Study Acronym: SAMSON

NCT02668016

Study title: Self-Assessment Method for Statin side-effects Or Nocebo (SAMSON) trial

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This protocol describes a participant-empowering within-subject randomised controlled trial and the development of a practical technology to support 21st century primary prevention decisions and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. This study will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Study Management Group

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- Co-investigators: Dr Susan Connolly, Dr Judith Finegold, Dr James Howard, Professor Neil Poulter, Professor Simon Thom.
- Imperial Clinical Trials Unit (ICTU) Operations Manager:
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- Trial Manager/Nurse/Investigator: Ms Frances Wood.

Clinical Queries

Clinical queries should be directed to Dr James Howard who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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1 INTRODUCTION

1.1 BACKGROUND

Cardiovascular disease remains the main cause of death world-wide[1,2,3,4] despite advances in medical therapy[5,6,7,8,9,10]. Highly effective preventive regimes are available, but adherence is poor[11,12,13,14,15] . There are many causes of non-persistence with medication[16]. Many participants who have indications to receive preventative medication see it as only appropriate for the sick, and – not seeing themselves as sick – seek to avoid medication[17,18]. Non-adherence tends to be higher with poor health literacy, lower socioeconomic class[19] and increasing age[20].

Statins reduce cardiovascular event rate by a large proportion[21,22,23] but many participants outside trials do not persist with therapy, often because of adverse symptoms that they attribute to the medication. Growing societal suspicion of high adverse event rates in real-life experience is now discouraging even first-time initiation of therapy.

When an adverse symptom is experienced after initiation of a statin, the clinician has a limited repertoire of steps to take. Commonly the drug is stopped and re-tried after an interval with the participant - quite appropriately - advised to bring any recurrence of symptoms to medical attention. In other cases an alternative statin may be tried, with a similar warning to be alert for recurrent symptoms.

Analysis of the 83,880 participants who have received statins versus placebo in double-blinded randomised placebo controlled trials[24] shows no sign of a tendency for greater adverse *symptom* rate on statins versus placebo, if one sets aside increased glucose which is almost never the symptom stated as a reason for stopping statins.

Just as the placebo effect describes a favourable psychobiological effect following the administration of a placebo, the nocebo effect describes the adverse effect a participant experiences through taking a medication, not due to the medication itself. Previous studies quantified the nocebo effect by measuring adverse drug reactions when a placebo is administered and have reported nocebo effects ranging from 19% to 27%[25,26,27]. The nocebo effect is influenced by many factors[28], but undoubtedly the information a participant is given about a drug modifies their expectations and therefore their response[29]. Conditioning from previous negative experience also strongly influences the nocebo effect[30].

1.2 RATIONALE FOR CURRENT STUDY

Front-line clinicians cannot currently test for an individual participant whether symptoms experienced are the pharmacological result of a statin or due to other phenomena e.g. nocebo. The value of such a tool would be twofold:

- It would allow individual participants to establish for themselves whether they truly suffered a side effect from the drug, or are victims of nocebo - which may in fact be commoner
- By separating the components it would permit clinical researchers to explore the determinants of each, opening opportunities to obtain better outcomes

1. *Hypothesis 1:* that >30% of participants enrolling for the study will complete it.
2. *Hypothesis 2*: Overall >50% of symptom burden is nocebo rather than pharmacological
3. We will define the Nocebo proportion of side effects as shown in Figure 1:

$$Nocebo\ proportion = \frac{Nocebo\ component}{Total\ side\ effect(Pharmacological + Psychological}$$

4. *Hypothesis 3*: that the majority of participants, at 6 months after completion, will either be taking statins or have declined statins for reasons other than perceived side effects.

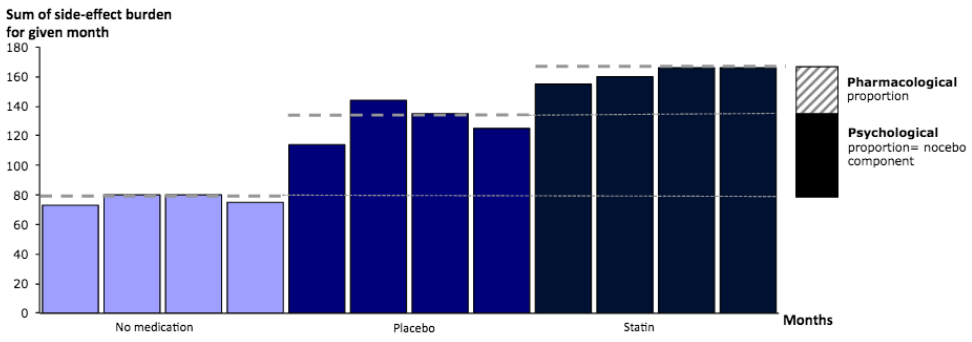


Figure 1: Example of a possible result from a single participant.
Each participant will undergo twelve randomly ordered 1-month periods. There will be four periods of no medication, four periods of placebo and four periods of statin. The placebo and the statin pills will be identical in appearance. Participants will record on a daily basis side-effects experienced.
At the end of the study, the one-month sessions are sorted into the order shown above. The participant can then observe directly how much of the increase in symptoms seen with statin is also seen with placebo.

2 STUDY OBJECTIVES

This project will develop, test and deliver a method for this, in the following stages:
1. We will develop a method for determining within an individual participant to what extent experienced symptoms are associated with the statin or merely nocebo effect
2. We will evaluate in a cohort of participants who have stopped statins because of adverse symptoms, in what proportion of them, the symptoms are truly due to the statin

3 STUDY DESIGN

3.1 PRE-RANDOMISATION EVALUATIONS

A participant and public involvement group have already provided feedback to assist the development of the study proposal. Their feedback is summarised in Appendix 1. The phone application has also been piloted among healthy volunteers and feedback summarized in appendix 2.

3.2 PILOT STUDY: SEMI-STRUCTURED INTERVIEW TO EXPLORE AND MEASURE SYMPTOM EXPERIENCE TO REFINE MEASUREMENT TOOLS FOR THE MAIN TRIAL

Participants: Prior to the trial we will recruit 20 participants who are either 1) currently taking statins with and without adverse symptoms or 2) have previously ceased statin therapy due to adverse symptoms.
Method: The interviews will have two parts. Firstly, we will conduct a brief interview to explore individuals' current or past experience of statins. Secondly, participants will fill out a structured questionnaire that assesses the intensity within each participant of several commonly described statin side-effects, each on a scale of 0-100. These would include muscle aches, fatigue, headache, and gastrointestinal symptoms. In addition, the participants will be asked to complete and comment on the daily and monthly questionnaires planned for the main trial to assess their appropriateness. At the same session participants will have a cognitive interview[31] to determine their reasoning whilst filling out various different scales. The interviews will be audio-recorded and transcribed using Nvivo software. The exploratory part of the interviews will be interpreted using thematic analysis[32] and the cognitive interviews using a content analysis approach[33].

Scale refinement: The scales used in the main trial will be refined based on the findings from the interviews, and any modifications piloted among further participants.

3.3 RANDOMISED CONTROLLED TRIAL: EVALUATING IN A COHORT OF PARTICIPANTS THE PROPORTION OF ADVERSE SYMPTOMS TRULY DUE TO THE STATIN RATHER THAN THE NOCEBO EFFECT

Participants: 50 participants will be recruited to the trial.

Method: At baseline each participant will have a detailed interview with the study doctor to assess past medical history and previous symptoms attributed to statins and assess if they are eligible to be enrolled. Eligible participants will be enrolled on InForm which will allocate each participant a random predefined order to take the study interventions in. These random codes will be generated by the ICTU statistician and supplied to the production pharmacy. The participant will be dispensed HDPE containers which are in this pre-specified order assigned on inform. Each participant will receive 12 sets of HDPE containers pre-labelled. 4 sets of HDPE containers will contain no medication, 4 will contain 1-month supply of matched placebo and 4 will contain 1-month supply of atorvastatin 20mg. At the start of the next calendar month after the screening visit the participants will commence the trial intervention. The research nurse will call the participant to remind them to start on the 1st day of the next month after screening and thereafter the participants will also receive a monthly reminder on their phone to switch to the next set of HDPE containers each month. Each day participants will rate their daily symptom on a phone application and will also complete 3 additional questionnaires on a monthly basis. The study nurse will call the participant at the end of each month to assess their progress in the trial. Each participants will return their boxes at dispensing visits (if applicable) and at the study end in order for a pill count to be undertaken to assess medication adherence. The placebo and atorvastatin pills will be visually identical.

The study enrols participants not intending to re-start clinical use of statins. Participants' other medications will continue to be managed as normal by their own physicians, with no restriction on starting, stopping or changing doses For safety reasons the participant's own physician will be asked to consult the investigators prior to consideration of starting, or amending the dose of, any other lipid lowering medication

3.4 STUDY OUTCOME MEASURES

For the trial, each participant will receive a smartphone or if preferred can have the application downloaded to their existing phone to allow real-time daily documentation of symptoms experienced on a visual analogue scale of 0-100. Example screen-shots (which will be further refined based on the findings from the pilot study) are shown in Appendix 3. Participants will receive training on the simple touch-screen interface and a leaflet with further information will also be provided. An optional daily reminder can be setup on the participants' phones. Participants will rate symptoms every day, with the daily scores aggregated into a monthly score. This is preferable over scoring only once a month, because participants may struggle to remember and aggregate their symptom burden especially if it varies between days.

Each month participants will fill out two validated questionnaires on the impact of their side-effects on their quality of life. These are EuroQol (EQ-5D-3L),[34] a well-validated measure of health related quality of life, and the Treatment Satisfaction Questionnaire for Medicine (TSQM) questionnaire, a validated treatment satisfaction questionnaire. EQ-5D-3L assesses five domains of health and overall self-rated health using a visual analogue scale. EQ-5D-3L is conventional for assessing efficacy of medication on quality of life but may not be sufficient for assessing side effects,[35] therefore the TSQM[36] questionnaire will also be used. Use of both a health related quality of life questionnaire and a treatment satisfaction questionnaire will allow assessment of participants' multiple health states, overall self-rated health status and treatment satisfaction, and provide a test of both convergent validity and measurement invariance for the monthly aggregate symptom burden score.

We will also ask participants to fill in a short questionnaire detailing any potentially confounding life events over the previous month e.g. change of daily routine, holidays, bereavement, etc. At the end of study visit, participants will have an exit interview exploring the nature of symptoms occurring during the study in case they may differ from those described in the baseline interview. Participants will also be shown their individual nocebo proportion at the end of study visit. The Participant is then able, as in normal life, to decide to continue on a statin or not. We will follow-up the participants at 6 months after the end of study visit and evaluate:

a) Whether they are now taking a statin and, if not, the reason
b) Whether they currently believe that most of the side-effects previously attributed to the statin, were indeed a pharmacological effect of the statin.

4 PARTICIPANT ENTRY

4.1 INCLUSION CRITERIA FOR MAIN TRIAL:

- Aged 18 years or older
- Previously taken one or more statins
- Withdrawn from statins because of perceived side effects
- Developed side effects within 2 weeks of initiation
- Clinical indication for statins for primary or secondary prevention of cardiovascular disease or dyslipidaemia

4.2 EXCLUSION CRITERIA FOR MAIN TRIAL:

- History of any condition that causes chronic pain
- History of severe mental illness (as their experience of symptoms may already be altered)
- Current taking fibrates (because of the risk of interaction with statins but will not exclude participants taking ezetimibe).
- History of statin intolerance with creatine kinase elevation greater than 5 times the upper limit of normal
- History of statin intolerance with anaphylaxis
- History of statin intolerance with myalgia and rise in serum creatine kinase

- History of statin intolerance with rhabdomyolysis
- History of statin intolerance with liver function abnormalities, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the ULN
- Currently taking antiretrovirals with known interaction to statins
- Currently taking any drug other than antiretrovirals with known interaction to statins
- Pregnant or breast feeding
- Side effects taking longer than 2 weeks to present (because in such participants much longer blocks of treatment would be required, if the present study is positive such studies will be planned for the future)*
- In clinical judgement of study doctor, participant should not be enrolled on the study

**All participants excluded for this reason will be logged so that the proportion excluded will be known. The study will be explained to consecutive eligible participants, and those giving informed consent will be recruited.*

4.3 WITHDRAWAL CRITERIA

If during the study, participants choose to re-start clinical statin therapy, they will withdraw from the study and start open medication.

4.4 UNBLINDING PROCEDURE

In the unlikely event unblinding is necessary it will be possible for the Chief Investigator to quickly and easily unblind to treatment using the unblinding function of the trial database. A back-up unblinding list will be held at the pharmacy.

5 PHARMACOVIGILANCE

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An *AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (summary of product characteristics). When the outcome of the adverse reaction is not consistent with

the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the summary of product characteristics which occur in a more severe form than anticipated are also considered to be unexpected.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

- Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

  Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

5.2 CAUSALITY

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the

	participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

5.3 REPORTING PROCEDURES

There is only one study site and the principal investigator is also the chief investigator of the study. All adverse events will be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting will be directed to the Chief Investigator in the first instance. A flowchart is given below to aid in the reporting procedures.

5.3.1 NON SERIOUS ADVERSE REACTIONS/ADVERSE EVENTS

All such toxicities, whether expected or not, should be recorded in the toxicity section of the relevant case report form

5.3.2 SERIOUS ADVERSE REACTIONS/ADVERSE EVENTS

Fatal or life threatening SAEs and SUSARs should be reported on the day that the site is aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be gained within 5 days if the reaction has not resolved at the time of reporting.

5.3.3 SERIOUS ADVERSE EVENTS

An SAE form should be completed by the site within 24 hours. However, hospitalisations for elective procedures of a pre-existing condition do not need reporting as SAEs.

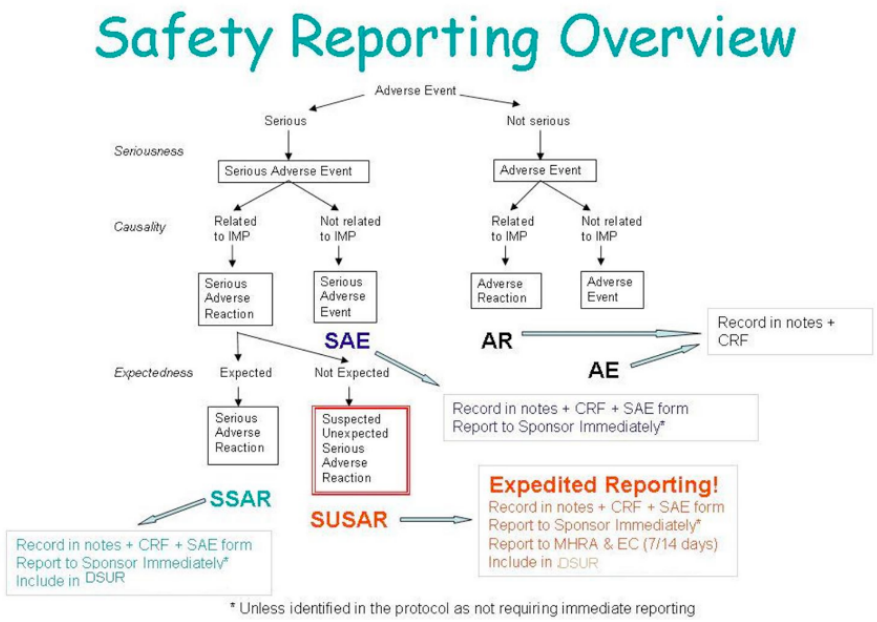
All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

5.3.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS

In the case of suspected unexpected serious adverse reactions, the staff at the site should:

Complete the SAE case report form and send it immediately (within 24 hours, preferably by fax), signed and dated to the MHRA, REC and sponsor together with relevant treatment forms and anonymised copies of all relevant investigations. The study team will notify the MHRA, REC and sponsor of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All local investigators will be informed.



6 IMP MANAGEMENT AND ACCOUNTABILITY

6.1 MANAGEMENT/SUPPLY OF IMPS

An up-to-date summary of product characteristics (SmPC) of Atorvastatin will be included in the Trial Master File (TMF), which will be reviewed at least annually and any change should be notified and an updated SmPC added to the TMF.

Research staff will be delegated IMP management responsibilities by the CI. The CI in conjunction with research staff delegated IMP management responsibilities must:

a. Maintain records that document shipment, receipt handling, return and destructions of the IMP
b. Maintain a system for retrieving IMPs and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired reclaim).
c. Maintain a system for the handling of unused IMP(s) and for the documentation of returned IMPs

d. Maintain records of batch sample analyses, characteristics and storage conditions, e.g. temperature logs.

6.2 DRUG ACCOUNTABILITY

Drug accountability logs will be kept for dispensing IMP and for reconciling returned medication. The accountability log will detail:

- Subject identification code
- Date dispensed
- Dose
- Date of expiry
- Quantity dispensed
- Batch number
- Date returned
- Quantity returned
- Recorder's initials

All IMPs should be stored and dispensed by the delegated research staff and managed to the same standards as licensed medicines.

6.3 LABELLING

The IMP (atorvastatin 20mg OD or placebo) will be labelled, to ensure all supplies are in consistent packaging with consistent labelling to maintain blinding. They will be labelled with:

i. The name of the investigator
ii. Sponsor:
iii. Product name, form and strength or placebo
iv. Date of supply
v. Name and address of site
vi. Trial specific code
vii. Code for the trial subject
viii. Directions (as specified)
ix. "Keep out of reach of children"

As it is a blinded trial, the coding system for the investigational product includes a mechanism that permits rapid identification of the product in the unlikely case of a medical emergency.

6.4 TRIAL SPECIFIC SOPS

The CI, in conjunction with the research staff at the site should ensure that the following trial specific SOPs are in place before starting the trial:

- Receipt and recording of safe delivery of IMPs
- Safe Handling and storage of IMPs
- Code Breaking
- Preparation and dispensing of IMPs
- Return and disposal of unused IMPs
- Maintaining a pharmacy study file

7 ASSESSMENT AND FOLLOW-UP

Participants will attend a screening visit where the study doctor will receive written informed consent from them if they decide to participate. Then the study doctor will assess the participants eligibility for the study by evaluating their past medical history and previous statin intolerance. Participant's blood pressure will also be measured and if a participant does not have a recent lipid profile recorded in the last 12 months, they will be offered the option of having one undertaken as part of the screening visit. The study doctor will determine if the participant is suitable to be enrolled in the study. If suitable, they will be enrolled on inform.

Unscheduled assessments will not be performed unless participants develop adverse events which the chief investigator considers 'related' to the trial procedure or Atorvastatin therapy.

Scheduled follow-up telephone calls will be undertaken during every month during the 12-month period of the trial. Furthermore, participants scoring will be monitored by study nurse and if they show severe discomfort or if participants are not scoring on their phone unscheduled telephone follow-up calls will be made and if required a unscheduled study visit to see the study doctor and perform unscheduled tests as deemed necessary by the study doctor.

End of study will be defined as when the specified number of patients have been recruited, all patients have completed the 18-month phone interview and the database is locked.

The 12-month follow-up contact may be combined with the end of study visit, if so this would be a face-to-face visit at the study centre or by telephone if the participant is unable to attend in-person during the COVID pandemic. The end of study visit may take place up to 31 days after the 12-month telephone follow-up.

8 STATISTICAL AND DATA ANALYSIS

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Our study's principal hypotheses will be tested as follows:

Hypothesis 1 will be tested by calculating the proportion of respondents completing the study, and the corresponding 95% confidence interval for this estimate, and examining whether the confidence interval lies completely above a value of 0.3 or not.

To test **Hypothesis 2**, comparisons between the average monthly symptom burden (measured by the monthly aggregate of symptom scores) resulting from no treatment/placebo/statin treatment periods will be made using a longitudinal multilevel model. The most basic model to test hypothesis 2 would be:

To test **Hypothesis 2**, we will calculate the nocebo ratio across all patients. This is to avoids attempting to analyse the pathological distributions that would arise for patient whose mean statin symptom score is close or less than their no treatment score, because the nocebo ratio becomes disruptively extreme. Combining the data

across all patients to yield a single statin, placebo and no treatment symptom score allows a representative and interpretable nocebo ratio to be provided.

Hypothesis 3 is that the majority of patients will be taking statins, or have a non-side effect reasons for not doing so, at 6 months after study completion. This will be a descriptive statistic of the sample, which does not require inference of the population mean. No further statistical analysis is therefore necessary

8.1 POWER CALCULATIONS

Hypothesis 1: We hypothesise that of the patients enrolling for the study, 50% or more will complete the study. Our intention is to report the proportion of patients completing the study and its 95% confidence interval. Based on the binomial principle, $SE_p = \sqrt{p \cdot q / n}$, the number of patients planned after the calculation below (50) will permit this proportion to be stated with a 95% confidence interval of $\pm 1.96\sqrt{\frac{1}{2} \cdot \frac{1}{2} / 50}$. Thus the proportion will be reported with a margin of error of ±14% or smaller. If the long-run proportion of patients who would finish the study is ~70%, then a sample size of 50 gives 85% power to detect this at the 5% significance level.

Hypotheses 2 and 3: These hypotheses address the sample of participants and not the population at large. They therefore do not need a sample size calculations.

9 MONITORING

9.1 RISK ASSESSMENT

This study is adopted by the Imperial Clinical Trials Unit (ICTU). ICTU will risk assess the study and undertake monitoring responsibilities relevant to the trial's estimated level of risk.

10 REGULATORY APPROVALS

10.1 CLINICAL TRIALS AUTHORISATION

The study will be performed in compliance with UK clinical trial regulations. Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Authority (MHRA) will be obtained prior to the start of the study. In addition, the Regulatory Authority must approve amendments (as instructed by the Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.

10.2 ETHICAL APPROVAL

Prior to enrolment of subjects, written approval from the REC must be obtained for named sites, the protocol and any amendments, the Patient Information Sheet and Consent Form, any other written information that will be provided to the subjects, any advertisements that will be used and details of any subject compensation. The study must be submitted for Site Specific Assessment (SSA) at Imperial College Healthcare NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in

research on human subjects adopted by the World Medical Assembly, 7th Version of the Declaration of Helsinki (2013). The REC will be sent annual progress reports, annual safety reports and will also be informed about the end of the trial within the required timelines.

10.3 INFORMED CONSENT

Prior to informed consent being received participants will be given ethically and trust approved version controlled information sheets regards the study and given at least 24 hours but preferably at least a week to read this information prior to consent.

For the pilot study the research nurse who is experienced in receiving informed consent for qualitative research will undertake the informed consent process with participants. Participants will be given the option of attending in-person or by telephone. If consent is undertaken in-person, written informed consent will be received from the participant prior to undertaking the interview and copy of the consent form will be given to the participant for their records. If a participant opts for a telephone interview, the participant information sheet, a separate telephone consent form and the questionnaires will be sent to the participant in advance of the telephone call. The study nurse will then receive verbal consent over the telephone prior to turning on the voice recorder and will sign the consent form. A copy of the completed telephone consent form will be sent to the participant. The voice recorder will only be turned on once verbal consent has been fully received and the study nurse will always seek permission of the participant prior to turning on the telephone voice recorder and then will also state clearly the voice recorder has been turned on and then start the interview.

For the main trial participants will be consented by the Research Fellow or Chief investigator/Principal investigator. The research fellow will be a cardiology SpR (MB BS MRCP); who will be able to assess mental capacity and understands the principles of informed consent.

Only participants who are able to fully consent to the study will be recruited. As there is an extra time commitment associated with the study, and much of the study is in addition to usual care, only participants who have capacity to refuse will be approached. There is no funding available for translation so people who cannot speak or write in English will be unable to participate. It will be highlighted to participants that they can withdraw their consent at any stage.

10.4 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

10.5 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

10.6 SPONSOR
Imperial College London will act as the Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

10.7 FUNDING
The British Heart Foundation are funding this study. Travel reimbursement for site visits has been allocated.

10.8 AUDITS
The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

11 TRIAL MANAGEMENT

11.1 TRIAL MANAGEMENT GROUP
A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial and will include independent members.

The day-to-day management of the study will be co-ordinated through Imperial College London by research nurse Ms Frances Wood, who will be supervised by research fellow James Howard and Consultant Cardiologist Professor Darrel Francis.

The study has been adopted under the Imperial Clinical Trials Unit (UKCRC ID number 18).

11.2 DATA MONITORING COMMITTEE
A Data Monitoring Committee (DMC) will be convened to review safety data annually and advise the TMG if the trial should continue. A Charter will be devised to list the roles and responsibilities of the members.

12 DATA MANAGEMENT
Inform will be used to manage the data for the study. InForm is a validated data capturing system with a full audit trail.

13 ARCHIVING
Following the end of the study, when deemed practical, all essential documents will be archived for a minimum of 10 years as per Imperial College London guidelines.

14 PUBLICATION POLICY
We plan to disseminate the results of this study through publication in peer reviewed scientific journals, conference presentations and publication on Imperial College London website.

15 REFERENCES

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SIGNATURE PAGE 1 (Principal Investigator)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title:

Sponsor's reference :

Signed: Darrel Francis

Professor Darrel Francis
Consultant Cardiologist
Imperial College London

Date: 21 July 2020

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: 15SM2947

Sponsor's reference :

Signed: Ruth Nicholson

Ruth Nicholson
Research Governance Manager
Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust

Date: 21/07/2020

APPENDICES

16.1 APPENDIX ONE: PATIENT AND PUBLIC INVOLVEMENT FEEDBACK

DRN
Diabetes Research Network
North West London LRN

NHS
National Institute for
Health Research

Feedback from participant and public involvement group

- **What are your initial feelings about the research?**
  "I think the study is very important as a lot of people have complained about certain types of statins prescribed. They have complained about muscle cramps and other adverse reactions.
  "I felt a little uneasy. If I have already had side effects from taking statins I do not think I would want to restart even if it might help others in the long run. I would rather wait to see if findings from such research would benefit me. Some prospective participants might have a different view to mine and would be prepared to risk side effects again, especially if they were being monitored whilst on the trial and they knew they could pull out from trial. (In my own case I was started on a statin and felt really unwell but was then quickly changed to a different statin which up to now has shown no side effects) Good to see phone app technologies which might be useful"
  "Potentially useful, but I will not volunteer to participate. Having had serious muscle problems with 20 mg Simvastatin, which stopped within a week of ceasing to take them, I consider it important to assess specifically the side effects. I seriously doubt the claim that studies of 80,000 ""showed no tendency to experience more unwanted side effects with statins than with a placebo drug."" Many diabetics contributing to the diabetes.co.uk/forum experience problems with statins."
  "Very positive as there are lots of differing views about statins with non-medical people"

- **Do you think the research question is important?**
  "I suppose so, if statins have great benefits and it was found in evidence gathered already from 80,000 participants (referred to in info) that there was no tendency to experience more unwanted side effects with statins than placebo"
  "Yes - hopefully participants will be better & specifically informed. I was not - apart from the small print in the leaflet. It may show whether other health conditions are

affected by statins, or statins affect the health conditions - e.g. diabetes, blood glucose, dementia, blood pressure,"
"Yes as it clearly sets out the reasons for the research."

- **Do you feel that the treatment and assessment plan will be acceptable to the participants?**
  "For those wanting to take part, yes."
  "Yes."
  "I think as long as it is non-invasive, there should not be any concerns."
  "Yes as it explains the procedure for the research clearly."

- **What issues do you think will affect people's decision to take part in the study?**
  "Some people might worry about using a Smartphone app, more elderly perhaps but others will embrace the technology. See box 1 re decision to take part after experiencing side effects. This can weigh heavily on a person if it affected day to day life and worries. However they might feel they have more monitoring and contact. I do generally think with more support and feedback some people would pursue taking statins. However in ordinary settings, you are prescribed and then don't have long enough to talk to a doctor or nurse about side effects etc. It's all well and good having these wonderful medications and maybe clinicians play down minor side effects even though they are more important to participants."
  "The severity of side effects previously experienced."
  "I cannot think of negative decisions."

16.2 APPENDIX TWO: VOLUNTEER FEEDBACK

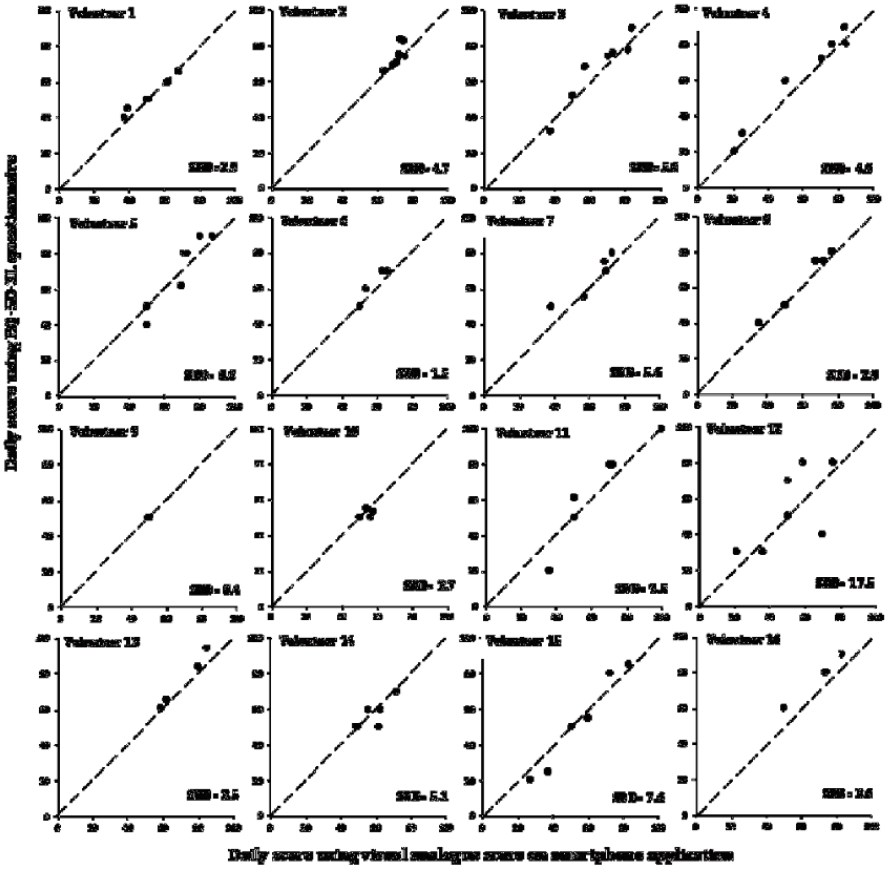
Feedback from healthy participants trialling daily visual analogue score

The application was trialled for one week by sixteen volunteers, without any cardiovascular diagnosis and on no regular medication, to verify acceptability in independent hands unconnected with the study and to validate the visual analogue scoring system against the EQ-5D-3L system.

Protocol: We did not ask participants to report side effects (because they are not on tablets) but instead report how cold or warm they have felt in the past 24 hours, on both the visual analogue scale on a smartphone and a hot/cold question using the EQ5DL scoring system.

Results: 16 healthy volunteers aged 37 ± 11.7 years completed both scoring systems on a daily basis for 1 week. The responses for each volunteer are shown in Figure 2. This showed good agreement with the EQ-5D-3L method (SDD between 0.4 and 17.5).

Figure 2: Correlation between the visual analogue daily scoring system and the EQ5DL scoring system for all 16 participants



Volunteer Feedback:

1. How long did it take you to use the application each day?

<30 seconds	30 seconds- 1 min	1-2 minutes	2-5 minutes	>5 minutes
11	4	1		

2. How easy to use did you find the application?

Very easy	Easy	Medium	Hard	Impossible to use on a daily basis
11	4	1		

3. How easy did you find the response scale on the smartphone to use to rate how hot/cold you were

Very easy	Easy	Medium	Hard	Impossible to use on a daily basis
12	3	1		

Comments/ Feedback:

"Easy to use app, took <30 seconds on each day. No concerns- would be easy to use on a daily basis"

"Forgot to record my responses over the weekend as not used to having 2 phones. Perhaps having the app as part of my regular phone would have improved/aided my memory."

"Overall very simple and easy to use."

"Very easy to use."

"I am technologically savvy, I feel someone less technologically able, who has not used a touch screen-like device before may struggle. I therefore, think instructions with picture like diagrams would be helpful."

"The system was easy to operate, unfortunately I struggled to remember to monitor every day. I didn't use the reminder service which would have helped."

16.3 APPENDIX THREE: EXAMPLE OF PHONE APPLICATION SCREENSHOTS

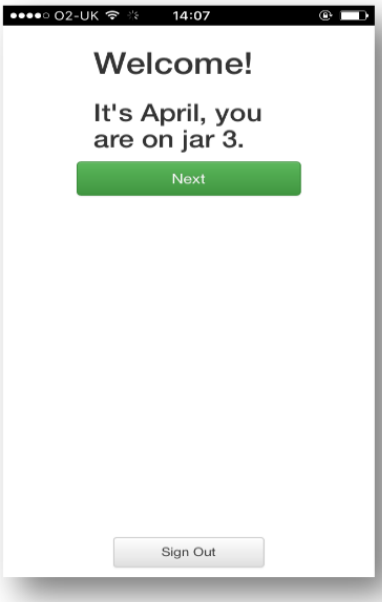


Figure 1. Welcome menu, indicating trial progress and the current designated box of medication.

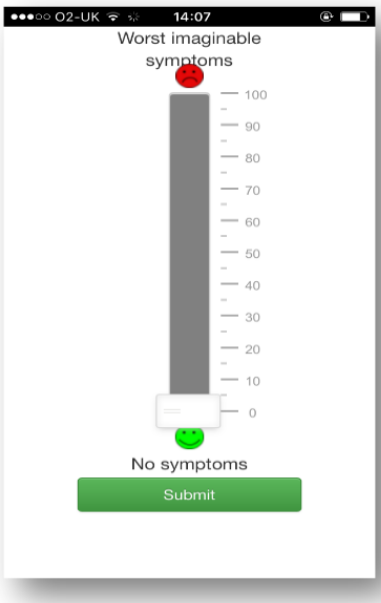


Figure 2. Visual analogue scale using touch-sensitive controls to assess quality of life.

Figure 3. Touch-screen selection of tablet compliance.

16.4 APPENDIX FOUR: SIMPLIFIED MEDICINAL PRODUCT DOSSIER, SUMMARY OF PRODUCT CHARACTERISTICS, DATA SHEETS, STABILITY INFORMATION, TSE CERTICATES FOR RAW MATERIALS USED FOR MANUFACTURE OF PLACEBO AND INVESTIGATIONAL MEDICINAL PRODUCT LABEL FORM

Simplified Investigational Medicinal Product Dossier
for Atorvastatin 20mg film-coated tablets and Matching Placebo for use in the Self Assessment Method for Statin side-effects Or Nocebo (SAMSON) Trial

VERSION 02, 12 May 2016

AUTHOR: Tim White

Signatures: _____

S DRUG SUBSTANCE
Not applicable

P INVESTIGATIONAL MEDICINAL PRODUCT UNDER TEST

P.1 Description and Composition of the Investigational Medicinal Product:
The IMP is Atorvastatin 20mg film-coated tablets.
MA holder: Ranbaxy (UK) Limited, Building 4, Chiswick Park, 566 Chiswick High Road, London, W4 5YE, United Kingdom.
See Appendix 1 for Summary of Product Characteristics.

Component	Reference	Amount
Atorvastatin 20mg film-coated tablets.	PL 14894/0714	q.s**

**amount to be specified by Sponsor

The tablets will be package in HDPE containers with a silica gel dessicant supplied by Brownell Limited (London, NW10 7XF). The packs will be stored at ambient room temperature.

See Appendix 2 for Data Sheet and Appendix 3 for MSDS for silica gel dessicant.

P.2 Pharmaceutical Development:
Not applicable

P.3 Manufacture:
P.3.1 Manufacturer(s)

Manufacture and release of the IMP is carried out by:
Guys & St Thomas NHS Foundation Trust
GSTFT Pharmacy Manufacturing Unit
13th Floor Tower Wing
Guy's Hospital
Great Maze Pond
London
SE1 9RT

A copy of MIA(IMP) has been included as part of this submission.

P.3.2 Batch Formula
It is expected that 2 batches of a total of around 7,440 tablets will be packed. *(Given the simple composition a batch formula has not been included)*

P.3.3 Description of Packaging Process and Process Controls
Intact Atorvastatin 20mg film-coated tablets are counted on a counting tray. They are visually inspected and packed into HDPE bottles. A Supervisor check of the tablet

quantity and presence of dessicant takes place prior to container closure.

P.4 Specifications

P 4.1 Specification for Atorvastatin 20mg film-coated tablets.

Test	Acceptance criteria	Method
Raw Materials	Tested, approved for use and in date	Inspection of batch documentation
Production Documentation	Complete and correct	Inspection of batch documentation
Labels	Correct format, batch number and expiry date, and legible	Inspection of batch documentation
Container	Clean, undamaged and well sealed	Visual inspection
Appearance	Tested, approved for use and in date.	Visual inspection PL 14894/0714
	White to off white, film-coated oval tablets about 6.6 mm wide and about 12.1 mm long, debossed with 'A31' on one side and plain on other side	
Presence of Active	The spectra displays a maximum at 243nm and the absorbance is above 0.1AU.	GSTFT method
Environmental Monitoring	No major defects in microbiological or physical environmental monitoring	Inspection of microbiological monitoring records and FMS reports.

P.4.2 Analytical Procedures

Test Solution

Crush one tablet and pour in a 100ml volumetric flask.
Make to volume with Methanol:Water (50:50) and shake.
Filter and pipette 1ml the filtrate into a 20ml volumetric flask. Make to volume with Methanol:Water (50:50) and mix (Test Solution).

Scan the Test Solution using Methanol:Water (50:50) as a blank between 200nm and 330nm.
The spectra displays a maximum at 243nm and the absorbance is above 0.1AU.

P.4.3 Excipients of Animal or Human Origin

Refer to PL 14894/0714.

P.4.4 Validation of Analytical Procedures

Method for identification of presence of active was validated in house.

P.5 Batch Analyses

Manufacture of the drug product has not yet been completed; however, given the simple process and specification it is proposed not to provide batch analysis data.

P.6 Container Closure System

The tablets will be packed in HDPE containers with HDPE closures.

P.7 Stability:
Stability data issued by the MA holders indicates that there is no impact on product quality from storage for 36 months in HDPE containers with a 1g silica gel dessicant (see Appendix 4). The SPC indicates that the product has a shelf-life of 2 years from the date of manufacture in its original blister laminate container. It is therefore proposed to give the packed tablets a shelf life up to and not exceeding the assigned shelf life of the marketed stock it is packed from.

Placebo to Atorvastatin 20mg film-coated tablets.
Drug Substance
Not applicable

P.8 Description and Composition
The placebo is a white, oval tablet about 6.6 mm wide and about 12.1 mm long, debossed with 'A31' on one side and plain on other side, identical in appearance to Atorvastatin 20mg film-coated tablets PL 14894/0714

Component	Reference	Amount
Lactose Monohydrate	BP	84.25%
Microcrystalline Cellulose (Avicel PH-102)	BP	15.0%
Magnesium Stearate	BP	0.75%

Tablets are packaged into HDPE containers and stored at ambient room temperature.

P.9 Pharmaceutical Development:
Not applicable

P.10 Manufacture
P10.1 Manufacturer(s)
Manufacture and release of the IMP is carried out by:
Guys & St Thomas NHS Foundation Trust
GSTFT Pharmacy Manufacturing Unit
13th Floor Tower Wing
Guy's Hospital
Great Maze Pond
London
SE1 9RT

A copy of MIA(IMP) has been included as part of this submission.

P.10.2 Batch Formula
It is expected that 2 batches of a total of 7,440 tablets will be packed. *(Given the simple composition a batch formula has not been included)*

P.10.3 Description of Packaging Process and Process Controls
The individual powder components are blended together and the blend is gravity fed into a D-Press Tablet Machine. Tablets are formed by direct compression of the dry powder blend. In-process samples are taken and compared for likeness with licensed active comparator. Tablet weight is devised according to the similarity to the active. Samples are taken at 10 minute

intervals in-process for testing. The tablets are visually inspected, counted and packed into HDPE containers.

A Supervisor check of the tablet quantity and presence of dessicant takes place prior to final packed container closure.

P.11 Specifications

P.11.1 Specifications for Placebo Tablets

Test	Acceptance criteria	Method
Raw Materials	Tested, approved for use and in date.	Inspection of batch documentation
Production Documentation	Complete and correct	Inspection of batch documentation
Labels	The label format agrees with the master. The batch number and expiry date are correct. The labels are clear and legible	Inspection of batch documentation
Container	Clean, undamaged and well sealed.	Visual inspection
	Tested, approved for use and in date.	Method according to container specification
Appearance	White, oval tablet about 6.6 mm wide and about 12.1 mm long, debossed with 'A31' on one side and plain on other side, identical in appearance to active (Atorvastatin 20mg film-coated tablets PL 14894/0714)	Visual inspection
Thickness of tablet	Close match to active. (Atorvastatin 20mg film-coated tablets PL 14894/0714)	Visual inspection
Uniformity of Weight	Not more than 2 tablets weigh more than ± 5% of the average weight and no tablets weigh more than ± 10% of the average weight.	Method according to procedure adhering to BP limits
Friability	Not more than 1.0% weight loss.	Method according to procedure adhering to BP limits
Disintegration Time	Not greater than 15 minutes.	BP 2014 (in-house limits)
Hardness	Not less than 50N	BP 2014 (limits supplied)
Absence of Active	The test solution shows no absorbance maximum at 243nm.	GSTFT method. *Negative result for presence of active.*

Environmental Monitoring	No major defects in microbiological or physical environmental monitoring	Inspection of microbiological monitoring records and FMS reports.

P.11.2 Analytical Procedures
See method in P.4.2.

The spectra displays a maximum at 243nm and the absorbance is above 0.1AU.

P.11.3 Validation of Analytical Procedures
Method for identification of absence of active was validated in house.

P.11.4 Excipients of Animal or Human Origin:
The raw materials that will be used for the manufacturing of the placebo tablets meet the criteria described by monograph "*Products with risk of transmitting agents of animal spongiform encephalopathies. (no. 1483, Ph. Eur.* 4th *Ed.* and any subsequently revised version" a certificate of suitability for the batch that will be used will be acquired and is part of the release specification.
See Appendix 5 for sample TSE certificates of raw materials.

P.11.5 Batch Analyses
Manufacture of the drug product has not yet been completed; however, given the simple process and specification it is proposed not to provide batch analysis data.

P.12 Container Closure System:
See P.6.

P.13 Stability:
Once packed into HDPE containers, a shelf-life equal to that of the matching active shall be assigned. Shelf life however not to exceed that of the bulk placebo packed down from. This Lactose monohydrate:Microcrystalline Cellulose 85%:15% formulation has been used successfully in previous batches for direct compression of dry powder blends to produce white placebo tablets and a shelf life of 24 months has been assigned to this. This product is currently undergoing stability studies to extend the shelf life to 5 years.

Appendix 1 – Summary of Product Characteristics: Atorvastatin 20mg film-coated tablets (Rnabaxy PL14894/0714)
Appendix 2 – Data Sheet: Non Indicating Silica Gel Dessicant (Brownell Limited)
Appendix 3 - Data Sheet: Non Indicating Silica Gel Dessicant (Brownell Limited)
Appendix 4 – stability information of PL 14894/0714 in HDPE containers with 1g silica gel dessicant provided by MA holders.
Appendix 5 – Sample TSE Certificates for Raw Materials used for manufacture of placebo tablets.

Appendix 1 – Summary of Product Characteristics: Atorvastatin 20mg film-coated tablets (Ranbaxy PL14894/0714)

Atorvastatin 20 mg Film-coated Tablets

Summary of Product Characteristics Updated 17-May-2019 | Ranbaxy (UK) Limited a Sun Pharmaceutical Company

1. Name of the medicinal product

Atorvastatin 20 mg Film-coated Tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 20mg of atorvastatin as atorvastatin calcium trihydrate.

Excipient with known effect:

Contains 76.7 mg lactose monohydrate, 5.6 mg sodium.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

White to off white, film-coated oval tablets about 6.6 mm wide and about 12.1 mm long, debossed with 'A31' on one side
and plain on other side

4. Clinical particulars

4.1 Therapeutic indications

Hypercholesterolaemia:

Atorvastatin is 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
nonpharmacological measures is inadequate.

Atorvastatin is also 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

Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event (see
section 5.1), as an adjunct to correction of other risk factors.

4.2 Posology and method of administration

Posology

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue
on this diet during treatment with atorvastatin.

The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response.

The usual starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

Co-administration with other medicines

In patients taking hepatitis C antiviral agents elbasvir/grazoprevir concomitantly with atorvastatin, the dose of atorvastatin should not exceed 20 mg/day (see sections 4.4 and 4.5).

Primary Hypercholesterolaemia and Combined (Mixed) Hyperlipidaemia

The majority of patients are controlled with 10 mg atorvastatin once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Heterozygous Familial Hypercholesterolaemia

Patients should be started with atorvastatin 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous Familial Hypercholesterolaemia

Only limited data are available (see section 5.1).

The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily (see section 5.1). Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Prevention of Cardiovascular disease

In the primary prevention trials, the dose was 10mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

Renal impairment

No adjustment of dose is required (see section 4.4).

Hepatic impairment

Atorvastatin should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2). Atorvastatin is contraindicated in patients with active liver disease (see section 4.3).

Older people

Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.

Paediatric use

Hypercholesterolaemia:

Paediatric use should only be carried out by physicians experienced in the treatment of paediatric hyperlipidaemia and patients should be re-evaluated on a regular basis to assess progress.

For patients aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day with titration up
to 20 mg per day. Titration should be conducted according to the individual response and tolerability in paediatric
patients. Safety information for paediatric patients treated with doses above 20 mg, corresponding to about 0.5 mg/kg, is
limited.
There is limited experience in children between 6-10 years of age (see section 5.1). Atorvastatin is not indicated in the
treatment of patients below the age of 10 years.
Other pharmaceutical forms/strengths may be more appropriate for this population.
Method of administration
Atorvastatin is for oral administration. Each daily dose of atorvastatin is given all at once and may be given at any time of
day with or without food.

4.3 Contraindications

Atorvastatin is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit
of normal
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive
measures (see section 4.6).
- treated with the hepatitis C antivirals glecaprevir/pibrentasvir

4.4 Special warnings and precautions for use

Liver Effects
Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who
develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who
develop increased transaminase levels should be monitored until the abnormality (ies) resolve. Should an increase in
transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of
atorvastatin is recommended (see section 4.8).
Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history
of liver disease.
Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or
transient ischemic attack (TIA) there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin

80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or
lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and
benefits of atorvastatin 80 mg is uncertain and the potential risk of haemorrhagic stroke should be carefully considered
before initiating treatment (see Section 5.1).
Skeletal muscle effects
Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause
myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition
characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria
which may lead to renal failure.
Before the treatment
Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level
should be measured before starting statin treatment in the following situations:
- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of
other predisposing factors for rhabdomyolysis
- Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special
populations including genetic subpopulations (see section 5.2)
In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is
recommended.
If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.
Creatine kinase measurement
Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible
alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at
baseline (> 5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the results.
Whilst on treatment

- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.
- If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤5 x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- Atorvastatin must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Concomitant treatment with other medicinal products

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, niacin or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

There have been very rare reports of immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

Atorvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.
Statin therapy may be re-introduced seven days after the last dose of fusidic acid.
In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of atorvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.
Paediatric use
Developmental safety in the paediatric population has not been established (see section 4.8).
Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.
Diabetes Mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.
Excipients
Atorvastatin contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Atorvastatin contains less than 1 mmol sodium (23 mg) per tablet, i.e. essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of co-administered medicinal products on atorvastatin
Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2). Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.4).
CYP3A4 inhibitors
Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, some antivirals used in the treatement of HCV (e.g. elbasvir/grazoprevir) and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1). Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1). An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and coadministration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.
CYP3A4 inducers

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous coadministration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transport inhibitors

Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended (see Table 1).

Gemfibrozil / fibric acid derivatives

The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored (see section 4.4).

Ezetimibe

The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.

Colestipol

Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was coadministered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either medicinal product was given alone.

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet

unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.
If treatment with systemic fusidic acid is necessary, atorvastatin treatment should be discontinued throughout the
duration of the fusidic acid treatment. **See also section 4.4.**
Colchicine
Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been
reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing
atorvastatin with colchicine.
Effect of atorvastatin on co-administered medicinal products
Digoxin
When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state digoxin concentrations
increased slightly. Patients taking digoxin should be monitored appropriately.
Oral contraceptives
Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of
norethindrone and ethinyl oestradiol.
Warfarin
In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin
caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to
normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant
interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking
coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of
prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at
the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or
discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or
with changes in prothrombin time in patients not taking anticoagulants.
Paediatric population
Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population
is not known. The above mentioned interactions for adults and the warnings in section 4.4 should be taken into account
for the paediatric population.
Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin

Co-administered medicinal product and dosing regimen	Atorvastatin Dose (mg)	Ratio of AUC&	Clinical Recommendation#
Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (days 14 to 21)	40 mg on day 1, 10 mg on day 20	↑ 9.4 fold	In cases where coadministration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended
Telaprevir 750 mg q8h, 10 days	20 mg SD	↑ 7.9 fold	
Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	↑ 8.7 fold	
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	↑ 5.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance
Clarithromycin 500 mg BID, 9 days	80 mg OD for 8 days	↑ 4.4 fold	doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.
Saquinavir 400 mg BID/ Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 4-18, 30 min after atorvastatin dosing	40 mg OD for 4 days	↑ 3.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Darunavir 300 mg BID/Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days		

↑ 3.3 fold
Itraconazole 200 mg OD, 4 days 40 mg SD ↑ 3.3 fold
Fosamprenavir 700 mg BID/ Ritonavir 100
mg BID, 14 days
10 mg OD for 4
days
↑ 2.5 fold
Fosamprenavir 1400 mg BID, 14 days 10 mg OD for 4
days
↑ 2.3 fold
Nelfinavir 1250 mg BID, 14 days 10 mg OD for
28 days
↑ 1.7
fold^
No specific recommendation
Grapefruit Juice, 240 mL OD * 40 mg, SD ↑ 37% Concomitant intake of large quantities of
grapefruit juice and atorvastatin is not
recommended.
Diltiazem 240 mg OD, 28 days 40 mg, SD ↑ 51% After initiation or following dose adjustments
of diltiazem, appropriate clinical monitoring of
these patients is recommended.
Erythromycin 500 mg QID, 7 days 10 mg, SD ↑ 33%^ Lower maximum dose and clinical monitoring
of these patients is recommended.
Amlodipine 10 mg, single dose 80 mg, SD ↑ 18% No specific recommendation.
Cimetidine 300 mg QID, 2 weeks 10 mg OD for 2
weeks
↓ less
than 1%^
No specific recommendation.
Antacid suspension of magnesium and
aluminium hydroxides, 30 mL QID, 2 weeks
10 mg OD for 4
weeks
↓ 35%^ No specific recommendation.
Efavirenz 600 mg OD, 14 days 10 mg for 3
days
↓ 41% No specific recommendation.
Rifampin 600 mg OD, 7 days (coadministered)
40 mg SD ↑ 30% If co-administration cannot be avoided,
simultaneous co-administration of
atorvastatin with rifampin is recommended,
Rifampin 600 mg OD, 5 days (doses with clinical monitoring.

separated)
40 mg SD ↓ 80%
Gemfibrozil 600 mg BID, 7 days 40mg SD ↑ 35% Lower starting dose and clinical monitoring of
these patients is recommended.
Fenofibrate 160 mg OD, 7 days 40mg SD ↑ 3% Lower starting dose and clinical monitoring of
these patients is recommended.
Boceprevir 800 mg TID, 7 days 40mg SD ↑ 2.3 fold Lower starting dose and clinical monitoring of
these patients is recommended. The dose of
atorvastatin should not exceed a daily dose
of 20 mg during co-administration with
boceprevir.
Glecaprevir 400 mg OD/ Pibrentasvir 120
mg OD, 7 days
10 mg OD for 7
days
8.3 Co-administration with products containing
glecaprevir or pibrentasvir is contraindicated
(see section 4.3).
Elbasvir 50 mg OD/ Grazoprevir 200
mg OD, 13 days
10 mg SD 1.95 The dose of atorvastatin should not exceed a
daily dose of 20 mg during co-administration
with products containing elbasvir or
grazoprevir.
& Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no
change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).
See sections 4.4 and 4.5 for clinical significance.
* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products
metabolized by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for
the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of
atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites).
^ Total atorvastatin equivalent activity
Increase is indicated as “↑”, decrease as “↓”
OD = once daily; SD = single dose; BID = twice daily; TID = three times daily; QID = four times daily
Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products
Atorvastatin and

dosing regimen
Co-administered medicinal product
Medicinal product/Dose (mg) Change
in AUC&
Clinical Recommendation
80 mg OD for 10
days
Digoxin 0.25 mg OD, 20 days ↑ 15% Patients taking digoxin should be monitored appropriately.
40 mg OD for 22
days
Oral contraceptive OD, 2 months
- norethindrone 1 mg
-ethinyl estradiol 35 µg
↑ 28%
↑ 19%
No specific recommendation.
80 mg OD for 15
days
* Phenazone, 600 mg SD ↑ 3% No specific recommendation
10 mg, SD Tipranavir 500 mg BID/ritonavir 200 mg BID,
7 days
No
change
No specific recommendation.
10 mg, OD for 4 days Fosamprenavir 1400 mg BID, 14 days ↓ 27% No specific recommendation.
10 mg OD for 4 days Fosamprenavir 700 mg
BID/ritonavir 100 mg BID, 14 days
No
change
No specific recommendation.
& Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change)
* Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance
of phenazone.
Increase is indicated as "↑", decrease as "↓"
OD = once daily; SD = single dose

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of child-bearing potential should use appropriate contraceptive measures during treatment (see section 4.3).
Pregnancy
Atorvastatin is contraindicated during pregnancy (see section 4.3). Safety in pregnant women has not been established.

No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Animal studies have shown toxicity to reproduction (see section 5.3).
Maternal treatment with atorvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.
For these reasons, atorvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with atorvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3.)
Breast-feeding
It is not known whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk (see section 5.3). Because of the potential for serious adverse reactions, women taking atorvastatin should not breast-feed their infants (see section 4.3). Atorvastatin is contraindicated during breastfeeding (see section 4.3).
Fertility
In animal studies atorvastatin had no effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Atorvastatin has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 atorvastatin vs. 7311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.
Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for atorvastatin.
Estimated frequencies of reactions are ranked according to the following convention: Common (≥1/100 to < 1/10);
Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (≤ 1/10,000); Not known (cannot be estimated from the available data)
Infections and infestations:
Common: nasopharyngitis.
Blood and lymphatic system disorders

Rare: thrombocytopenia.
Immune system disorders
Common: allergic reactions.
Very rare: anaphylaxis.
Metabolism and nutrition disorders
Common: hyperglycaemia.
Uncommon: hypoglycaemia, weight gain, anorexia
Psychiatric disorders
Uncommon: nightmare, insomnia.
Nervous system disorders
Common: headache.
Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.
Rare: peripheral neuropathy.
Eye disorders
Uncommon: vision blurred.
Rare: visual disturbance.
Ear and labyrinth disorders
Uncommon: tinnitus
Very rare: hearing loss.
Respiratory, thoracic and mediastinal disorders
Common: pharyngolaryngeal pain, epistaxis.
Gastrointestinal disorders
Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.
Hepatobiliary disorders
Uncommon: hepatitis.
Rare: cholestasis.
Very rare: hepatic failure.
Skin and subcutaneous tissue disorders
Uncommon: urticaria, skin rash, pruritus, alopecia.
Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
Musculoskeletal and connective tissue disorders
Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.
Uncommon: neck pain, muscle fatigue.
Rare: myopathy, myositis, rhabdomyolysis, muscle rupture, tendonopathy, sometimes complicated by rupture.
Very rare: lupus-like syndrome
Not known: immune-mediated necrotizing myopathy (see section 4.4)
Reproductive system and breast disorders
Very rare: gynecomastia.
General disorders and administration site conditions

Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.
Investigations
Common: liver function test abnormal, blood creatine kinase increased.
Uncommon: white blood cells urine positive.
As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving
atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically
important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on atorvastatin.
These elevations were dose related and were reversible in all patients.
Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on
atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper
range occurred in 0.4% atorvastatin-treated patients (see section 4.4).
Paediatric Population
The clinical safety database includes safety data for 249 paediatric patients who received atorvastatin, among which 7
patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the age range of 10 to
17.
Nervous system disorders
Common: Headache
Gastrointestinal disorders
Common: Abdominal pain
Investigations
Common: Alanine aminotransferase increased, blood creatine phosphokinase increased
Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same
as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.
Class Effects
• Sexual dysfunction.
• Depression.
• Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).
• Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6
mmol/L, BMI>30kg/m2, raised triglycerides, history of hypertension).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued

monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any
suspected adverse reactions via the Yellow Card Scheme, website www.mhra.gov.uk/yellowcard or search for MHRA
Yellow Card in the Google Play or Apple App store.

4.9 Overdose

Specific treatment is not available for atorvastatin over dosage. Should an overdose occur, the patient should be treated
symptomatically and supportive measures instituted, as required. Liver function tests and serum CK levels should be
monitored. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly
enhance atorvastatin clearance.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA-reductase inhibitors, ATC code: C10AA05
Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the
conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.
Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the
plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolised primarily
through the high affinity to LDL (LDL receptor).
Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and
subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface
for enhanced uptake and catabolism of LDL.
Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained
increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin
is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not
usually responded to lipid-lowering medicinal products.
Atorvastatin has been shown to reduce concentrations of total-C (30% - 46%), LDL-C (41% - 61%), apolipoprotein B
(34% - 50%), and triglycerides (14% - 33%) while producing variable increases in HDL-C and apolipoprotein A1 in a
dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia,
nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent

diabetes mellitus.
Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and
cardiovascular mortality.
Homozygous familial hypercholesterolaemia
In a multicenter 8 week open-label compassionate-use study with an optional extension phase of variable length, 335
patients were enrolled, 89 of which were identified as homozygous familial hypercholesterolaemia patients. From these
89 patients, the mean percent reduction in LDL-C was approximately 20%. Atorvastatin was administered at doses up to
80 mg/day.
Atherosclerosis
In the Reversing Atherosclerosis with Aggressive Lipid- Lowering Study (REVERSAL), the effect of intensive lipid
lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40 mg on coronary
atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart
disease. In this randomised, double- blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18
months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.
The median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in
the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin the effects
of atorvastatin were statistically significant (p=0.02). The effect of intensive lipid lowering on cardiovascular endpoints (e.
g. need for revascularisation, non fatal myocardial infarction, coronary death) was not investigated in this study.
In the atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/L ± 0.8 (78.9 mg/dl ± 30) from baseline 3.89
mmol/l ± 0.7 (150 mg/dl ± 28) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/l ± 0.7 (110
mg/dl ± 26) from baseline 3.89 mmol/l ± 0.7 (150 mg/dl ± 26) (p<0.0001). Atorvastatin also significantly reduced mean
TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG levels by 20% (pravastatin: -6.8%, p<0.0009), and mean
apolipoprotein B by 39.1% (pravastatin: -22.0%, p<0.0001). Atorvastatin increased mean HDL-C by 2.9% (pravastatin:
+5.6%, p=NS). There was a 36.4% mean reduction in CRP in the atorvastatin group compared to a 5.2% reduction in the
pravastatin group (p<0.0001).
Study results were obtained with the 80 mg dose strength. Therefore, they cannot be extrapolated to the lower dose

strengths.
The safety and tolerability profiles of the two treatment groups were comparable.
The effect of intensive lipid lowering on major cardiovascular endpoints was not investigated in this study. Therefore, the
clinical significance of these imaging results with regard to the primary and secondary prevention of cardiovascular
events is unknown.
Acute coronary syndrome
In the MIRACL study, atorvastatin 80 mg has been evaluated in 3,086 patients (atorvastatin n=1,538; placebo n=1,548)
with an acute coronary syndrome (non Q-wave MI or unstable angina). Treatment was initiated during the acute phase
after hospital admission and lasted for a period of 16 weeks. Treatment with atorvastatin 80 mg/day increased the time to
occurrence of the combined primary endpoint, defined as death from any cause, nonfatal MI, resuscitated cardiac arrest,
or angina pectoris with evidence of myocardial ischaemia requiring hospitalization, indicating a risk reduction by 16%
(p=0.048). This was mainly due to a 26% reduction in re-hospitalisation for angina pectoris with evidence of myocardial
ischaemia (p=0.018). The other secondary endpoints did not reach statistical significance on their own (overall: Placebo:
22.2%, Atorvastatin: 22.4%).
The safety profile of atorvastatin in the MIRACL study was consistent with what is described in section 4.8.
Prevention of cardiovascular disease
The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomized, double-blind,
placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients
were hypertensive, 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels
≤6.5 mmol/l (251 mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥55
years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C >6, peripheral vascular disease, left
ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included
patients were estimated to have a high risk for a first cardiovascular event.
Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either
atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).
The absolute and relative risk reduction effect of atorvastatin was as follows:
Event Relative Risk
Reduction (%)

No. of Events (Atorvastatin vs Placebo)	
Absolute Risk Reduction[1] (%)	
p-value	
Fatal CHD plus non-fatal MI	
Total cardiovascular events and revascularization procedures	
Total coronary events	
36%	
20%	
29%	
100 vs. 154	
389 vs. 483	
178 vs 247	
1.1%	
1.9%	
1.4%	
0.0005	
0.0008	
0.0006	

[1]Based on difference in crude events rates occurring over a median follow-up of 3.3 years.

CHD = coronary heart disease; MI = myocardial infarction.

Total mortality and cardiovascular mortality were not significantly reduced (185 vs. 212 events, p=0.17 and 74 vs. 82 events, p=0.51). In the subgroup analyses by gender (81% males, 19% females), a beneficial effect of atorvastatin was seen in males but could not be established in females possibly due to the low event rate in the female subgroup. Overall and cardiovascular mortality were numerically higher in the female patients (38 vs. 30 and 17 vs. 12), but this was not statistically significant. There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD plus non-fatal MI) was significantly reduced by atorvastatin in patients treated with amlodipine (HR 0.47 (0.32-0.69), p=0.00008), but not in those treated with atenolol (HR 0.83 (0.59-1.17), p=0.287).

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomized, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤4.14 mmol/l (160 mg/dl)

and TG ≤6.78 mmol/l (600 mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking,
retinopathy, microalbuminuria or macroalbuminuria.
Patients were treated with either atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410) for a median follow-up of 3.9
years.
The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37%	83 vs. 127	3.2%	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs 64	1.9%	0.0070
Strokes (Fatal and non-fatal)	48%	21 vs. 39	1.3%	0.0163

[1]Based on difference in crude events rates occurring over a median follow-up of 3.9 years.
AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI =
myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.
There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level. A
favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the
atorvastatin group, p=0.0592).
Recurrent stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (HR 0.85; 95% CI, 0.72-1.00; p=0.05 or 0.84; 95% CI, 0.71-0.99; p=0.03 after adjustment for baseline factors) compared to placebo. All cause mortality was 9.1% (216/2365) for atorvastatin versus 8.9% (211/2366) for placebo.

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%, p=0.01) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo.

• The risk of hemorrhagic stroke was increased in patients who entered the study with prior hemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57), and the risk of ischemic stroke was similar between groups (3/45 for atorvastatin versus 2/48 for placebo; HR 1.64; 95% CI, 0.27-9.82).

• The risk of hemorrhagic stroke was increased in patients who entered the study with prior lacunar infarct (20/708 for atorvastatin versus 4/701 for placebo; HR 4.99; 95% CI, 1.71-14.61), but the risk of ischemic stroke was also decreased in these patients (79/708 for atorvastatin versus 102/701 for placebo; HR 0.76; 95% CI, 0.57-1.02). It is possible that the net risk of stroke is increased in patients with prior lacunar infarct who receive atorvastatin 80 mg/day.

All cause mortality was 15.6% (7/45) for atorvastatin versus 10.4% (5/48) in the subgroup of patients with prior hemorrhagic stroke. All cause mortality was 10.9% (77/708) for atorvastatin versus 9.1% (64/701) for placebo in the subgroup of patients with prior lacunar infarct.

Paediatric Population

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 6-17 years old

An 8-week, open-label study to evaluate pharmacokinetics, pharmacodynamics, and safety and tolerability of

atorvastatin was conducted in children and adolescents with genetically confirmed heterozygous familial hypercholesterolemia and baseline LDL-C ≥4 mmol/L. A total of 39 children and adolescents, 6 to 17 years of age, were enrolled. Cohort A included 15 children, 6 to 12 years of age and at Tanner Stage 1. Cohort B included 24 children, 10 to 17 years of age and at Tanner Stage ≥2.

The initial dose of atorvastatin was 5 mg daily of a chewable tablet in Cohort A and 10 mg daily of a tablet formulation in Cohort B. The atorvastatin dose was permitted to be doubled if a subject had not attained target LDL-C of <3.35 mmol/L at Week 4 and if atorvastatin was well tolerated.

Mean values for LDL-C, TC, VLDL-C, and Apo B decreased by Week 2 among all subjects. For subjects whose dose was doubled, additional decreases were observed as early as 2 weeks, at the first assessment, after dose escalation.

The mean percent decreases in lipid parameters were similar for both cohorts, regardless of whether subjects remained at their initial dose or doubled their initial dose. At Week 8, on average, the percent change from baseline in LDL-C and TC was approximately 40% and 30%, respectively, over the range of exposures.

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 10-17 years old

In a double-blind, placebo controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (FH) or severe hypercholesterolaemia were randomised to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks.. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was >3.36 mmol/l. Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase. The mean achieved LDL-C value was 3.38 mmol/l (range: 1.81-6.26 mmol/l) in the atorvastatin group compared to 5.91 mmol/l (range: 3.93-9.96 mmol/l) in the placebo group during the 26-week double-blind phase.

An additional paediatric study of atorvastatin versus colestipol in patients with hypercholesterolaemia aged 10-18 years demonstrated that atorvastatin (N=25) caused a significant reduction in LDL-C at week 26 ($p<0.05$) compared with colestipol (N=31).

A compassionate use study in patients with severe hypercholesterolaemia (including homozygous

hypercholesterolaemia) included 46 paediatric patients treated with atorvastatin titrated according to response (some subjects received 80 mg atorvastatin per day). The study lasted 3 years: LDL-cholesterol was lowered by 36%.
The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.
The European Medicines Agency has waived the obligation to submit the results of studies with atorvastatin in children aged 0 to less than 6 years in the treatment of heterozygous hypercholesterolaemia and in children aged 0 to less than 18 years in the treatment of homozygous familial hypercholesterolaemia, combined (mixed) hypercholesterolaemia, primary hypercholesterolaemia and in the prevention of cardiovascular events (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption:
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.
Distribution:
Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins.
Biotransformation:
Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various betaoxidation products. Apart from other pathways these products are further metabolized via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin.
Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.
Elimination:
Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in

humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30
hours due to the contribution of active metabolites.
Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3
(OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a
substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP),
which may limit the intestinal absorption and biliary clearance of atorvastatin.

Special Populations

Elderly **:** Plasma concentrations of atorvastatin and its active metabolotes are higher in healthy elderly subjects than in
young adults while the lipid effects were comparable to those seen in younger patient populations.

Paediatric: In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage ≥ 2 (N=24) paediatric patients
(ages 6-17 years) with heterozygous familial hyper-cholesterolemia and baseline LDL-C ≥ 4 mmol/L were treated with 5
or 10 mg of chewable or 10 or 20 mg of film-coated atorvastatin tablets once daily, respectively. Body weight was the
only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in paediatric
subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC
were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (women:
approximately 20% higher for Cmax and 10% lower for AUC). These differences were of no clinical significance,
resulting in no clinically significant differences in lipid effects among men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its
active metabolites.

Hepatic Insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased
(approximately 16-fold in Cmax and approx.11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh
B).

SLOC1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the
OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin,

which may lead to an increased risk of rhabdomyolysis (see section 4.4).
Polymorphism in the gene encoding OATP1B1
(SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this
genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients.
Possible consequences for the efficacy are unknown.

5.3 Preclinical safety data

Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay.
Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h
reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular
carcinomas in females.
There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of
embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic; however, at
maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed
and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of
placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether
atorvastatin or its metabolites are excreted in human milk.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Colloidal anhydrous silica
Croscarmellose sodium
Sodium hydrogen carbonate
Sodium carbonate, anhydrous
Hydroxypropylcellulose
Magnesium stearate
Butylhydroxyanisole
Butylhydroxytoluene
Tablet coating:
Opadry YS-1-7040 white
Hypromellose
Macrogol 8000
Titanium dioxide (E171)
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Cold form blister laminate (structure: oriented polyamide/ aluminium foil/ PVC) with the backing of hard tempered,
aluminium foil coated with heat seal lacquer on inner side
Packs of 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 film-coated tablets each
(Not all pack size may be marketed)

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Ranbaxy (UK) Limited

Address

5th Floor, Hyde Park, Hayes, 3, 11 Millington Road,
Hayes, UB3 4AZ, UK

Telephone

+44 (0) 208 848 8688

Medical Information Direct Line

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Out of Hours contact

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Cserv.uk@sunpharma.com

Medical Information e-mail

medinfoeurope@sunpharma.com
5th floor, Hyde Park, Hayes 3
11 Millington Road
Hayes, UB3 4AZ
United Kingdom

8. Marketing authorisation number(s)

PL 14894/0714

9. Date of first authorisation/renewal of the authorisation

29/08/2012

10. Date of revision of the text

14/05/2019

Company Contact Details

Ranbaxy (UK) Limited a Sun Pharmaceutical Company

BROWNELL LIMITED DATA SHEET

HUMIDITY CONTROL AND MOISTURE MEASUREMENT

NON-INDICATING SILICA GEL PRODUCT INFORMATION

COLOUR	Opaque beads of desiccant.
RESIDUAL MOISTURE	Mean: (Typical) Less than 1% by weight. Maximum: Not more than 2% by weight.
ADSORBTION	30 - 35% by weight at 55% RH @ 20° C
BEAD SIZE	Ideal: 3 - 5mm diameter. Allowable: 2 - 5mm diameter.
BULK DENSITY	720Kg per cu meter. Tolerance ± 5%.
COMPOSITION	98.2% SiO_2
PORE SIZE	20 – 25 Angstroms

TYPICAL EQUILIBRIUM ADSORPTION @ 20°C (W.T.%) AT:

10%RH	8
20%RH	12
40%RH	25
50%RH	30
60%RH	35

REACTIVATION TEMP	120° C. Maximum. for 3-4 hours

CONFORMS TO SPECIFICATION BS7554

BROWNELL LTD Unit 2 Abbey Road Industrial Estate,
Commercial Way, Park Royal, London NW10 7XF
E mail: *info@brownell.co.uk*
Tel: 020 8965 9281 Fax: 020 8965 3239

BROWNELL LIMITED

Material Safety Data Sheet
NON-INDICATING SILICA GEL

MCS/107/MSDS Issue 4

1. Product Identification

Synonyms:	Silica, amorphous; Silica, precipitated and gel.
CAS No:	112926-00-8.
Molecular Weight:	Not applicable.
Chemical Formula:	SiO_2.
Product Codes:	See detail drawings.

2. Composition/Information on Ingredients

Ingredient	CAS No	Percent
Silica Gel	112926-00-8	> 98.2%

3. Hazards Identification

Emergency Overview

SAFETY DATA	Ratings (Provided here for your convenience)
Health Rating:	Moderate
Flammability Rating:	None
Reactivity Rating:	None
Contact Rating:	Slight
Lab Protective Equip:	GOGGLES; LAB COAT; FILTERED MASK; PROPER GLOVES
Storage Colour code:	None
Potential Health Effects	This product contains synthetic amorphous silica; not to be confused with crystalline silica such as quartz, cristobalite or tridymite or with diatomaceous earth or other naturally occurring forms of amorphous silica that frequently contain crystalline forms.
Inhalation:	May cause dryness and irritation to mucous membranes, nose, and throat. Symptoms may include coughing, sore throat, and wheezing.
Ingestion:	No adverse effects expected.
Skin Contact:	May cause irritation with dryness and abrasion.
Eye Contact:	May cause irritation, redness and pain.

From: Lina Festila [Lina.Festila@sunpharma.com]
Sent: 06 July 2015 09:27
To: White Timothy
Cc: Medinfoeurope
Subject: Atorvastatin 20 mg film-coated tablets Stability Data response
Ranbaxy reference no.: ***MIATORUK15007***
Product: ***Atorvastatin 20 mg film-coated tablets***

Dear Timothy,

Atorvastatin (crystalline) 20mg Tablet formulation, as marketed in EU by Ranbaxy a Sun Pharma company, has been shown to continue to meet its quality criteria when stored in HDPE container with 1g desiccant sachet for up to 36 months.

It should be noted that Ranbaxy does not have any supporting stability data for product in HDPE container WITHOUT desiccant sachet. It should be noted that the Ranbaxy product is marketed in the UK and rest of EU in a cold form blister laminate only with a registered shelf-life of 2 years from date of manufacture.

If you require any further clarification, please do not hesitate to ask.

Kind Regards

Lina Festila
Medical Information Supervisor

From: Raluca Bontas (Gavrea)
Sent: Friday, May 29, 2015 10:04 AM
To: timothy.white@gstt.nhs.uk
Cc: Medinfoeurope
Subject: Atorvastatin 20 mg film-coated tablets Stability Data

Ranbaxy reference no.: ***MIATORUK15007***
Product: ***Atorvastatin 20 mg film-coated tablets***

Dear Timothy,

I have forwarded your query to our Quality Assurance Department and I will let you know of their answer as soon as possible.

For other information please contact us through email: medinfoeurope@ranbaxy.com or phone at number (0) 208 742 5292.

Yours sincerely,

Raluca Bontas,
MEDICAL INFORMATION OFFICER.

Dr. Raluca Bontaş, DVM
MEDICAL INFORMATION OFFICER
Medical Europa

SC Terapia SA
a SUN PHARMA company
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Edisonstraat 1, 5928 PG Venlo
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PETER GREVEN
Your partner for oleochemicals

STATEMENT

Company	**To whom it may concern**		
To	To whom it may concern	Designation	E-Mail
From	Sandra Bongaerts	Date	July 26, 2013

Subject: **Declaration concerning BSE/TSE**

Name of Material: **LIGAMED MF-2-V (Magnesium Stearate)**

We hereby declare that above-mentioned material for use in food, drugs and medical application are not manufactured of fatty acid of animal origin but only fatty acid of 100% vegetable origin is used. The stearic acid, which is used, is derived from palm oil and is originated in Malaysia. Furthermore in our production facility in Venlo are only fatty acids used based on vegetable origin. Also during the process the material does not come in contact with any animal derived products. As a consequence the EU directive 1999/82/EEC, CPMP Note fore Guidance and EMEA (European Medicines Agency) regulation 410-01 rev. 3 is not applicable.

Sandra Bongaerts
QA-Assistant
Peter Greven Nederland C.V.

Venlo, July 26, 2013

An die interessierte Partei / To whom it may concern

Dr. Stefan Dreiheller
Quality Unit / Regulatory Affairs

Date of issue: 18.11.2015
Page 1/1
Doc.-No. EIP-1003
Revision 5

TSE / BSE-Statement

Meggle products:

- Lactose Monohydrate Ph. Eur. / USP-NF / JP: CapsuLac® 60, FlowLac® 90, FlowLac® 100, GranuLac® 70, GranuLac® 140, GranuLac® 200, GranuLac® 230, PrismaLac® 40, SacheLac® 80, SorboLac® 400, SpheroLac® 100, Tablettose® 100, Tablettose® 70, Tablettose® 80
- Lactose Monohydrate USP-NF / Ph. Eur. / JP: InhaLac® 70, InhaLac® 120, InhaLac® 230, InhaLac® 250, InhaLac® 251, InhaLac® 400, Lactose monohydrate Low Endotoxin
- Anhydrous Lactose Monohydrate USP-NF / Ph. Eur. / JP: DuraLac® H

This statement is valid for all deliveries.

The product complies with the Ph. Eur. General Text 5.2.8: *Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.* The General Text is identical with the Note for guidance EMA/410/01 rev. 3, published in the Official Journal of the European Union (2011/C 73/01).

With reference to Ph. Eur. General Text 5.2.8:
- In the light of the current scientific knowledge and irrespective of the geographical origin, bovine milk is unlikely to present any risk of TSE/BSE contamination.
- The mentioned conditions regarding bovine milk derivatives are fulfilled and therefore, the products are unlikely to present any TSE/BSE risk and shall therefore be considered compliant with the Note for Guidance.

The milk is sourced from healthy animals in the same conditions as milk collected for human consumption.

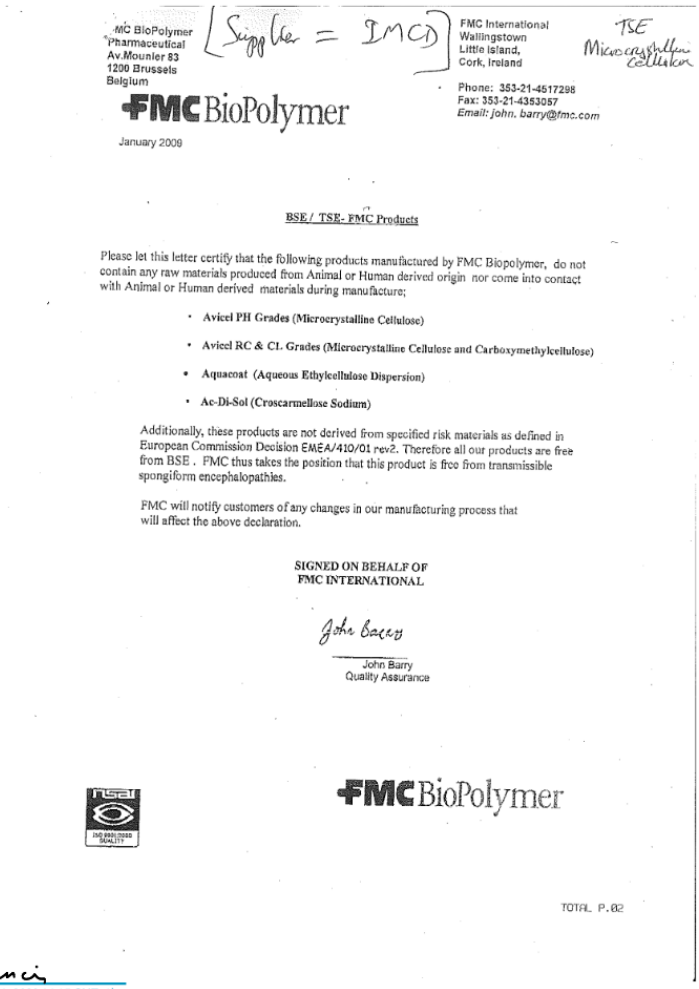
For production site Molkerei MEGGLE Wasserburg GmbH & Co.KG, Wasserburg, Germany:
The sourcing of the milk is constantly, officially supervised according to EC Hygiene Regulations (EC) No 852/2004 and (EC) No 853/2004. Besides milk, no other ruminant materials with the exception of calf rennet are used. The calf rennet is produced in accordance with the process described in the risk assessment report EMEA/CPMP/BWP/337/02/Public/Final performed by the Committee for Proprietary Medicinal Products (CPMP) and its Biotechnology Working Party (BWP). In accordance with Public Statement EMEA/CPMP/571/02 of February 27 2002 the TSE risk is negligible if the calf rennet is produced in accordance with the process described in this risk assessment.

For production site Davisco Foods International, Inc., Le Sueur, MN, USA:
The sourcing of the milk is constantly, officially supervised according to the FDA Pasteurized Milk Ordinance 2009. Besides milk, other ruminant materials incl. calf rennet are not used.

Freundliche Grüße / Best regards

Dr. Stefan Dreiheller

Molkerei MEGGLE Wasserburg GmbH & Co. KG • Megglestr. 6-12 • 83512 Wasserburg • Telefon +49 (0) 8071 73-0 • Fax +49 (0) 8071 73-444
info@meggle.de • www.meggle-group.com • Geschäftsführung MEGGLE Wasserburg Verwaltungs GmbH vertreten durch:
Drs. Sil H. van der Ploeg MBA (Vorsitzender), Josef Bock • Dr. Franz Mayer • Dr. Egmont G. Pfeifer
Amtsgericht Traunstein HRA 7828 • USt-IdNr.: DE813497582 • St-Nr. 156/116/00116



FMC BioPolymer
Pharmaceutical
Av.Mounier 83
1200 Brussels
Belgium

[Supplier = IMCD]

FMC International
Wallingstown
Little Island,
Cork, Ireland

Phone: 353-21-4517298
Fax: 353-21-4353057
Email: john. barry@fmc.com

TSE
Microcrystalline Cellulose

FMC BioPolymer

January 2009

BSE / TSE- FMC Products

Please let this letter certify that the following products manufactured by FMC Biopolymer, do not contain any raw materials produced from Animal or Human derived origin nor come into contact with Animal or Human derived materials during manufacture;

- Avicel PH Grades (Microcrystalline Cellulose)
- Avicel RC & CL Grades (Microcrystalline Cellulose and Carboxymethylcellulose)
- Aquacoat (Aqueous Ethylcellulose Dispersion)
- Ac-Di-Sol (Croscarmellose Sodium)

Additionally, these products are not derived from specified risk materials as defined in European Commission Decision EMEA/410/01 rev2. Therefore all our products are free from BSE . FMC thus takes the position that this product is free from transmissible spongiform encephalopathies.

FMC will notify customers of any changes in our manufacturing process that will affect the above declaration.

SIGNED ON BEHALF OF
FMC INTERNATIONAL

John Barry
Quality Assurance

FMC BioPolymer

TOTAL P.02

Signature: Darrel Francis (Jul 21, 2020 14:15 GMT+1)

Email: d.francis@imperial.ac.uk

Signature: Ruth Nicholson (Jul 21, 2020 14:45 GMT+1)

Email: r.nicholson@imperial.ac.uk

SAMSON Protocol V.1.4 10th April 2020 CLEAN-1

Final Audit Report 2020-07-21

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