Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisations

Scientific conclusions

Overall summary of the scientific evaluation of Tavanic and associated names (see Annex I)

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 for 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.

The SPC 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 fluoroquinolon.

It is hereafter summarised the main points discussed for the harmonisation of the different sections of the SmPC.

Section 4.1 – Therapeutic Indications

<u>Respiratory Tract Infections</u> (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 via nationally or mutual recognition procedure (MRP) with 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)". Three pivotal studies supported this indication, granted in the EU since 1997. 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. 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 fluororoquinolones 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 above mentioned 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 considerations 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 fluoroquinolon 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 via nationally or MRP. There were three pivotal studies supporting this indication. 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. 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 fluororoquinolon 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 four pivotal studies. 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 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. This indication was not approved in one MS, due to the fact that the pivotal studies (five 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 as an alternative (i.e. second line treatment) 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.

Based on the review of all the data currently available, 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 as 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: 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.

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:

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.

Section 4.2 – Posology and method of administration

For the majority of the approved indications, 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/pharmacodinamic 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 ration 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 fluoroquinolon 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 elderly are more vulnerable for tendon injury if received 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 fluoroquinolon 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 fluoroquinolon 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' 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 sentence on *M. tuberculosis*, which is considered class labelling and which is included in the Company Core Data Sheet (CCDS).

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 fluoroquinolones 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 provide by the MAH in which possible causal relationship in some cases without alternative explanations in combination with biological plausibility were identified.

In addition, information on the hepatotoxicity was complemented to refer that reported cases of jaundice and severe liver injury with levofloxacin, 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 SPC

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 SPC 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.

QUALITY – MODULE 3

The MAH submitted a proposal for harmonisation of the Quality module. Information on development, manufacture and control of the film coated tablets and solution for infusion has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the products should have a satisfactory and uniform performance in the clinic.

Based on the review of data the CHMP adopted a harmonised Module 3.

Grounds for the variation to the terms of the marketing authorisations

In conclusion, based on the assessment of the MAH proposal and responses and following the discussions of the committee, the CHMP adopted harmonised sets of Product Information documents for the film-coated tablets and solution for infusion of Tavanic and associated names, taking into account the pharmaceutical forms. In particular, the indications and their associated posology recommendations were harmonised.

A harmonised Module 3 was also adopted. Based on the above, the CHMP considers the benefit/risk ratio of Tavanic and associated names to be favourable and the harmonised Product Information documents to be approvable.

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC
- The committee considered the identified divergences for Tavanic and associated names regarding the therapeutic indications and the posology and method of administration sections, as well as in the remaining sections of the SmPCs
- The committee reviewed the data submitted by the MAH from the existing clinical studies, the pharmacovigilance data and the published literature justifying the proposed harmonisation of the product information
- The committee agreed the harmonisation of the summary of product characteristics, labelling and package leaflets proposed by the marketing authorisation holders.

the CHMP has recommended the variation to the terms of the marketing authorisations for which the summary of product characteristics, labelling and package leaflets are set out in Annex III for Tavanic and associated names (see Annex I).