Pharmaceutical Quality of Nine Generic Orlistat Products Compared with Xenical®

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Orlistat · Xenical · Pharmaceutical quality · Generics

Introduction
Orlistat (N-formyl-L-leucine (S)-1-[(2S,3S)-3-hexyl-4-oxooxetan-2-yl][methyl]dodecyl ester) (fig. 1) is a potent irreversible inhibitor of gastrointestinal lipases that hydrolyse triacylglycerols in the gastrointestinal tract to free fatty acids and monoglycerides [1, 2]. This inhibition prevents absorption of up to one third of all dietary fat, [3] and therefore can promote weight loss, maintain lost weight, and prevent weight regain in obese patients [4]. The relationship between orlistat daily dose and fecal fat excretion is determined by gastrointestinal lipase inhibition [3]. The dose-response curve demonstrates a steep portion for doses of up to approximately 400 mg daily. The orlistat daily dose that produces 50% of the maximum effect is approximately 100 mg/day.

Orlistat is patented and chemically synthesised using stereotype specific methods which result in ≥99.5% pure product. It is manufactured and marketed as 120 mg capsules under the brand name Xenical by F. Hoffmann-La Roche Ltd (Roche, Basel, Switzerland) since its launch in 1998. Xenical has proven to be an invaluable drug in the long-term treatment of obese and overweight patients. As of July 2009, more than 35 million patients had received Xenical. During research and development, Roche also evaluated a less expensive fermentation process to produce orlistat using the microorganism Streptomyces toxytricini. However, chemical analyses revealed a considerable range of impurities in the final product, and this process was abandoned.

Orlistat is polymorphic, existing in distinct crystalline forms A and B. Xenical is polymorph form B. Orlistat is highly lipophilic and practically insoluble in water, having no pKₐ value within physiological pH. Orlistat powder is ‘sticky’, which has consequences for manufacture and dispensing into capsules. Roche has overcome these difficulties in Xenical capsule production by using a patented granular ‘pellets’ for-
mulation that includes a disintegrant [5]. Stability tests of Xenical carried out by Roche revealed a slow decline in dissolution rates over the 3-year shelf life at a storage temperature of 25 °C and relative humidity of 60%.

Although the Xenical patent has expired in 2009, generic orlistat has been manufactured and available for purchase for several years in those countries whose national laws do not support patent protection.

The current study compares the pharmaceutical quality of Xenical with nine generic products. All products were assessed against Roche standard operating procedures (SOPs) that describe the qualitative and quantitative pharmaceutical tests for physical and chemical purity of orlistat from both chemical and fermentative synthesis processes. The analysis processes for chemically synthesised orlistat were accepted by regulatory authorities as part of the Xenical registration documentation. Values of reference were the official Roche specifications for product testing at release or at shelf-life, where appropriate.

### Material and Methods

**Generic Products**

Samples of nine generic orlistat products, all 120 mg capsule preparations, were purchased for testing (table 1).

**Table 1. Details of Xenical and generic orlistat products tested**

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Country</th>
<th>Batch</th>
<th>Manufacture date</th>
<th>Expiry date</th>
<th>Shelf-life, months</th>
<th>Test date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenical</td>
<td>Roche Pharma</td>
<td>Switzerland</td>
<td>B2637</td>
<td>July 2006</td>
<td>July 2009</td>
<td>36</td>
<td>August 2006</td>
</tr>
<tr>
<td>Cuvarlix</td>
<td>Pharmaniaga</td>
<td>Malaysia</td>
<td>8L184</td>
<td>September 2008</td>
<td>September 2010</td>
<td>24</td>
<td>February 2009</td>
</tr>
<tr>
<td>Fingras</td>
<td>Phoenix</td>
<td>Argentina</td>
<td>15026</td>
<td>(1)</td>
<td>(1)</td>
<td>unknown</td>
<td>December 2006</td>
</tr>
<tr>
<td>Obelit</td>
<td>Intas Pharma</td>
<td>India</td>
<td>H5018W</td>
<td>(1)</td>
<td>(1)</td>
<td>unknown</td>
<td>December 2005</td>
</tr>
<tr>
<td>Xenipus</td>
<td>Elea</td>
<td>Argentina</td>
<td>L8114</td>
<td>(1)</td>
<td>(1)</td>
<td>unknown</td>
<td>December 2006</td>
</tr>
<tr>
<td>Xiluet</td>
<td>Servimedic</td>
<td>Uruguay</td>
<td>01</td>
<td>(1)</td>
<td>February 2008</td>
<td>unknown</td>
<td>April 2007</td>
</tr>
<tr>
<td>Xinpex</td>
<td>Craveri</td>
<td>Argentina</td>
<td>9661</td>
<td>(1)</td>
<td>(1)</td>
<td>unknown</td>
<td>December 2006</td>
</tr>
<tr>
<td>Zerocal</td>
<td>Pharmosa/Weidar Chemical and Pharmaceutical Co. Ltd</td>
<td>Taiwan</td>
<td>735002</td>
<td>February 2007</td>
<td>February 2009</td>
<td>24</td>
<td>May 2007</td>
</tr>
</tbody>
</table>

(1) = Not stated on packaging.

**Pharmaceutical Quality Tests**

The tests were colour of capsule contents, identification of the active pharmaceutical ingredient (API) and the crystalline form, melting temperature, particle size, dissolution, fill mass of capsules, content of orlistat and of impurities.

**Colour of Capsule Contents**

Colour was assessed visually according to the standards described in the ‘Munsell Book of Color’ [6].

**Identification of API and Crystalline Form**

Infrared spectroscopy was used with a suspension of 5 mg capsule content in Nujol/sodium chloride plates. The spectrum was recorded in the range of 4,000–650/cm using a Nicolet 20 SXB spectrophotometer and compared to the reference spectra of the polymorphic forms A and B of orlistat.

**Melting Temperature**

Melting temperature of the capsule content was determined using a Mettler DSC-821e DSC module equipped with a Mettler TSO801RO sample robot and STAREs, TA-8000 evaluation and control system (Mettler Toledo, Greifensee, Switzerland). Determinations were made using between 6.0 and 13.0 mg of capsule content in a 40 μl sealed aluminium crucible under a nitrogen atmosphere, across the temperature range 25–60 °C, and using a ramp rate of 1 °C/min. Polymorphic form B has a melting point of 43.6 °C.

**Particle Size**

Particle size analysis was performed by laser diffraction, using a MasterSizer 2000, (Malvern Instruments, Worcestershire, UK) fitted with a Sicracco 2000 dry powder feeder (Malvern Instruments) operated at 25 ºC. Dissolution testing was performed using the Ph. Eur. rotating paddle apparatus in a dissolution medium that was developed especially for orlistat...
substance due to its hydrophobicity. The dissolution medium comprised
an aqueous solution containing 3% of sodium lauryl sulphate, 0.5% of so-
dium chloride, adjusted to pH 6.0 with phosphoric acid; sink conditions
were achieved because the solubility of orlistat in this medium is approxi-
mately 0.3 g in 100 ml. The rate of dissolution was determined individually
for six capsules of each generic product, in a vessel with a paddle stirrer at
75 rpm and containing 900 ml of medium. Aliquots of 10 ml were removed
after 15, 30, 45 and 60 min. These aliquots were filtered through a 1 μm
Acrodisc glass fibre filter or 0.2 μm Acrodisc filter ( Pall Medical, Milan,
Italy) and cooled to 20 °C, and 20 μl samples of the resultant clear solution
were assayed using high performance liquid chromatography (HPLC) and
spectrophotometry. The specification for Xenical dissolution rate at shelf-
life was a Q-value of 65% after 45 min according to Ph. Eur.

**Fill Mass of Capsules**

Twenty capsules were emptied, their contents mixed together weighed
and the average weight calculated. Xenical specification for fill mass was
228.2–252.2 mg per capsule.

**Content of Orlistat and of Impurities**

The content of orlistat and impurities was determined using HPLC.
Twenty capsules were emptied and their contents mixed together, from
which 100 mg was dissolved in 70 ml mobile phase, agitated by ultrasound
for 1 min, then made up to 100 ml before being agitated for a further
15 min. A portion of the resulting solution was filtered (0.45 μm pore size,
Millex HV; Millipore, Volketswil, Switzerland) and stored for up to 48 h
at 4 °C. Samples (20 μl) were then injected onto the HPLC analytical
column (150 mm × 3.9 mm Nova Pak C18, 4 μm; Waters, Baden-Dättwil,
Switzerland), and eluates monitored at 195 nm (Hewlett Packard G1314A
variable wavelength detector). The mobile phase comprised acetonitrile
(860 ml), water (140 ml) and 5% phosphoric acid (1 ml). Mobile phases
were degassed (Hewlett Packard G1322A vacuum degasser) and pumped
(Hewlett Packard G1311A quat pump) at 1.0 ml/min.

The specification for content of API was 114.0–126.0 mg (95–105%)
orlistat per capsule of Xenical. The specification for the limit for all impur-
ities in Xenical was 0.5% and 2.5% at release and at shelf-life, respec-
tively. The shelf-life limits were between 0.2 and 1.2% for five specific
degradation products. Each other characterised impurity, which included
precursors, stereoisomers, side-chain homologues, amino acid analogues
or other degradation products, was limited at 0.3%. The limits were 0.5%
for all unidentified impurities at shelf-life.

### Table 2. Physical characteristics of Xenical and generic orlistat products, following removal from capsules

<table>
<thead>
<tr>
<th>Drug product</th>
<th>Description</th>
<th>Melting temperatureª, °C</th>
<th>Polymorphic crystalline form</th>
<th>Average fill massb, mg</th>
<th>Average orlistatc content, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenical</td>
<td>white / off-white pellets</td>
<td>43.6</td>
<td>B</td>
<td>240.6</td>
<td>118.3</td>
</tr>
<tr>
<td>Cobese</td>
<td>almost white powder</td>
<td>43.1</td>
<td>A</td>
<td>231.2</td>
<td>113.7</td>
</tr>
<tr>
<td>Cuvarlix</td>
<td>off-white highly agglomerated powder</td>
<td>44.8</td>
<td>A</td>
<td>243.8</td>
<td>120.1</td>
</tr>
<tr>
<td>Fingras</td>
<td>off-white powder</td>
<td>42.2</td>
<td>B and A</td>
<td>248.9</td>
<td>116.2</td>
</tr>
<tr>
<td>Lesofat</td>
<td>off-white pellets</td>
<td>42.1</td>
<td>A</td>
<td>245.8</td>
<td>116.2</td>
</tr>
<tr>
<td>Obelit</td>
<td>off-white powder</td>
<td>NT</td>
<td>A</td>
<td>260.6</td>
<td>114.6</td>
</tr>
<tr>
<td>Xeniplus</td>
<td>off-white powder</td>
<td>42.2</td>
<td>A</td>
<td>252.3</td>
<td>117.8</td>
</tr>
<tr>
<td>Xiluet</td>
<td>off-white irregular balls</td>
<td>41.1</td>
<td>B (some A)</td>
<td>244.7</td>
<td>114.1</td>
</tr>
<tr>
<td>Zerocal</td>
<td>white powder</td>
<td>NT</td>
<td>A</td>
<td>184.4</td>
<td>126.4</td>
</tr>
</tbody>
</table>

NT = Not tested.

ªSpecification 42–44 °C.

bSpecification 228.2–252.2 mg.

cSpecification 114.0–126.0 mg.

All pharmaceutical quality tests were conducted in GMP-regulated
Quality Control and Development Laboratories of F. Hoffman La-
Roche, in Basel, by certified personnel.

**Results**

Five generic products did not fully detail dates of manufacture
and/or expiry (table 1). The age of product when tested was
unknown for Fingras, Obelit, Xeniplus, and Xinplex. Xiluet
was tested within 10 months of expiry. The remaining generic
products were tested between 3 and 6 months of manufacture.
Where stated, the maximum shelf life claimed for generic
products was 2 years, i.e. 1 year less than Xenical.

**Colour, Appearance, Crystalline Form, and Melting
Temperature**

All generic products were white or off-white in colour, similar
to Xenical (table 2). Lesofat, Xiluet, and Xinplex were pel-
leted or granular formulations resembling Xenical; however,
five of the remaining generic products were powders and the
contents of the Cuvarlix capsules remained in a single lump
(fig. 2). Six of the generic products consisted solely of poly-
morphic form A and three products (Xiluet, Fingras, and Xin-
plex) were mixtures of form A and B. Melting temperatures
were determined for six generic products, and all were similar
to Xenical.

**Particle Size Distribution**

Xenical exhibited a narrow range particle size distribution
with a median (D50) of 1,100 μm (fig. 3). Cobese, a typical
powder formulation, exhibited a wider range of particle sizes
with bimodal values of 100 and 900 μm. Particle size distribu-
tions of the granular formulations Xiluet, Xinplex, and Leso-
fat were similar to that of Xenical (fig. 4), with a median size

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Taylor/Arnet/Fischer/Simpson
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![Table 2. Physical characteristics of Xenical and generic orlistat products, following removal from capsules](image)

**Fig. 2.** Physical appearance of capsules and contents of Xenical and three generic products.

**Fig. 3.** Comparison of particle size distribution for Xenical and Cobese.

**Fig. 4.** Particle size distribution of Xenical and generic orlistat products.

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Pharmaceutical Quality of Nine Generic Orlistat Products Compared with Xenical®

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impurity content. Two generic products, Obelit and Xinplex, failed the dissolution test.

All nine generic products contained side-chain homologues (range 0.8–2.4%, fig. 5B). Three generic products (Cuvarlix, Zerocal, and Obelit) were generally poor dissolution (Q 65) rate at shelf life specification for dissolution rates (fig. 6). Obelit exhibited marked variation in dissolution rates with many values falling below the acceptable dissolution rate; Cuvarlix exhibited very poor dissolution.

### Table 2: Fill Mass and Orlistat Content of Capsules

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Fill Mass (mg)</th>
<th>Orlistat Content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenical</td>
<td>114.0–126.0</td>
<td>114.0</td>
</tr>
<tr>
<td>Lesofat</td>
<td>112.0–124.0</td>
<td>114.0</td>
</tr>
<tr>
<td>Fingras</td>
<td>110.0–122.0</td>
<td>114.0</td>
</tr>
<tr>
<td>Cobese</td>
<td>113.0–125.0</td>
<td>114.0</td>
</tr>
<tr>
<td>Xinplex</td>
<td>114.0–126.0</td>
<td>114.0</td>
</tr>
<tr>
<td>Quell</td>
<td>114.0–126.0</td>
<td>114.0</td>
</tr>
<tr>
<td>Zerocal</td>
<td>112.0–124.0</td>
<td>114.0</td>
</tr>
<tr>
<td>Not tested</td>
<td></td>
<td>Not tested</td>
</tr>
</tbody>
</table>

### Table 3: Number of Violations of Roche Specifications

<table>
<thead>
<tr>
<th>Violation Type</th>
<th>Number of Violations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shelf-life</td>
<td>≤ 2.5%</td>
</tr>
<tr>
<td>Dissolution</td>
<td>≤ 0.5%</td>
</tr>
<tr>
<td>Orlistat</td>
<td>≤ 1.5%</td>
</tr>
</tbody>
</table>

**Fig. 5.** Summary of impurities (%) in Xenical and generic orlistat products: A Total organic impurity content. B Total side chain homologues. C Unidentified impurities.

**Fig. 6.** Dissolution rate (%) at 45 min for Xenical and generic products.
Impurities

All generic products contained side-chain homologues present in the genetic products were due to different chemicals, including side-chain homologues and amino acid analogues not present in Xenical.

Discussion

Orlistat is polymorphic, existing in two distinct crystalline forms with similar physical properties in terms of solubility, dissolution rate of the pure substance, and hygroscopicity. This explains our findings of similar melting temperatures among the generic products tested compared to Xenical.

Number of Violations of Roche Specifications

All nine generic products contained side-chain homologues (range 0.8–2.4%, fig. 5B). Three generic products (Cuvarlix, Xinplex, and Xeniplus) each contained excessive amounts of side-chain homologues and amino acid analogues not present in Xenical.

Discussion

All generic products failed to meet the Roche specification for total of all impurities of 0.5% at release, and five generic products (Zerocal, Obelit, and Xinplex) each contained more than five individual side-chain homologues (data not shown).

Table 3. Generic orlistat products ranked by number of violations of Roche specification

<table>
<thead>
<tr>
<th>Product Manufacturer</th>
<th>Pharmaceutical quality parameter</th>
<th>Total violations (minimum)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-year shelf-life</td>
<td>granules/particle size distribution</td>
</tr>
<tr>
<td>Obelit Intas Pharma</td>
<td>F</td>
<td>?</td>
</tr>
<tr>
<td>Zerocal Wecklar</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Cobese Ranbaxy</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Cuvarlix Pharmamia</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Xeniplus Elea</td>
<td>F</td>
<td>?</td>
</tr>
<tr>
<td>Xiluet Servimedic</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Fingras Phoenix</td>
<td>F</td>
<td>?</td>
</tr>
<tr>
<td>Lesofat InnoGen Pharma Group</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Xinplex Craveri</td>
<td>F</td>
<td>?</td>
</tr>
<tr>
<td>Fails (minimum)</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

F = Fail; ? = indeterminate; F = inadequate labelling.
*Not included in pharmaceutical quality parameters.
†Pures average orphanstat content, but particles were very variable and some contained no orphanstat.
Previous studies have found some generic products to be less uniform in terms of unit fill mass and amount of active ingredient and to contain more impurities than the innovator product [7–11]. We compared the pharmaceutical quality of synthetically produced orlistat (Xenical) with nine generic products. The wide spectrum and identity of impurities was consistent with these products being produced via fermentation processes. We could identify two areas of concern: dissolution rate and impurity content, with corresponding potential consequences on dose delivery and toxicological issues, respectively. Both may also have an impact on efficacy and safety, respectively. We did not include the wholesale or retail costs of products although this can be a major argument for the development and usage of generic products.

Stability tests of Xenical carried out by Roche revealed a slow decline in dissolution rates over a 3-year period at a storage temperature of 25 °C and 60% relative humidity. Although successful dissolution in vitro does not guarantee equivalent dissolution in vivo and does not always reflect in vivo availability, such tests are required for registration to demonstrate batch-to-batch consistency during manufacture. The dose-response of orlistat exhibits considerable variability among individuals [3], which was attributed to how well orlistat mixed with the fat content of a meal [12]. This step might be influenced by the dissolution of the product. Suggestively, in a clinical comparison of orlistat formulations, a granulated formulation tended towards superior efficacy over a powdered formulation in increasing dietary fat excretion [13]. In this context, the very low dissolution rate shown by Cuvanx and the large variation in dissolution rates observed with Obelit are causes for clinical concern as they indicate that little orlistat might be available and, hence, that the products would be expected to have markedly reduced efficacy. Such clinical efficacy concerns with generic products can only be addressed by controlled clinical studies, designed to meet the same end-efficacy concerns with generic products can only be addressed orlistat might be available and, hence, that the products would be serious due to their possible accumulation in these patients. As with the requirement for efficacy studies, the onus should be on generic manufacturers to provide clinical evidence that their products, particularly when less pure than the patented product, are not associated with additional side-effects.

Conclusions

The pharmaceutical quality of nine generic products was compared with Xenical. The wide spectrum of impurities indicates that the generic products were produced using fermentative processes. On the basis of the poor dissolution rates and the wide spectrum of impurities observed, we must question whether the nine generic products tested can be said to represent pure, safe and consistent alternatives to Xenical.

Disclosure

PWT, IA and INS have provided consultancy services to F. Hoffmann La-Roche Ltd. AF is an employee of F. Hoffmann La-Roche Ltd.

References