EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 July 2012
EMA/543953/2012
Patient Health Protection

Assessment report for Tavanic and associated names

Pursuant to Article 30 of Directive 2001/83/EC

International Non-proprietary Name of the active substance: levofloxacin

Marketing authorisation holder: Sanofi-Aventis group of companies and associated companies

Procedure no: EMEA/H/A-30/1262

Referral under Article 30 of Directive 2001/83/EC

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 11 October 2010 the European Commission presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, as amended, in order to harmonise the national summaries of product characteristics, labelling and package leaflets of the medicinal products:

Tavanic and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the October 2010 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Dr. Martina Weise (DE) as rapporteur and Dr. Gonzalo Calvo Rojas (ES) as co-rapporteur. In February 2011, the Co-Rapporteurship was transferred to Dr. Concepcion Prieto Yerro (ES).

Tavanic and associated names are approved in the following EU Members States: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and United Kingdom.

Tavanic and associated names are not approved in Iceland and in Norway.

2. Scientific discussion during the referral procedure

2.1. Introduction

Tavanic (levofloxacin) is a synthetic antibacterial agent of the fluoroquinolone class and is the S(-) enantiomer of the racemic drug substance ofloxacin. As a fluoroquinolone antibacterial agent, levofloxacin inhibits DNA synthesis by acting on the DNA/DNA-gyrase complex and topoisomerase IV.

Levofloxacin has a broad *in vitro* antibacterial spectrum that includes Gram-positive organisms such as *Streptococcus pneumoniae* regardless of resistance phenotype, methicillin-susceptible *Staphylococcus aureus and Streptococci spp.,* fastidious *Gram-negative* bacteria such as *Haemophilus influenzae*, *Moraxella catarrhalis* and *Enterobacteriaceae* such as *Escherichia coli* and *Klebsiella spp.*, and organisms responsible for atypical infection such as *Legionella*, *Mycoplasma* and *Chlamydophila*. Therefore, levofloxacin is active against a diverse range of common causative pathogens for sinusitis, acute exacerbation of chronic bronchitis (AECB), community-acquired pneumonia (CAP), urinary tract infections (UTIs) and skin and soft tissue infections (SSTIs).

Levofloxacin is currently indicated in adults for the treatment of respiratory tract infections (RTIs), SSTIs, complicated and uncomplicated UTIs and chronic bacterial prostatitis (CBP). Levofloxacin is also indicated in a few atypical indications like urosepsis, digestive and hepatobiliary infections, Anthrax curative treatment, and hospital-acquired pneumonia (HAP). In this harmonisation procedure the MAH claimed for RTIs indications (restricted), SSTIs, complicated and uncomplicated UTIs, chronic bacterial prostatitis and anthrax treatment.

Worldwide, levofloxacin was first approved in 1993 in Japan followed by the United States in 1996. In the EU the approval of levofloxacin was first granted in the United Kingdom (UK) in 1997 followed by eleven other Member States (MS): Austria, Belgium, Denmark, Finland, Germany, Ireland, Italy, Luxembourg, the Netherlands, Portugal and Spain through the mutual recognition procedure (MRP) with UK as reference MS. Tavanic is also approved nationally in thirteen other MS: Bulgaria, Cyprus, Czech Republic, Estonia, France, Greece, Hungary, Lithuania, Malta, Poland, Slovakia, Slovenia and Sweden.

Tavanic is available as film coated tablets (250 mg and 500 mg) and as solution for infusion (5mg/ml in presentations of 250mg/50ml and 500mg/100ml). A 750 mg strength in film coated tablet and as solution for infusion 750 mg/150 ml was approved in some MS. This strength and presentation was linked with the indication for HAP which the MAH did not claim in this harmonisation procedure. The MAH voluntarily withdrew the marketing authorisation (MA) for the 750 mg film coated tablets and varied the terms of the MAs for the solution for infusion to remove the 150 ml presentation during this referral procedure. Thus, the outcome of this referral procedure does not include any evaluation of levofloxacin 750 mg.

Due to the combination of the MRP and National granted MAs some divergent information has been identified in the product information (PI) for Tavanic. Hence, Tavanic was included in the list of products for PI harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended. Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product (and its associated names), the European Commission notified the CHMP/EMA Secretariat of an official referral under Article 30 of Directive 2001/83/EC as amended in order to resolve divergences amongst the nationally authorised PIs and thus to harmonise its divergent PIs across the European Union.

2.2. Critical Evaluation

2.2.1 Quality aspects

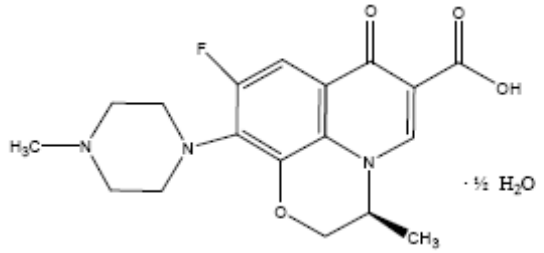
The MAH took also the opportunity to harmonise the Quality dossier for Tavanic and associated names as part of the Article 30 referral procedure.

The harmonised dossiers were provided for the drug substance (levofloxacin) and for products containing this substance, including: Tavanic 250 mg and 500 mg film coated tablets, and Tavanic 5 mg/ml solution for infusion.

The product is presented as film-coated tablets and solution for infusion containing 250 mg, 500 mg and 5mg/ml of levofloxacin as active substance respectively. The composition is described in section 6.1. of the SmPC. The product is packed in the primary packaging described in section 6.5 of the SmPC.

Drug Substance

Levofloxacin is a light yellowish-white to yellowish-white crystals or crystalline powder, freely soluble in glacial acetic acid and chloroform; sparingly soluble in water, acetone, and methanol; and slightly soluble in ethyl acetate and ethanol. The chemical name is (-)-(S)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate and the structural formula is as follows:



Levofloxacin is optically active and exists as a single hemihydrate crystalline form.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Levofloxacin is not fully described in the European Pharmacopoeia or a pharmacopoeia of a member state. The active substance specification includes tests for appearance, odour, identification (precipitation reaction, qualitative test for fluoride, IR), optical rotation, pH, purity, water content, residue for ignition, assay, microbial contamination, bacterial endotoxins, ethanol and methanol.

Batch analysis data (n=3) of the active substance are provided. Batch analysis data was also provided to support the process changes of an alternate solvent and an alternate starting material compared to levofloxacin manufactured by the current process. The results are within the specifications and consistent from batch to batch.

Three batches of the active substance packed were put on long term (25°C±2/60%RH, 25°C/75%RH and 21°C - 31°C /21 – 93 %RH) for up 72 months, 30 days and 36 moths respectively, and accelerated (40°C/75%RH) for up 6 months stability testing ICH conditions. Photo stability test following ICH guidelines Q1B was performed on 3 batches. Results on stress conditions 50°C/20-90%RH and 30°C/92%RH were also provided on 3 batches.

The following parameters were tested for stability: appearance, odour, optical rotation, pH, colour and clarity of solution, optical isomer, related substances, water content, and assay.
Additional stability studies were also performed to support manufacturing changes for a solvent change and a starting material change.

The stability results justify the proposed retest period. The Marketing Authorisation Holder agreed to describe the recommendation of storage in the next version of the ASMF.

Drug Product

Film coated tablets

Pharmaceutical development

The product development has taken into consideration the physicochemical characteristics of the active substance. The manufacturing process development was focused on the critical steps of the process.

The goal of formulation development was to develop a physically and chemically stable tablet, showing a rapid dissolution and absorption of the active ingredient. With consideration to the desired final market presentation, a film coated tablet was preferred. The formulation factors which may impact product quality were identified and classified. Each factor was assessed for its potential impact on quality attributes of the finished product. The compatibility of the active substance with excipients was also evaluated. All these studies resulted in the choice of the current formulation. A coated tablet was developed mainly to improve taste and handling in packaging.
Bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed commercial formulation. Results of studies performed during development and of clinical studies on bioavailability and bioequivalence confirm that the consistent quality characteristics of the batches investigated during development can be regarded as representative for commercial manufacturing.

Breakability has been tested according to the Ph Eur requirements on one batch of each strength. The subdivision of the tablets is adequately demonstrated. All the excipients used are in compliance with the compendial excipients of the PhEur. Only the colouring agents are tested according to USP/NF.

The finished product is packed in blisters consisting of a sheet of transparent polyvinylchloride, and an aluminium foil coated with heat-sealing coating. Each batch is accepted for use based on certificates of analysis provided by the suppliers showing compliance with the current specifications. In addition, the supplier guarantees that the PVC film complies with the European Pharmacopoeia monograph, chapter 3.1.11 “Materials based on non-plasticised poly(vinyl chloride) for containers for dry dosage forms for oral administration” and with the relevant EEC Directives (i.e. EEC Directive 2002/72/EC) relating to plastic materials and articles intended to come into contact with foodstuffs. Any supplier of the materials who guarantees the specifications could be used. Specifications and IR reference spectra were provided.

Adventitious agents

For the manufacturing of the finished product no animal and/or human derived material is used. This applies to the drug substance as well as to all excipients used for the manufacture of the drug product. The drug product complies with the requirements of the note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 2).

Manufacture of the product

The manufacturing process consists of 5 main steps: mixing, spray granulation in a fluid-bed apparatus, lubrication, compression to tablets and film-coating.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and is satisfactory. The in process controls are adequate for this film coated tablet preparation.
The batch analysis data on 3 batches shows that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product specifications include appropriate tests for appearance, identification (LC, optical rotation, coloring agents), uniformity of dosage units (Ph Eur), assay (HPLC), impurities (HPLC), uniformity of mass (Ph Eur), in vitro dissolution (Ph Eur), microbial contamination.
Batch analysis results in 3 batches confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability data of 3 batches of each strength stored under long term for up to 60 months at 25±2ºC/60%±5 RH and 30ºC±2/65%RH and for up to 6 months under accelerate at 40±2ºC/75%±5 RH according to ICH conditions were provided. The batches of the film coated tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for the same parameters as for release.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

Solution for infusion

Pharmaceutical development

The product development has taken into consideration the physicochemical characteristics of the active substance. The active substance is sparingly soluble in water. Thus, hydrochloric acid is used to convert levofloxacin hemihydrate into levofloxacin hydrochloride in order to improve the solubility. Sodium chloride contributes to the isotonicity of the parenteral preparation. Hydrochloric acid and Sodium hydroxide may be used for pH-adjustment, if necessary.

A parenteral formulation of levofloxacin, containing 5 mg of the drug substance per 1 ml, was chosen as finished product. The product fulfils the requirements of the Ph.Eur. and the USP for parenteral preparations. Levofloxacin 5 mg/ml solution for infusion is commercially available since 1997 (100 ml) respectively 1998 (50 ml). The drug product fulfils the requirements of the monographs *"Parenteralia / Injections"* (Ph.Eur.) and *"Injections"* (USP).

The miscibility of the solution for infusion with different prevalent carrier solutions was tested in a compatibility study. The drug product is compatible with 0.9 % Sodium chloride solution, 5 % glucose solution, 2.5 % glucose -ringer solution, or different solutions for parenteral nutrition (amino mixes). The drug product solution must not be mixed with Heparin solution or alkaline solutions, e.g. sodium bicarbonate solution.

The manufacture of levofloxacin 5 mg/ml solution for infusion is done according to GMP. All steps of the manufacturing process are well-established standard procedures. The drug product is terminally sterilized according to a validated procedure.

All excipients used for manufacture of Levofloxacin 5 mg/ml solution for infusion were tested for compliance with the compendial monographs of the European Pharmacopoeia. Reference is made to the current edition of pharmacopoeia, including their supplements.

Colourless infusion vials with a nominal capacity of 50 or 100 ml, respectively, are used as container for the drug product. They fulfil the requirements of the Ph Eur for glass containers for pharmaceutical use (glass type I). The infusion vials are closed with infusion stoppers made out of chlorobutyl rubber, which fulfil the requirements of the Ph Eur for rubber closures for containers for aqueous parenteral preparations (elastomer type I). The vials are further sealed with aluminium flanged caps, containing tear-off lids made out of polypropylene, which are not in direct contact with the drug product solution. The suitability of the primary packaging material is substantiated by the results of the stability tests. Incompatibilities with the active ingredient or the non-active constituents were not observed. Sufficient light protection is achieved by the secondary packaging material.

Adventitious agents

For the manufacturing of the finished product no animal and/or human derived material is used. The drug product complies with the requirements of the note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 2).

Manufacture

Levofloxacin 5 mg/ml solution for infusion is manufactured under GMP conditions, using well-established manufacturing procedures such as dissolving, mixing, filtration, and filling. The drug product is terminally sterilized.
The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and is satisfactory. The in process controls are adequate for this solution for infusion preparation.
The batch analysis data on 3 batches shows that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product specifications include appropriate tests for description (clarity, color, particulate contamination), identification (LC, Optical rotation), assay (LC), impurities (LC), pH-value, sterility (Ph Eur), bacterial endotoxins (Ph Eur), osmolality (Ph Eur), extractable volume (Ph Eur), and particulate matter (Ph Eur) .

Batch analysis results in 3 batches confirm consistency and uniformity of manufacture and indicate that the process is under control. The Marketing Authorisation Holder agreed to update the acceptance criteria for the bacterial endotoxins as recommended.

Stability of the product

Stability data of 3 batches in 50 ml vials and 7 batches in 100 ml vial batches stored under long term for 36 months at 30±2°C/65±5% RH and for up to 36 months and under accelerate at +40±2°C/75±5% RH for up to 6 months according to ICH conditions were provided. Samples were tested for description (clarity, color, particulate contamination), assay (95%-105%), impurities (LC), Ph-value, sterility (Ph Eur), bacterial endotoxins, and particulate matter.

A photostability study has been provided that has been performed according to ICH1 guideline Q1B “Photostability testing of New Drug Substances and Products”. After exposure to light, all the results are within specifications and no significant changes have occurred at the end of the photostability study, which demonstrates a satisfactory photostability of the drug product.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

Conclusions

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.2 Clinical aspects

The SmPC harmonisation considered all relevant therapeutic and regulatory guidelines in the EU. The proposal presented by the MAH reflected the latest scientific information including Core Safety Information (harmonisation of the safety sections of the SmPC: 4.3 to 4.9) agreed in April 2011 as an outcome of the PSUR worksharing, recent safety reviews of fluoroquinolones and new worldwide data on safety of fluoroquinolone.

The main points discussed regarding the harmonisation of the different sections of the SmPC are summarised hereafter.

Section 4.1 – Therapeutic Indications

Respiratory Tract Infections (RTIs)

Levofloxacin is approved in the most three common RTIs indications: acute bacterial sinusitis (ABS), acute exacerbation of chronic bronchitis (AECB) and community-acquired pneumonia (CAP). The most important pathogens in these indications are *S. pneumoniae*, *H. influenzae* with the addition of intracellular/atypical bacteria for CAP. Hospital-acquired pneumonia (HAP) is also a RTI for which levofloxacin was approved for in two MS and for which the MAH is not pursuing its maintenance as summarised below.

Acute bacterial sinusitis (ABS)

This indication is approved for levofloxacin tablets in all MS identified above (see section 2.1) via national or mutual recognition procedures (MRP) with the exception of one MS.

All MRP SmPCs list “Acute bacterial sinusitis” in the indication section and also specified “(adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections)”.

The three pivotal studies for this indication, granted in the EU since 1997 were:

- Study B1 - FF/93/355/01: Evaluation of the efficacy and safety of oral levofloxacin 500 mg once a day for 10 days in the treatment of acute maxillary sinusitis in adults. An open label, multicenter study;
- Study B2 - M92-040: A multicenter, randomised study to compare the safety and efficacy of oral levofloxacin with amoxicillin/clavulanate potassium in the treatment of acute sinusitis in adults;
- Study B3 - N93-006: A multicenter, non-comparative study to evaluate the safety and efficacy of oral levofloxacin in the treatment of acute sinusitis in adults.

The major objections preventing the granting of this indication in one MS was the X-ray criteria for the corroboration of the clinical diagnosis of sinusitis which was not defined clearly in one of the studies.

Five additional studies since then have been performed by the MAH. Although not all studies included bacteriological studies, in those that did eradication rates were high. Levofloxacin was of equivalent efficacy to reference therapies in the comparative trials. Of particular note is the study by *Gehanno et al* which included only patients with ABS with a high risk of complications and showed a clinical success rate of 94%. Nevertheless this was an open label and non-comparative study. Efficacy in this study was consistent regardless of the localization of the infection or the pathogen involved. There are few if any other studies published in which an antibiotic is studied exclusively in patients with ABS with a high risk of complications.

In clinical practice, the most commonly prescribed antibiotics for sinusitis are betalactams (amoxicillin with or without clavulanic acid, oral second and third-generation cephalosporins), macrolides, and antipneumococcal fluoroquinolones. However, the role of macrolides has dramatically decreased in many countries due to the increased level of *S pneumoniae* resistance. Current treatment guidelines usually recommend antipneumococcal fluoroquinolones for severe ABS, or where previous treatment has failed, or for infections involving resistant pneumococci.

Based on the current available data, considering the current treatment guidelines and also taking into account the current SmPC wording for other fluororoquinolone products with regards this indication, the MAH proposed the following restricted wording:

Acute bacterial sinusitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections) in severe cases at risk of complications (such as frontal, sphenoidal, ethmoidal or pansinusitis), or in case of known or suspected bacterial resistance to commonly used classes of anti-infectives (according to history of patients or national and /or regional resistance data), or if previous anti-infective treatment has failed.

A general consideration to be taken into account is that ABS is generally a non-severe infection associated with high spontaneous cure rates (90%). Due to the high spontaneous cure rates in this kind of infection, data showing superiority over placebo or comparators in more severe ABS are considered as a prerequisite to outweigh the extensive risks and to keep the benefits and risks balanced only in situations where beta-lactams, doxycycline or macrolides cannot be used for any reason or failed. The studies mentioned above do not permit to overcome this issue as no placebo-controlled studies were performed. The committee noted that for another fluoroquinolon agent a placebo-controlled study failed to show superiority over placebo in terms of clinical response.

Therefore, on the basis of the efficacy data provided by the MAH for ABS, Pharmacokinetic/Pharmacodynamic and the extensive risk profile of levofloxacin it was agreed that the wording for the ABS indication should be in line with the wording agreed for other the fluoroquinolone agents.

The MAH agreed that Tavanic film coated tablets is indicated for the treatment of ABS in adults only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

Acute exacerbation of chronic bronchitis (AECB)

This indication has been approved for levofloxacin tablets in all MS identified above (see section 2.1) via nationally or MRP. The pivotal studies supporting this indication were:

- Study B4 - K90-070: A multicenter, active-controlled, randomized study to evaluate the safety and efficacy of oral levofloxacin versus cefaclor in the treatment of acute bacterial exacerbation of chronic bronchitis in adults;
- Study B5 - M92-024: A multicenter, randomized study to compare the safety and efficacy of oral levofloxacin with that of cefuroxime axetil in the treatment of acute bacterial exacerbation of chronic bronchitis in adults;
- Study B6 - HR355/2/MN/301/CB: A multinational, multicenter, randomized, double blind, double dummy, 3-arm study to assess the efficacy, safety and tolerance of oral levofloxacin in comparison with cefuroxime axetil in the treatment of adult patients with acute exacerbation of chronic bronchitis

Nine additional studies (and one re-analysis of data from the registration studies) have become available. Levofloxacin has been studied in large AECB controlled trials with an active comparator but no placebo-controlled study has been conducted. The cardinal sign of purulent sputum, was required for entry into a number of the more recent studies with levofloxacin. Although not all trials included bacteriological studies, in those that did eradication rates were high. Levofloxacin was of equivalent efficacy to reference therapies in comparative studies. Of particular note is the recent study by *Petipretz et al. (2007)* which included patients with severe disease – 40% with at least one risk factor – and also patients with Gram-negative infections. The re-analysis by *Zuck et al.* had previously found that the efficacy of levofloxacin was maintained in the presence of increased numbers of risk factors, a finding that was not true for the comparator drugs (cefaclor, cefuroxime).

Although levofloxacin is not considered the drug of choice for the treatment of AECB, it is recommended as one of the possible alternatives for the treatment in the case of frequent exacerbations and in the case of severe chronic obstructive pulmonary disease (COPD). Betalactams, macrolides, and fluoroquinolones are the most commonly used antibiotics for the treatment of AECB. Fluoroquinolones are particularly useful in severe cases due to their coverage of Gram-negative organisms as well as the more common *H. influenzae* and *S. pneumoniae*.

The European Respiratory Society guideline (ERS, 2005) proposes levofloxacin as an alternative antibiotic for both hospital and community management of AECB with no risk factors for *P. aeruginosa*.

In this case, “alternative” is defined as: to be used in case of hypersensitivity to a preferred drug or widespread prevalence of clinically relevant resistance in the population being treated.

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) endorses the “Guideline for the management of adult lower respiratory tract infections” that establishes quinolones as second-choice treatment in case of clinically relevant pneumococcal resistance against amoxicillin and tetracyclines, or major intolerance.

Based on the current available data, considering the current treatment guidelines and also taking into account the current SmPC wording for other fluororoquinolone products with regards this indication, the MAH proposed the following restricted wording:

Acute bacterial exacerbations of chronic bronchitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections) in patients with severe underlying COPD and/or other risk factors, or in case of known or suspected bacterial resistance to commonly used classes of anti-infectives (according to history of patients or national and /or regional resistance data), or if previous anti-infective treatment has failed.

The proposed harmonised indication wording was considered to better reflect the current overall European treatment recommendations. However, considering that AECB can be a less severe infection, with high spontaneous resolution rate for which bacteria can be found in only 50% of all exacerbations and in order to better reflect the current treatment guidelines the following wording was agreed by the MAH to be harmonised in the EU:

Tavanic film coated tablets is indicated for the treatment of AECB in adults only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

Community-acquired pneumonia (CAP)

This indication has been approved in all MS based on the following pivotal studies:

- Study B7 - FF/93/355/02: Evaluation of the efficacy and safety of oral levofloxacin 500 mg once daily *vs.* 500 mg twice daily vs. amoxicillin/clavulanic acid 500/125 mg thrice daily for 7 to 10 days in the treatment of community-acquired pneumonia in adults;
- Study B8 - K90-071: A multicenter, active-controlled, randomized study to evaluate the safety and efficacy of levofloxacin versus ceftriaxone sodium or cefuroxime axetil in the treatment of community-acquired pneumonia in adults;
- Study B9 - M92-075: A multicenter, noncomparative study to evaluate the safety and efficacy of levofloxacin in the treatment of community-acquired pneumonia in adults;
- Study B10 - HR355/2/MN/301/LR (16): Open, controlled, randomized, multinational, comparative study of the efficacy, safety and tolerance of levofloxacin (HR355) versus ceftriaxone in the treatment of hospitalized patients with pneumonia;

The CAP indication is approved for both tablets and IV formulation of levofloxacin. Since the granting of this indication in the EU, twenty two additional studies have become available including 4 recent trials of levofloxacin used as a comparator *versus* tigecycline (2 studies), docycycline (one study) and nemonoxacin (one study). Overall, levofloxacin showed to be at least as effective as other treatment recommended as first-line options, e.g. intravenous ceftriaxone and/or oral cefuroxime axetil plus macrolides and also to amoxicillin/clavulanic acid.

Antibiotic therapy is indicated and usually starts empirically, covering typical organisms with or without atypical organisms. Antibiotic therapy may subsequently be changed in the light of culture results and clinical response. Patients with CAP who are moderately to severely ill, are usually hospitalized. Betalactams, macrolides and antipneumococcal fluoroquinolones are the most commonly used antibiotics for the treatment of CAP, as monotherapy or in combination, depending on the patient risks and the severity.

Guidelines for CAP are more complex than those for other respiratory infections as they take into account several criteria like age and / or comorbidities, severity of the disease and the management as out- or in-patients. In the European guidelines, levofloxacin is recommended as an alternative antibiotic, with the possibility of use as a first-line agent in countries with a high level of clinically relevant resistance to the first-line drugs.

To more concisely define the role of levofloxacin in this indication, the MAH initially proposed the following harmonised wording for the tablets and IV solution:

Community-acquired pneumonia in patients with additional risk factors or requiring hospitalization, or in case of known or suspected bacterial resistance to commonly used classes of anti-infectives (according to history of patients or national and /or regional resistance data), or if previous anti-infective treatment has failed.

This proposal for a restricted indication is in line with the current EU treatment guidelines to not overall recommend fluoroquinolones as a first line treatment option. The MAH agreed that the harmonised wording for levofloxacin should also be in line with wording for other fluoroquinolones. Therefore, it was agreed to reflect in the SmPCs for both tablets and IV that Tavanic is indicated for the treatment of CAP in adults only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

Skin and Soft Tissue Infections (SSTIs)

This indication has been approved in all MS for both tablets and IV formulation, except in one MS. The pivotal studies supporting this indication were:

• Study B13 - K90-075: A multicenter, active-controlled, randomized study to evaluate the safety and efficacy of levofloxacin versus ciprofloxacin HCl in the treatment of mild to moderate skin and skin structure infections in adults;
• Study B14 - L91-031: A multicenter, double-blind, randomized study to compare the safety and efficacy of oral levofloxacin with that of ciprofloxacin HCl in the treatment of uncomplicated skin and skin structure infections in adults;
• Study B15 - DPL3355-E18: A multicenter, double-blind, randomised study to compare the safety and efficacy of oral levofloxacin with that of amoxicillin/clavulanic acid in the treatment of uncomplicated skin and soft tissue infections in adults;
• Study B16 - K90-074: A multicenter, active-controlled, randomized study to evaluate the safety and efficacy of levofloxacin versus ticarcillin disodium/clavulanic acid (Timentin) followed by amoxicillin/clavulanic acid (Augmentin) in the treatment of complicated skin and skin structure infections in hospitalized adults;
• Study B17 - L91-038: A multicenter, randomized study to compare the safety and efficacy of levofloxacin with that of imipenem-cilastatin sodium (Primaxin) followed by ciprofloxacin hydrochloride in the treatment of complicated skin and skin structure infections in hospitalized adults;

This indication was not approved in one MS, due to the fact that the studies did not use a conventional comparator also considering that, for uncomplicated SSTI the use of fluoroquinolones is not considered appropriate and for complicated SSTI the results were not clearly favouring levofloxacin.

It is noted that fluoroquinolones, including levofloxacin are not recognised as reference treatment for staphylococci and streptococci. The gold standard for these pathogens remains penicillin (with the exception of MRSA - Methicillin-resistant staphylococcus aureus). However, most MRSA isolates are resistant to levofloxacin. Taking into account these considerations, and that the limited number of available guidelines currently recommend fluoroquinolones only in specific and complicated conditions e.g. polymicrobial infections involving Gram-negative organisms, the MAH agreed to amend the initially proposal for ("*Skin and soft tissue infections when commonly recommended antibacterial agents are considered inappropriate for the treatment of this infection")* to reflect the current practice that levofloxacin should be *indicated only for complicated SSTIs when recommended antibacterial agents are considered inappropriate for the treatment of this infection*.

In addition the warning section of the SmPC now refers to the co-resistance of the fluroquinolones including levofloxacin to MRSA.

Urinary tract infections (UTIs)

Complicated urinary tract infections (cUTIs) including pyelonephritis (PN)

Complicated UTIs (cUTIs) including pyelonephritis (PN), has been submitted and approved in all except one EU MS, where only the indication for *acute pyelonephritis (APN)* was approved. The main pivotal studies supporting the MRP approval were:
• Study B11 - L91-058: A multicenter, double blind, randomized study to compare the safety and efficacy of oral levofloxacin with that of ciprofloxacin HCl in the treatment of complicated urinary tract infections in adults;
• Study B 12 - L91-059 : A multicenter, randomized study to compare the safety and efficacy of oral levofloxacin with that of lomefloxacin in the treatment of complicated urinary tract infections in adults;

Study PNAC 03/01, a multicenter, prospective, non-comparative study conducted in France to evaluate the efficacy and safety of levofloxacin 500 mg once daily for 7 to 14 days in the treatment of community-acquired acute pyelonephritis in adults was the basis for the granting of the indication in acute pyelonephritis (APN).

This indication is approved for levofloxacin tablets and IV solution. Since then, three other studies have been subsequently published, one in cUTI, one in urosepsis and one in cUTI and PN.

Based on the review of all these ten studies, the MAH proposed to harmonise the wording for levofloxacin tablets and IV solution to be recommended in PN and complicated urinary tract infections with consideration being given to official guidance on the appropriate use of antibacterial agents. It was further agreed that consideration should be given to the European guidelines whereby quinolones are only recommended as first line therapy if the resistance rate for E. coli (responsible for 70-80% of all UTIs caused by Gram-negative) is below 10%. Therefore a specific warning for the pattern of resistance to fluoroquinolones resistance to E. coli is included in section 4.4 of the SmPC.

Uncomplicated urinary tract infections (uUTIs)

Uncomplicated UTIs indication has been approved for 250 mg tablets of levofloxacin in all MS except in three MS. The pivotal study was study LOFBO-UTI-060: A multicenter, double-blind, randomized study to compare the safety and efficacy of oral levofloxacin with that of Floxin (ofloxacin) in the treatment of uncomplicated urinary tract infections in women.

This study included only acute cystitis patients and not uncomplicated pyelonephritis, even those might be encompassed within the classification of “uncomplicated UTI”. Since uUTI is defined as a presence of episodes of acute cystitis and acute pyelonephritism, the MAH proposed to harmonise this indication for “uncomplicated cystitis” to better reflect the patients population included in the study. A cross reference to the warning sections with regards resistance patterns was agreed.

Chronic bacterial prostatitis

Chronic bacterial prostatitis (or ‘prostatitis’) is an approved indication for levofloxacin in all MS with exception for two MS. The pivotal study was CAPSS-101, a large registration study that showed levofloxacin to be equivalent to ciprofloxacin in well-documented chronic bacterial prostatitis, and these data have ever since been supplemented by two published studies.

This indication is approved for both tablets and IV formulation of levofloxacin. The harmonised SmPC wording agreed for the prostatitis indication was: “Chronic bacterial prostatitis”.

Inhalation Anthrax

This indication was only approved in one MS for both tablets (for post-exposure prophylaxis and curative treatment of anthrax) and IV solution (for the curative treatment) since 2001 in accordance with national recommendations. The MAH provided all data available for this indication namely, *in vitro* data, non-clinical data, pharmacokinetic data and data published by the US Centers of Disease Control and Prevention (CDC) and proposed an harmonised indication. Since Anthrax is life-threatening, especially when the route of infection is inhalation it was agreed the following harmonised wording for:

Tablets – *Inhalation Anthrax: post-exposure prophylaxis and curative treatment*
IV solution - *Inhalation Anthrax: post-exposure prophylaxis and curative treatment*

In addition, it was agreed to include precautions for use in case of treatment of anthrax in section 4.4 to include reference for consultation of national and/or international consensus documents.

Digestive Indications

Digestive indications have been approved only in one MS and for tablets and IV solution: "biliary infections" and "intestinal infections" are listed. These indications were supported by two studies:

- French study (HR355/3037): a multicentre, prospective, non-comparative study designed to evaluate the efficacy and safety of levofloxacin (500 mg administered once daily i.v for ≤48 hours following defervescence and digestive signs then po, or initially po) in the treatment of adults with community-acquired acute lithiasic cholecystitis or angiocholitis confirmed by echography, endoscopy or another imaging method. The clinical success rate was 94.9% at 4 to 10 days after the end of treatment. Bacteriologically documented cases were 24 and 16 patients in modified intent-to-treat and clinical per protocol populations, respectively.
- Study B18 - HR355/2/MN/305/AH (conducted in the other EU countries): was an open, randomised, multinational, multicentre study of the efficacy, safety and tolerance of levofloxacin (HR355) plus metronidazole vs. ciprofloxacin plus metronidazole in the treatment of patients with intra-abdominal infection. The clinical cure rates in the per protocol population (primary endpoint) at follow-up 3 weeks were similar in the levofloxacin and ciprofloxacin groups (86.8% and 88.9%, respectively).

Considering the limited experience in clinical controlled trials and the sample size and comparator in the mentioned studies, the digestive indications were not retained. The indications "biliary infections" and "intestinal infections" are not proposed by the MAH for inclusion in the harmonised EU SmPC.

The harmonised therapeutic indications for Tavanic, film coated tablets 250 mg and 500 mg and for solution for infusion 5mg/ml which have been agreed are found in section 2.4 "Recommendations" of this report.

Section 4.2 – Posology and method of administration

For the majority of the approved indications, the posology recommended was not too much divergent amongst the SmPC for the different MS. In fact, the posology was overall harmonised in practically all MS, the MAH proposed the following dosing recommendations:

- ABS (tablets only): 500 mg once daily for 10-14 days of treatment;
- AECB (tablets only): 250 – 500 mg once daily for 7 – 10 days;
- CAP (tablets and IV solution): 500 mg once or twice daily for 7 – 14 days;
- PN and cUTIs (tablets and IV solution): 250 – 500 mg once daily for 7-10 days;
- Uncomplicated cystitis (tablets only): 250 mg once daily for 3 days;
- Chronic bacterial prostatitis (tablets and IV solution): 500 mg for 28 days;
- cSSTIs (tablets): 250mg once daily or 500 mg once or twice daily for 7 to 14 days;
- cSSTIs (IV solution): 500 mg twice daily;

No other discrepancies in this section were detected in regard to special populations: impaired renal function and/or elderly.

The proposed harmonised lower dosage for AECB and for cSSTIs of 250 mg was further discussed in light of pharmacokinetic/pharmacodynamic profile of levofloxacin, the nature of infection and the most probable causative bacterial agent. In this regard, it is noted that the 500 mg dosage given once daily by oral route allow to reach a plasmatic peak concentration (Cmax) as of 5 to 6 mg/l and a Cmax/MIC ratio of 10-12 and an AUC of approximately 50 mg.h/l corresponding to an AUC/MIC ratio as of 50-100. These concentrations provide sufficient bactericidal activity on bacterial strains with sensitivity level up to 0.5-1 mg/l. This is adequate for most infective diseases (respiratory and skin) listed in the levofloxacin indications. The Cmax/MIC ratio of 10 and an AUC/MIC ratio of 100 are recommended in the literature to represent a rapid bactericidal activity. Therefore, the recommended dose for AECB and for cSSTIs were amended accordingly i.e. 250 mg once daily is deleted.

Further amendment was agreed with regards the duration of treatment for pyelonephritis and for cUTIs to be in line with the European Association of Urology (EAU) guidelines 2010 recommendations for levofloxacin treatment duration of 7-10 days for acute uncomplicated pyelonephritis, and 7-14 days (IV followed by possible oral switch) for severe cases (EAU guidelines 2010).

Section 4.3 – Contraindications

The discrepancies in this section regarded the use during pregnancy and in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency (divergence in one MS). Use during pregnancy was agreed to be kept in this section. With regards the contra indication in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency it was agreed to keep this relative contra indication in the warning section of the SmPC as it was approved in all but one MS.

In addition, this section of the SmpC was updated to reflect the core safety profile agreed in April 2011 as an outcome of the PSUR worksharing procedure.

Section 4.4 – Special warnings and precautions for use

There are differences between Member States concerning the individual paragraphs in this section.
The Core Safety Profile (CSP) approved as an outcome of the PSUR work-sharing procedure finalised on 1 April 2011 was considered. The main differences in this section accepted by the CHMP are listed below.

The warning on pneumococcal pneumonia was deleted since it was considered covered by the information included in section 4.1 that levofloxacin should only be considered as alternative treatment in such cases. In addition, the information on the combination treatment that may be required in case of nosocomial infections due to *P. aeruginosa* was deleted since it is considered not appropriate to be included in this section. Furthermore, the wording is misleading as it implies that standard treatment is monotherapy.

A warning on the need to have an adequate diagnosis of ABS and AECB before the use of levofloxacin is added. As mentioned above, resistance of *E.coli* to fluoroquinolone and the need for prescribers to consider local prevalence resistance was included in this section.

Precaution for use in inhalation of anthrax was moved from section 5.1 to this section to warn prescribers on the need to refer to further guidance in this situation.

The warning on tendinitis and tendon rupture was amended to state that the risk of tendinitis and tendon rupture is increased in patients receiving daily doses of 1000 mg. This amendment is based on a newly submitted analysis showing that the elderly are more vulnerable to tendon injury if receiving daily 1000 mg compared to 750 mg, epidemiologic studies, additional risk in renal impaired patients without dose adjustment and taking into account the biological plausibility of dose dependent cytotoxicity of fluoroquinolones these findings suggests that dosages of 1000 mg per day are an additional risk factor for tendon injuries.

The warning on exacerbation of myasthenia gravis included in the CSP was revised based on the cumulative safety review presented by the MAH during this referral procedure. This review showed possible association within the fluoroquinolone class specifically the use of levofloxacin and exacerbation of myasthenia gravis although the reporting rate for this event remains extremely low.

The proposed harmonised warning on G-6-PD deficiency was supported by a review provided by the MAH on all G6PD cases and no new safety information was found. Monitoring cases of haemolytic anaemia in these patients is recommended.

A warning on severe bullous reactions was proposed by the MAH due to the seriousness of these reactions and considering that bullous eruptions were already included in section 4.8 of the SmPC.

The harmonised warning on dysglycaemia was further amended in light of the recent reported cases of hypoglycaemic coma with fluoroquinolone agents.

The warning on prevention of photosensitisation was revised to further recommend precaution during treatment and 48 hours following treatment discontinuation.

The harmonised warning on QT interval prolongation was amended in line with the updated recommendation from the CHMP's pharmacovigilance working party dated 16 April 2012 with regards fluoroquinolones and risk of QT-interval prolongation.

The warning on the superinfection was amended in line with the standard wording on this point included in the PI for all antibacterial agents.

The warning on hepatobiliary disorders was updated to reflect the current evidence suggesting a causal relationship between levofloxacin and hepatotoxicity which may result in a fatal outcome. The evidence was provided by the MAH including a cumulative review of all fatal cases due to hepatibilary disorders.

The warning under sub-heading "Interference with laboratory tests" was updated mainly to include a sentence on *M. tuberculosis*, which is considered class labelling..

A new warning was agreed by the MAH to be included on the potential occurrence of vision disorders and that in such cases an eye specialist should be consulted immediately. In this regard a recent published epidemiologic study revealed an increased risk (OR 4.5) of fluoroquinolone for retinal detachment.

Section 4.6 – Fertility, Pregnancy and Lactation

This section was further amended to clearly mention that treatment with levofloxacin is contraindicated during breastfeeding and to include information on fertility also in line with the CHMP *Guideline on risk assessment of medicinal products on human reproduction and lactation: From data to labelling, January 2009.*

Section 4.8 – Undesirable effects

The CHMP noted the MAH proposal for an harmonised text for this section. The CSP was considered when harmonising the listed adverse reactions between national SmPCs of Tavanic. The general text of frequencies classification, and the adverse reaction obtained from post-marketing experience were clarified, and the frequency of a number of events was revised. The method and the statistical approach together with the data provided were reviewed and the CHMP considered the estimated frequency to be appropriate.

The following new adverse reactions were added during this procedure:

- *Hypoglycaemic coma*, in line with the CCSI version 4 for levofloxacin submitted as part of the PSUR 27;
- *Benign intracranial hypertension*, in line with recent labelling changes made in the US in April 2012 for levofloxacin; These cases should be kept under closely monitoring and further discussed in future PSURs.
- *"Palpitation"* and "*ventricular tachycardia which may result in cardiac arrest"* supported by data from clinical trials and post-marketing data provided by the MAH;
- *Ligament rupture*, in line with a review provided by the MAH in which a possible causal relationship in some cases without alternative explanations in combination with biological plausibility was identified.

In addition, the information on the hepatotoxicity was complemented to refer that reported cases of jaundice and severe liver injury with levofloxacin, and to include cases with *fatal* acute liver failure, primarily in patients with severe underlying diseases.

Section 5.1 - Pharmacodynamic properties

The CHMP noted the MAH proposal for this section and further agreed on a number of revisions. In particular, the table of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints and the table of susceptible species were revised. Namely, the inclusion of *bacteroides sp.* other than *B. fragilis* was removed due to the natural intermediate susceptibility to levofloxacin. The EUCAST information was aligned with the current EUCAST recommendations. In conclusion, the CHMP adopted a harmonised wording for section 5.1

Other Sections of the SmPC

The MAH was asked to evaluate all other sections of the nationally approved SPCs and suggested appropriate changes in the text where divergences exist and in some cases summarised the information already included in these sections (e.g. in section 5.2 of the SmPC information on tissue distribution was summarised).

Package Leaflet (PL)

Following all the changes in the SmPC there are several corresponding changes to the Package Leaflet. The final PL wording was agreed by the CHMP. Considering the extent of the harmonisation of the PL a Readability Testing was agreed to be submitted after the adoption of this referral procedure.

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

In conclusion, the CHMP recommended the revision and harmonisation of the Product Information for Tavanic tablets (250 mg and 500mg) and solution for infusion (5mg/ml) and adopted the following harmonised indications:

Tavanic, film-coated tablets, 250 mg and 500mg

Tavanic is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

- *Acute bacterial sinusitis*
- *Acute exacerbations of chronic bronchitis*
- *Community-acquired pneumonia*
- *Complicated skin and soft tissue infections*

For the above-mentioned infections Tavanic should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

- *Pyelonephritis and complicated urinary tract infections (see section 4.4)*
- *Chronic bacterial prostatitis*
- *Uncomplicated cystitis (see section 4.4)*
- *Inhalation Anthrax: postexposure prophylaxis and curative treatment (see section 4.4)*

Tavanic may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Tavanic, solution for infusion, 5 mg/ml

Tavanic solution for infusion is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

- *Community-acquired pneumonia*
- *Complicated skin and soft tissue infections*

For the above-mentioned infections Tavanic should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

- *Pyelonephritis and complicated urinary tract infections (see section 4.4)*
- *Chronic bacterial prostatitis*
- *Inhalation Anthrax: postexposure prophylaxis and curative treatment (see section 4.4).*

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

2.5. Conclusions

The basis for this referral procedure was a harmonisation of the SmPC, labelling and package leaflet. The CHMP having considered:

- the rapporteur and co-rapporteur assessment reports,
- scientific discussion within the Committee,
- comments and commitments from the marketing authorisation holder,

the CHMP was of the opinion that the benefit/risk ratio of Tavanic and associated names is considered to be favourable. The CHMP adopted a positive opinion recommending the harmonisation of the SmPCs, labelling and package leaflets as set out in Annex III of the CHMP opinion for Tavanic and associated names (see Annex I).