to 1.95 μU/mL and remained in the range of 1.95 to 11.04 μU/mL while she did not miss weekly injections until May 2012. However, she developed pain at the LT4 injection site, and IM LT4 was discontinued.

Period 4: In March 2013, it was decided to start the patient on an LT4 soft gel capsule (300 mcg). Her serum TSH decreased to 0.03 μU/mL. In September 2013, her dose of LT4 given in soft gel capsules was decreased to 250 mcg then to 200 mcg daily. She has remained euthyroid since with TSH levels of 0.2 and 0.44 μU/mL on the respective doses. The patient's TFTs were measured 5 times while on the LT4 soft gel capsule (Table 1).

During the course of her 10-year follow-up, this patient developed stable congestive heart failure (CHF) with ejection fracture 35% (2004) and 45% (2007). She was started on appropriate medications including metoclopramide (2004), ergocalciferol (2004), metoprolol (May to June 2004), digoxin (June to October 2004), losartan (2008), hydralazine (2009), rosuvastatin (March- May 2011), and carvedilol (2012).

DISCUSSION

LT4 appears to be absorbed into the body through the jejunum and ileum, with residual absorption in the cecum (7). Normally, 70 to 100% of the administered dose is absorbed within the gastrointestinal tract, with maximal serum levels reached within 2 to 4 hours following ingestion (8). A mean daily dose of 1.6 ± 0.4 mcg per kg is required to normalize TSH levels in patients with hypothyroidism; a daily dose more than 2.4 mcg per kg is considered excessive (7).

Various medications and medical conditions may affect LT4 absorption (8,9), and patients need to be screened for these to differentiate between true malabsorption and pseudomalabsorption (Table 2). If pseudomalabsorption is suspected, an absorption test is performed in the outpatient setting. This test requires measuring baseline TSH and T4 levels before administering 1,000 mcg of LT4 orally, and then additional blood is drawn every 1 to 2 hours for a total of 6 hours (6). Our patient's LT4 absorption test demonstrated that her free T4 levels were clearly below the expected upper limit of normal level of 1.71 ng/dL (22 pmol/L) at 2 hours and up to 6 hours (Fig. 2) compared to the expected response described in the literature (6). We strongly believe that this abnormal test result was attributable to her diabetic gastroparesis as we ruled out other possible causes of malabsorption (Table 2). Also,

an endoscopy revealed a large amount of residual food in the patient's stomach after an overnight fast, confirming severe gastroparesis. This retained food was presumably binding the ingested LT4, thereby decreasing its absorption.

Our patient developed stable CHF. The possibility of LT4 malabsorption in subjects with CHF is documented in the literature without a clear explanation of its cause other than the hypothesis that uncontrolled CHF might cause bowel edema, which might impair LT4 absorption. Because our patient had stable CHF, we ruled it out as a possible cause of LT4 malabsorption. There is limited information regarding the drug interaction between LT4 and statins. Only 2 letters to the editor reported that concomitant use of LT4 with lovastatin or simvastatin resulted in an interaction between statin and LT4 requiring an LT4 dose increase (10,11). However, the proposed mechanism for this drug interaction via cytochrome P450 A4 has not been validated in the literature other than the hypothesis in the letter (11). Furthermore, our patient was only on rosuvastain therapy for 3 months in 2011.

Our patient became more hypothyroid without significant hyperemesis during 2 pregnancies despite a higher daily oral dose of LT4 (300-400 mcg). To our knowledge, this is the first case of T4 malabsorption exacerbation during pregnancy in a patient with diabetic gastroparesis. Pregnancy is associated with slowed gastric motility induced by hormones, especially progesterone. Animal studies have demonstrated the inhibitory effects of progesterone on gastrointestinal smooth muscle, resulting in slower gastric motility. In addition, prolonged small-bowel transit time has been observed in humans during pregnancy (12). Pregnancy may require a 30 to 50% LT4 dose increase in patients with hypothyroidism (13). However, our patient was severely hypothyroid even with an increased dose of LT4 tablet (350-400 mcg, 5.5-5.6 mcg/kg body weight) during her pregnancies and eventually became euthyroid with weekly LT4 IM injections. We speculate that there were 2 reasons for worsening of our patient's hypothyroidism during her pregnancies. First, the exacerbation was due to increased thyroid hormone requirements due to pregnancy itself. Second, her inability to maintain a euthyroid state throughout her pregnancies despite an increased dose of oral LT4 tablet was due to worsening of impaired LT4 absorption from diabetic gastroparesis, possibly induced by her pregnancies (Table 1).

Our patient became euthyroid with a decreased LT4 dose while taking the soft gel formulation (200 mcg) compared to her LT4 tablet formulation dose (350-400 mcg). Also, she has maintained a euthyroid state without wide fluctuations in TSH levels while taking a LT4 soft gel preparation for over 1 year. Moreover, the LT4 loading test was repeated using a 1,000 mcg LT4 soft gel capsule and demonstrated improved absorption compared to the standard LT4 tablet (Fig. 2).

Our patient has been euthyroid on a soft gel capsule LT4 preparation (200 mcg daily) for over 1 year. Furthermore, the repeat LT4 loading test with soft gel capsule (1,000 mcg) demonstrated improved LT4 absorption. Our patient's serum free T4 level at 2 hours (1.27 ng/dL) did not rise over the expected serum free T4 level of 1.71 ng/dL at 2 hours. However, her serum free T4 level at 6 hours steadily increased over 1.71 ng/dL (her previous LT4 loading test result at 6 hours was 1.64 ng/dL) (Fig. 2). This enhanced absorption with LT4 soft gel capsule explains why our patient has been remained euthyroid with a stable and lower dose of LT4 soft gel capsule compared to the conventional LT4 preparation daily dose (200 mcg vs. 350-400 mcg) in the past year. This soft gel capsule contains LT4 in glycerin with a soft gelatin protective shell. A case report described improved absorption compared to LT4 tablet in a person with concurrent proton pump inhibitor use (14). This formulation is listed pregnancy category A (15).

CONCLUSION

To conclude, this may be the first patient described in the literature in whom diabetic gastroparesis was associated with impaired oral LT4 absorption with exacerbation of the problem during pregnancies. Our experience with this patient suggests that rational management of this problem may include IM LT4 injections or oral LT4 soft gel capsule administration.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES

1. **Parkman HP, Hasler WL, Fisher RS; American Gastroenterological Association.** American Gastroenterological Association Technical Review on the Diagnosis and Treatment of Gastroparesis. *Gasteroenterology* 2004;127: 1592-1622.
2. **Camilleri M, Bharucha AE, Farrugia G.** Epidemiology, mechanisms and management of diabetic gastroparesis. *Clin Gastroenterol Hepatol*. 2011;9:5-12; quiz e7.
3. **Shin AS, Camilleri M.** Diagnostic assessment of diabetic gastroparesis. *Diabetes* 2013;62: 2667-2673.
4. **Roldan MB, Alonso M, Barrio R.** Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. *Diabetes Nutr Metab*. 1999;12:27-31.
5. **Kordonouri O, Hartmann R, Deiss D, Wilms, M, Gruters-Kieslich A.** Natural course of autoimmune thyroiditis in type 1 diabetes association with gender, age, diabetes duration and puberty. *Arch Dis Child*. 2005;90:411-414.
6. **Srinivas V, Oyibo SO.** Levothyroxine pseudomalabsorption and thyroxine absorption testing with use of high-dose levothyroxine: case report and discussion. *Endocrine Pract*. 2010;16:1012-1015.

7. **Sherman SI, Malecha SE.** Absorption and malabsorption of levothyroxine sodium. *Am J Ther.* 1995;2:814-818.
8. **Lips DJ, van Reisen MT, Voigt V, Venekamp W.** Diagnosis and treatment of levothyroxine pseudomalabsorption. *Neth J Med*. 2004;62:114-118.
9. **Liwanpo L, Hershman JM.** Conditions and drugs interfering with thyroxine absorption. *Best Pract Res Clin Endocrinol Metab*. 2009;23:781-792.
10. **Demke DM.** Drug interaction between thyroxine and lovastatin. *N Engl J Med*. 1989;321:1341-1342.
11. **Kisch E, Segall HS.** Interaction between simvastatin and L-thyroxine. *Ann Intern Med*. 2005;143:547.
12. **Baron TH, Ramirez B, Richter JE.** Gastrointestinal motility disorders during pregnancy. *Ann Intern Med*. 1993;118: 366-375.
13. **Abalovich M, Amino, N, Barbour LA, et al.** Management of thyroid dysfunction during pregnancy and postpartum: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2007;92:S1-S47.
14. **Vita R, Benvenga S.** Tablet levothyroxine (L-T4) malabsorption induced by proton pump inhibitor; a problem that was solved by switching to L-T4 soft gel capsule. *Endocr Pract*. 2013;18:1-11.
15. Tirosint® [package insert]. Akrimax Pharmaceuticals, LLC by IBSA Institut Biochimique SA 6903 Lugano, Switzerland; April 2012.