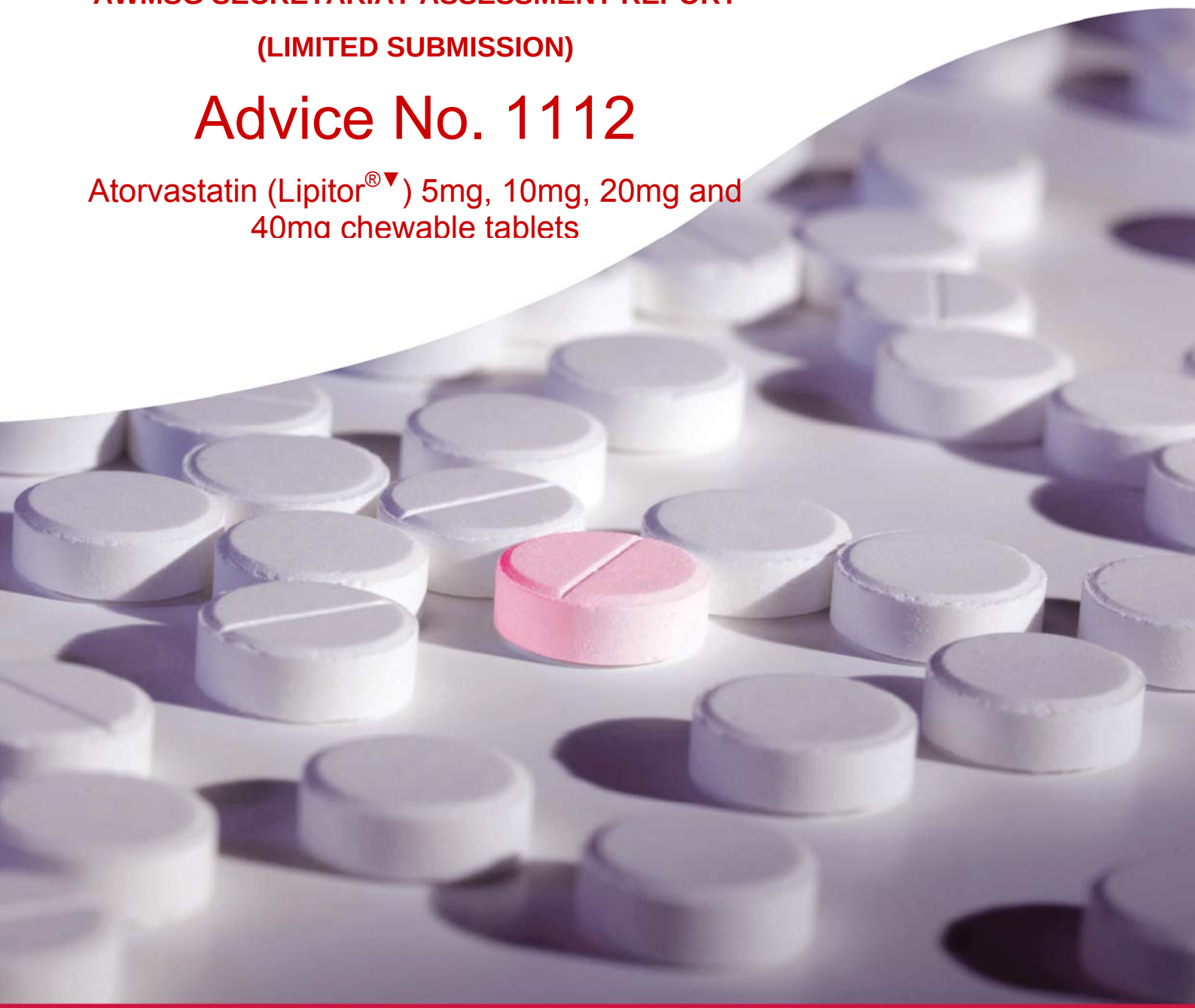
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 1112

Atorvastatin (Lipitor®▼) 5mg, 10mg, 20mg and 40mg chewable tablets



AWMSG Secretariat Assessment Report – Advice no. 1112
Atorvastatin (Lipitor®▼) 5 mg, 10 mg, 20 mg and 40 mg chewable tablets

This assessment report is based on evidence from a limited submission by Pfizer Ltd on 16 December 2011[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Hypercholesterolaemia Atorvastatin (Lipitor®▼) chewable tablets are indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to types IIa and IIb of the Fredrickson classification) when response to diet and other non-pharmacological measures is inadequate. Atorvastatin chewable tablets are indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable. Prevention of cardiovascular disease Atorvastatin chewable tablets are indicated for the prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors[2].
Dosing	The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin chewable tablets and should continue on this diet during treatment. The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dose should be made at intervals of four weeks or more. The usual starting dose is 10 mg once daily; the maximum dose is 80 mg once daily. Safety information for paediatric patients treated with doses above 20 mg per day is limited. Refer to the Summary of Product Characteristics (SPC) for specific dosing advice in adults and paediatric patients[2].
Marketing authorisation date	3 November 2010[3].
UK launch date	November 2011[1].

2.0 DECISION CONTEXT

2.1 Background

Cardiovascular disease (CVD) encompasses several disorders of the heart and blood vessels and is the main cause of death in England and Wales, accounting for one in three fatalities in 2005. CVD is a multifactorial disease and several determinants of CVD risk have been identified[4]. Current guidelines recommend identification of patients at high risk of CVD and management of all possible modifiable factors, such as diet, smoking status, alcohol consumption and cholesterol levels[4,5]

There are many rare inherited conditions that are characterised by abnormal plasma lipid levels and altered risk of coronary heart disease (CHD)[5]. Two of the most common disorders are familial combined hyperlipidaemia (FCH), which has an estimated prevalence of 0.5–2% in the general population[6], and familial hypercholesterolaemia (FH)[7]. Most FH patients have inherited an FH-associated genetic defect from only one parent and are therefore heterozygous. In the UK population, it is estimated that heterozygous FH affects 1 in 500 people, which can be extrapolated to 6,000 Welsh patients, assuming the same prevalence rate in Wales. In rare cases, a genetic defect can be inherited from both parents; this is termed homozygous FH or compound heterozygous FH and has an incidence of approximately one case per million people[7].

Statins such as atorvastatin inhibit the action of HMG-CoA reductase, the rate-limiting enzyme of cholesterol precursor production, thereby lowering plasma cholesterol and serum lipoprotein concentrations[2]. Current UK and EU guidelines recommend the use of statins for the prevention of CVD in patients judged to be at high risk, including patients with FH or FCH[4,5,7,8].

Atorvastatin chewable tablets have been granted marketing authorisation for the prevention of cardiovascular events and as an adjunct to diet for reduction of total-C LDL-C, apolipoprotein B, and triglycerides in patients with hypercholesterolaemia[3]. The applicant company suggests that the population most likely to use atorvastatin chewable tablets are FH patients aged 10–17 years[1].

2.2 Comparators

The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was atorvastatin (Lipitor®) film-coated tablets.

2.3 Guidance and related advice

- European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS). Guidelines for the management of dyslipidaemias (2011)[8].
- National Institute for Health and Clinical Excellence (NICE). Clinical Guideline 67. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (2008)[4].
- NICE. Clinical Guideline 71. Identification and management of familial hypercholesterolaemia (2008)[7].
- ESC. European guidelines on cardiovascular disease prevention in clinical practice (2007)[5].
- Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice (2005)[9]. This guidance is currently under review.
- The All Wales Medicines Strategy Group (AWMSG) template for the use of statins is under review.

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission focuses on demonstrating the bioequivalence of atorvastatin chewable and film-coated tablet formulations.

3.1 Bioequivalence study A2581174

This was an open label, randomised, single-dose, two-way crossover study to determine whether two 5 mg atorvastatin chewable tablets were bioequivalent to one 10 mg atorvastatin film-coated tablet over two five-day treatment periods[1]. Healthy volunteers (n = 76) aged 21–55 years were randomised to receive a single daily dose of either one 10 mg film-coated tablet or two 5 mg chewable tablets. Following a 14-day washout period, patients received the study treatment not administered during treatment period one[1]. Blood samples were taken before and after (0.25–72 hours) each dose[3,10]. Primary endpoints included area under the plasma concentration-time profile, from time zero to the time of the last quantifiable concentration (AUC_{last}); area under the plasma concentration-time profile, from time zero extrapolated to infinite time (AUC_{inf}); and maximum plasma concentration (C_{max})[11].

An overview of endpoint results is presented in Table 1. The 90% confidence intervals for the ratio of the adjusted geometric means of both C_{max} and AUC_{inf} lay within the acceptable range for bioequivalence (80%, 125%), therefore satisfying the bioequivalence criteria for both these endpoints[3,10].

Table 1. Overview of endpoint results from study A2581174[1].

Pharmacokinetic parameter (units)	Geometric means		Ratio of adjusted geometric mean (%)	90% Confidence Interval (CI) for ratio (%)
	Two 5 mg tablets of chewable atorvastatin (n = 75)	One 10 mg tablet of film-coated atorvastatin (n = 76)		
AUC_{inf} (ng.h/ml)	22.78	22.13	102.91	99.02,106.96
AUC_{last} (ng.h/ml)	20.48	19.80	103.48	99.34, 107.79
C_{max} (ng/ml)	3.80	3.51	108.13	98.75, 118.40

3.2 Comparative safety of atorvastatin chewable tablets

At the time of licensing, it was concluded that the safety profiles of the two atorvastatin formulations appear to be comparable based on the outcomes of study A2581174. Additionally, it was noted that the safety profile of atorvastatin in children appears to be similar to that described in adults and that no new adverse events have been described[3,10,12]. The Committee for Medicinal Products for Human Use (CHMP) highlighted two patients (from a population of 39) that had elevated levels of the enzyme alanine transaminases as a potential concern, but suggested that additional safety data could be provided by the ongoing study A2581173[10,12,13]. It was also noted that the Paediatric Investigation Plan (PIP) had been completed. In addition to a bioequivalence study in healthy adult volunteers, the PIP included an eight-week pharmacokinetic study in heterozygous FH patients aged 6 years to less than 18 years and a three-year study of the safety and efficacy of atorvastatin in this patient population[10,12]. The results of these studies are described in the SPC[2].

3.3 AWTTC critique

- Although the company submission suggests that use of atorvastatin chewable tablets will most likely be in FH patients aged 10–17 years[1], the company has not provided a rationale to support this and the licensed indication allows for treatment of a wider population[2].

- At the time of licensing, both CHMP and Medicines and Healthcare products Regulatory Agency (MHRA) concluded that the development of a paediatric-specific pharmaceutical form promotes treatment compliance and facilitates the administration of doses appropriate to this population. However, it was also noted that there was limited safety information in paediatric patients treated with atorvastatin doses above 20 mg[3,10,12], and this is reflected in the SPC[2]. Additionally, the lack of information regarding the safety of long-term use in paediatric patients was highlighted, although previous experience with other statins suggests that there is no detrimental effect on long-term growth or maturation[3,10,12].
- Chewable tablets may be more convenient to use because they do not require further manipulation, such as crushing/dispersing.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

Manufacturers are not required to submit evidence on cost-effectiveness for a limited submission, and literature searches by the Welsh Medicines Partnership identified no relevant studies.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company submission notes that atorvastatin (Lipitor®▼) chewable tablets are considered to be bioequivalent to the existing film-coated tablet formulation based on a single dose cross-over study in 76 healthy adults[1]. The licensed indications of the two formulations are the same. The company assumes that the chewable tablets will be used primarily in children and adolescents aged 10 to 17 years, and that switching from the film-coated to chewable atorvastatin tablets may occur in around 20% of patients. The company assumes that no patients taking other statins will switch to chewable atorvastatin tablets. On a per tablet basis the acquisition costs of the 10 mg and 20 mg chewable tablet and film-coated tablets are the same. Therefore, the company anticipates there will be no additional cost associated with the adoption of chewable atorvastatin tablets in NHS Wales[1].

5.1.2 AWTTC critique

On the basis of current list prices, there is no difference in acquisition costs between the film-coated tablet and the chewable tablet formulations of atorvastatin. Within the dose range of 10 mg to 20 mg daily, there is currently no budget impact anticipated with the use of the chewable tablet instead of the film-coated tablet formulations of atorvastatin. There is the potential for atorvastatin chewable tablets to be initiated in place of another statin where swallowing of film-coated tablets is problematic.

5.2 Comparative unit costs

On a per tablet basis the acquisition costs of the 10 mg and 20 mg chewable tablet and film-coated tablets are practically the same.

Table 2. Examples of drug acquisition costs for the treatment of hypercholesterolaemia in adults, adolescents and children aged 10 years or older.

Drug	Example regimen	Annual acquisition costs
Lipitor® (Atorvastatin) chewable tablets: 10 mg, 20 mg	10 mg – 20 mg once daily	£167.90 - £321.20
Lipitor® (Atorvastatin) film-coated tablets: 10 mg, 20 mg	10 mg – 20 mg once daily	£169.46 - £321.20
Costs are based on MIMS[14] list prices as of 20/01/2012.		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that atorvastatin chewable tablets may be suitable for prescribing by all prescribers within NHS Wales for the stated indication

6.2 AWMSG review

This report will be considered for review in June 2015.

6.3 Evidence literature search

Date of evidence search: 10 January 2012.
Date range of evidence search: no date limits were applied to database searches.

REFERENCES

1 Pfizer Ltd. Form C: limited appraisal submission. Atorvastatin (Lipitor®▼) chewable tablets. 2011.
2 Pfizer Ltd. Lipitor®▼ chewable tablets. Summary of Product Characteristics. Nov 2011. Available at: http://www.medicines.org.uk/EMC/medicine/25412/SPC/Lipitor+5mg%2c+10mg%2c+20mg%2c+40mg+chewable+tablets./. Accessed Jan 2012.
3 Medicines and Healthcare products Regulatory Agency. Public Assessment Report. Atorvastatin (Lipitor®) 5mg, 10mg, 20mg and 40mg chewable tablets. PL16051/006-9. 2010. Available at: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con102999.pdf. Accessed Jan 2012.
4 National Institute for Health and Clinical Excellence. Clinical Guideline 67. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. 2008. Available at: http://guidance.nice.org.uk/CG67. Accessed Jan 2012.
5 European Society of Cardiology. European guidelines on cardiovascular disease prevention in clinical practice. *Eur J Cardiovasc Prev Rehabil* 2007; 14 Suppl 2: S1-113. Available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/cvd-prevention.aspx.
6 Gaddi A, Cicero AF, Odoo FO et al. Practical guidelines for familial combined hyperlipidemia diagnosis: an up-date. *Vasc Health Risk Manag* 2007; 3 (6): 877-86.
7 National Institute for Health and Clinical Excellence. Clinical Guideline 71. Identification and management of familial hypercholesterolaemia. 2008. Available at: http://guidance.nice.org.uk/CG71. Accessed Jan 2012.
8 European Society of Cardiology, European Atherosclerosis Society. ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J* 2011; 32 (14): 1769-818. Available at: http://eurheartj.oxfordjournals.org/content/32/14/1769.full.
9 British Cardiac Society, British Hypertension Society, Diabetes UK et al. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005; 91 (suppl 5): v1-v52. Available at: http://heart.bmj.com/content/91/suppl_5/v1.short.
10 European Medicines Agency. Assessment report for Sortis and associated names. Procedure number: EMEA/H/A-29 PAD/1254. 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Sortis_1254_29_Paediatrics/WC500105635.pdf. Accessed Jan 2012.
11 Pfizer Ltd. NCT00777517: An open label, randomized, single dose, two-way crossover bioequivalence study comparing a pediatric appropriate formulation to a 10 mg commercial atorvastatin calcium tablet formulation in healthy subjects. 2009. Available at: http://clinicaltrials.gov/ct2/show/NCT00777517. Accessed Jan 2012.
12 European Medicines Agency. Assessment report for Sortis and associated names. Procedure number: EMEA/H/A-29 PAD/1253. 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Sortis_1253_29_Paediatrics/WC500105612.pdf. Accessed Jan 2012.
13 Pfizer Ltd. NCT00827606: A three year, prospective, open-label, study to evaluate clinical efficacy, safety and tolerability of atorvastatin in children and adolescents with heterozygous familial hypercholesterolemia. 2012. Available at: http://clinicaltrials.gov/ct2/show/NCT00827606. Accessed Jan 2012.
14 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2011. Available at: http://www.mims.co.uk/. Accessed Jan 2012.