ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM(S), STRENGTH(S) OF THE MEDICINAL PRODUCT(S), ROUTE(S) OF ADMINISTRATION, APPLICANT(S) / MARKETING AUTHORISATION HOLDER(S) IN THE MEMBER STATES

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Austria	Bayer HealthCare AG 51368 Leverkusen Germany		Octegra 400 mg - Infusionslösung	400 mg	Solution for infusion	Intravenous use	400 mg / 250 ml
Belgium	Bayer HealthCare AG 51368 Leverkusen Germany		Proflox	400 mg	Solution for infusion	Intravenous use	400 mg / 250 ml
France		Bayer HealthCare AG 51368 Leverkusen Germany	Octegra 400 mg / 250 ml, solution pour perfusion	400 mg	Solution for infusion	Intravenous use	400 mg / 250 ml
Germany	Bayer HealthCare AG 51368 Leverkusen Germany		Octegra 400 mg / 250 ml Infusionslösung	400 mg	Solution for infusion	Intravenous use	400 mg / 250 ml
Greece	Elpen Pharmaceutical Co, Inc 95, Marathonos Avenue 190-09 Pikermi Greece		Octegra	400 mg	Solution for infusion	Intravenous use	400 mg / 250 ml
Luxembourg	Bayer HealthCare AG 51368 Leverkusen Germany		Proflox	400 mg	Solution for infusion	Intravenous use	400 mg / 250 ml
Netherlands	Bayer HealthCare AG 51368 Leverkusen Germany		Octegra 400 mg/250 ml oplossing voor infusie	400 mg	Solution for infusion	Intravenous use	400 mg / 250 ml
Portugal		Bialfar - Produtos Farmacêuticos S.A. À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado Portugal	Proflox	400 mg	Solution for infusion	Intravenous use	400 mg / 250 ml

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION AND AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF OCTEGRA AND ASSOCIATED NAMES (SEE ANNEX I)

Moxifloxacin hydrochloride is a synthetic antibacterial agent of the fluoroquinolone class. The first submission of moxifloxacin IV for CAP in 2002 included data from 550 moxifloxacin-treated subjects from two controlled clinical trials, which were later supplemented with an additional 942 subjects from five additional CAP studies. The clinical development plan for cSSSI consisted of two controlled studies which were the basis for the approval. Moxifloxacin IV for CAP was approved through MRP in two subsequent waves, in 2002 and 2004. Moxifloxacin IV for cSSSI was approved in 2005 in all countries that had already approved the intravenous formulation for use in CAP. No consensus was reached on Day 60 of the CMD(h) referral and the procedure was therefore referred to the CHMP. The major concern was the need for further qualification of the conditions of use. It was considered that the same restrictions should apply to the indications for both CAP and cSSTI as already adopted by CHMP for oral moxifloxacin to treat CAP. Intravenous moxifloxacin is almost always followed by oral treatment and as such the restriction for use of oral moxifloxacin should be reflected in the SPC of the intravenous product. The CHMP adopted a List of Questions, to be addressed by the Applicant.

Treatment of cSSI

The Applicant discussed the efficacy and safety of sequential IV/oral moxifloxacin in the treatment of cSSSI and concluded that non-inferiority was demonstrated, and that the clinical studies and post-marketing safety data show no evidence that moxifloxacin-treated patients are at greater risk for morbidity, including cardiac and hepatic morbidity, than patients receiving comparator antibiotics. The CHMP noted the Applicant response but considered that the data indicated that moxifloxacin is probably not quite as good as comparative therapy. In addition, the lower 95% CI in the primary analyses exceeded or bordered on -10%, which adds to the opinion that IV/PO moxifloxacin is not an optimal overall treatment for cSSSI. Outcomes by pathogen did not reveal any potentially alarming differences between treatments. However, there was a suggestion that moxifloxacin may not be as effective against anaerobes, which might correlate with erratic in-vitro activity against anaerobic species. Most importantly, response rates in staphylococcal infections were comparable between treatments as were responses for the relatively small number of Group A streptococcal infections. Overall, the CHMP considers that the data regarding the efficacy of IV/PO moxifloxacin are not overly impressive and this fact needs to be weighed against the safety profile as discussed further below. The CHMP considers that the benefit-risk relationship for IV/PO moxifloxacin in the management of cSSSI is only favourable with qualification of the indication for use.

The Applicant presented the results from the two studies, concluding that the bacteriological responses to moxifloxacin were supportive of the clinical responses and that the bacteriological eradication rates for moxifloxacin indicated good consistency between the two studies. However, the CHMP maintained its position, stating that the clinical and microbiological responses point to a conclusion that moxifloxacin IV/PO is not among the optimal treatments for cSSSI.

The Applicant discussed the safety overview of sequential IV/oral moxifloxacin, overall and specifically in cSSSIs and analysed data on the incidence of liver events from sequential IV/oral clinical studies (overall and cSSSIs), stating that there was no difference in overall incidences of hepatic adverse events and adverse drug reactions between moxifloxacin and comparators. The cumulative review of spontaneous ADR reports of serious “possible drug related hepatic disorders” on IV only or IV/oral sequential treatment, suggested that serious moxifloxacin-induced hepatic events were very rare, unpredictable and idiosyncratic and that the benefit-risk has not changed for IV moxifloxacin. An analysis of cardiac safety in sequential IV/oral clinical studies (overall and cSSSIs) was presented, along with an overview of the incidence of treatment-emergent adverse events relevant as surrogates for arrhythmia. The Applicant then discussed the cumulative review of spontaneous ADR reports on “QT/QT_c prolongation” and “Torsade de Pointes” for IV only or IV/PO sequential treatment. The Applicant concluded that there are no differences between moxifloxacin and the comparator when comparing the total numbers and frequencies of reports on possible drug-related

hepatic disorders. The frequencies of cardiac adverse events and adverse events were similar and the post-marketing observational studies and post-marketing surveillance of spontaneous adverse events do not show any evidence that IV/oral moxifloxacin is associated with a significantly higher risk of developing liver or cardiac adverse events than standard therapy. The Applicant accepted the restriction of cSSSI to a second-line treatment together with a warning towards MRSA in section 4.4. The following wording was adopted:

"Complicated skin and skin structure infections only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection (see section 4.4)"

Treatment of CAP

The CHMP was of the opinion that the use of IV moxifloxacin for treatment of CAP should be qualified by the same wording as the cSSSI indication. The CHMP and requested the Applicant to further discuss this issue. The Applicant discussed in depth the advantages of moxifloxacin for the treatment of CAP requiring initial IV therapy, providing data from clinical studies on the efficacy of moxifloxacin IV/oral, hepatic safety in sequential IV/oral and from studies on the cardiac safety in IV/oral. The Applicant concluded that moxifloxacin has enhanced activity against penicillin/macrolide-susceptible and –resistant strains of *S. pneumoniae*, is active against pathogens associated with atypical pneumonia and is consistently effective in hospitalised patients requiring initial IV therapy. The Applicant also claimed growing evidence that moxifloxacin has the best PK/PD profile to avoid the selection of resistance amongst the respiratory fluoroquinolones currently available in Europe. A total of 6 IV/PO studies in CAP were presented, however, the pooling of data across studies was considered inappropriate and overall, the data suggested that moxifloxacin may not be quite as good as a very good comparative regimen. While there were no clear reasons to reject an indication for CAP, the CHMP considered that the less than impressive data has to be weighed against the safety concerns. The CHMP considers that the totality of the safety data relating to use of moxifloxacin (IV and oral and IV/PO) should be taken into account together when assessing the overall benefit-risk and therefore, the safety profile described for oral administration applies to intravenous administration, with the additional expectation that the difference in PK and in patient and infection characteristics for those in need of initial IV treatment is likely to increase any risks associated with systemic administration. The CHMP considered that the effects of moxifloxacin on QTc indicate a correlation between plasma concentration and QTc. The data collected during the first two CAP studies shows that patients were more likely to have a notable increase in QTc on intravenous moxifloxacin. The analysis of outlying QTc values demonstrated a consistent excess risk for moxifloxacin for the data from the CAP studies with ECG data. Potential co-morbidities do not change the fact that IV administration carried an excess risk over comparators, including in the study in elderly. The CHMP acknowledges that a drug prolonging the QTc does not necessarily translate into a higher risk of cardiac ADRs, including arrhythmias. However, in light of the ADR and cardiac safety data submitted by the Applicant, there were differences between the two treatment groups with respect to the incidence of clinical AEs that could be considered surrogates for QTc prolongation, as higher incidences of ventricular tachycardia and cardiac arrest were seen in the moxifloxacin group. In addition, the post-marketing data show that significant and serious ADRs associated with QTc prolongation do occur. Post-marketing data show that patients have been given moxifloxacin despite the contraindications and warnings in the SPC, therefore strengthening these precautions in the SPC is unlikely to achieve a major shift in behaviour. The fact that moxifloxacin undergoes considerable metabolism led to concerns regarding its hepatotoxic potential. Spontaneous reporting rates are higher for IV/sequential treatment than for oral treatment and the Applicant's argument that this is accounted for by the greater background morbidity in the population treated with IV/PO compared to those treated only with PO moxifloxacin can be partly accepted. However, such data may indicate a true excess risk of hepatotoxicity for the IV formulation. Regarding the risk of hepatic ADRs associated with IV/PO moxifloxacin, the greater background morbidity/clinical monitoring may partly explain the increased rates but it remains plausible that it is linked to the greater bioavailability of the IV formulation. The data indicates that moxifloxacin carries a risk of severe hepatotoxicity at least 2-fold greater than comparators and the CHMP considers that the consistency of these risk estimates is a strong signal of an increased risk of hepatotoxicity, supporting non-first line use in the proposed indications. In conclusion, the efficacy data for IV/PO moxifloxacin in treatment of CAP and cSSSI are considered to be

sufficient but not overwhelmingly convincing and suggest that IV/PO moxifloxacin is not among the optimal treatments for either of these indications. The CHMP does not concur with the argument that the benefit-risk is different for patients in need of initial IV treatment as it can be argued that these patients are actually at greater risk of experiencing ADRs.

The Applicant presented a summary of the monitoring of the susceptibility of relevant bacterial species to moxifloxacin through a systematic literature review. The data revealed no new decrease in moxifloxacin susceptibility and the Applicant concluded that the susceptibilities for relevant species were correctly reflected in section 5.1 of the SPC with no significant trends or changes. The Applicant also discussed the feasibility of European surveillance, proposing to undertake an annual surveillance plan to collect moxifloxacin MIC data in European countries. The CHMP considered that the literature reviews were neither valid nor helpful. Any prospective surveillance study would need to be very carefully designed such that data collected from year to year could be compared with some degree of confidence and the Applicant proposal would not fulfil this requirement. If any such data was necessary, the Applicant should work with already established projects, adequately designed to collect reliable data prospectively.

The Applicant discussed the many factors that affect the QT interval and stated that while prolongation of the QT_c interval is commonly used as a surrogate marker for the risk of developing ventricular arrhythmias such as Torsade de Pointes (TdP), there is no consensus on the degree of QT prolongation that is considered clinically significant. The relationship between moxifloxacin concentrations and change in QT_c interval was investigated in CAP and cSSSI studies and the Phase III trials suggested similar results for moxifloxacin and the comparators. In Phase III-IV clinical studies, the rates of cardiac adverse events, drug-related cardiac adverse events and serious cardiac adverse events were similar between moxifloxacin and the comparator. This applied to the overall incidence rates during IV/oral therapy and during initial IV therapy. Intravenous moxifloxacin was not associated with an increased incidence of events that would be considered surrogates for a QT_c-related arrhythmia. The Applicant concluded that the QT_c prolongation seen for moxifloxacin has not translated into a higher risk of developing clinical cardiac events, including arrhythmias, compared to other agents. The Applicant proposed the insertion of a section on QT_c interval in section 4.4, as well as the following box-warning at the beginning of section 4.4:

Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. The magnitude of QT prolongation may increase with increasing plasma concentrations due to rapid intravenous infusion. Therefore, the duration of infusion should not be less than the recommended 60 minutes and the intravenous dose of 400 mg once a day should not be exceeded. Refer to sections 4.3, 4.4 and 4.5.

The Applicant considers that the proposed SPC now contains adequate warning regarding the patient groups at risk and potential precautionary measures to be noted before administering IV moxifloxacin. Regarding section 5.2 of the SPC, the Applicant agreed to remove the CLSI disk diffusion and MIC breakpoint criteria for aerobic bacteria but retained the CLSI recommendations for anaerobes in the SPC, as there are no MIC breakpoints established by EUCAST making the CLSI standard the only reference available to guide physicians. The CHMP did not agree with the Applicant's conclusions, although the boxed warning was considered appropriate. The text proposed for 4.4 was shortened in order to make it clearer.

As a number of issues remained to be clarified, the CHMP adopted a List of Outstanding Issues to be addressed by the Applicant. The Applicant provided further justifications supporting the indication in CAP.

Efficacy in the treatment of CAP

The Applicant considered that moxifloxacin IV had demonstrated non-inferiority or superiority in six controlled studies involving over 1,100 moxifloxacin-treated patients. Moxifloxacin demonstrated efficacy against *S. pneumoniae* and pathogens associated with atypical pneumonia and the Applicant also discussed data obtained by the competence network CAPNETZ. Finally, the Applicant claimed that the superior potency and pharmacokinetics of moxifloxacin avoids the selection of quinolone resistant isolates of

S. pneumoniae. The CHMP noted that while the pre-defined non-inferiority margins had been met, the data indicates that IV moxifloxacin was not quite as good as the best available regimens. In addition, the comparisons made are not considered robust enough and the pooling of the data is inappropriate due to the very varied comparative regimens and patient populations treated. With regard to pathogens associated with atypical pneumonia, the data must be interpreted with extreme caution. The prevalence of resistance among pneumococci is very variable across the EU and this is reflected in different treatment guidelines, including the need to use high doses of beta-lactam agents, combination therapy or to use fluoroquinolones in some regions. There are no clinical data to demonstrate that moxifloxacin is active against pneumococci that are insusceptible to other fluoroquinolones as a result of acquired resistance. Neither the CAPNETZ data nor the meta-analysis support the conclusion that moxifloxacin is better than alternatives. PK/PD predictions of the relative likelihood of levofloxacin and moxifloxacin selecting for resistance are scientifically plausible but not fully validated clinically. The trends described require years of observations before a clear association between use of either fluoroquinolone and resistance patterns, including mutation patterns can be established. The proposed restricted indication does not preclude the use of moxifloxacin for the initial treatment of CAP if in accordance with the local/regional/national guidance. In conclusion, the CHMP accepts that moxifloxacin may be indicated for the treatment of CAP, however the data it must be remembered that safety and benefit-risk were the main concerns triggering the referral and therefore, the conclusion that moxifloxacin has acceptable efficacy must be placed into context.

Safety in the treatment of CAP

The Applicant reiterated that the QT_c changes observed did not translate into a higher risk to develop a clinical cardiac event. No TdPs were reported in over 15,000 patients in clinical studies and in over 90,000 patients in Post Marketing Studies and the frequency of treatment-emergent serious cardiac events was similar to that of the comparator. The Applicant again presented data for the pooled CAP studies, stating that adverse events and drug reactions were slightly less common in patients treated with moxifloxacin. The toxicological experiments did not indicate that the liver was a prominent target organ for moxifloxacin and no specific risk factors for severe hepatic events were identified. The CHMP maintained its previous position, as no new data was provided. Simple comparisons between moxifloxacin and pooled comparators are misleading due to the variety of comparative regimens used. An early evaluation of the effects of moxifloxacin on QTc showed a correlation between plasma concentration and QTc in healthy subjects and increases in QTc were significantly higher in healthy elderly subjects post-moxifloxacin versus placebo. Patients were more likely to have a notable increase in QTc on intravenous moxifloxacin than on oral moxifloxacin. The submitted ECG data and the analysis of outlying QTc values demonstrated a consistent excess risk of moxifloxacin in the studies with ECG data. All AEs that might potentially reflect arrhythmias need to be taken into account and therefore the concerns regarding hepatotoxicity were reiterated. On the grounds of safety and benefit-risk, the CHMP maintains its position that both indications for use of IV moxifloxacin should be qualified with the same wording as for the cSSSI indication.

The Applicant attended an oral explanation at the May 2009 CHMP, during which the Applicant argumentation and data previously submitted in the context of the written responses was re-iterated. The CHMP maintained its previous position. In addition, the Applicant was requested to commit to amend the SPC for the moxifloxacin tablets, in order to bring it in line with the IV formulation, and make it clear that the tablets may be used for cSSSI and CAP of any severity only when IV therapy has already resulted in substantial improvement in the patient's condition, such that a switch to oral treatment is considered appropriate. The wording to be implemented was agreed by the CHMP and communicated to the Applicant.

In conclusion, the CHMP is of the opinion that the efficacy of moxifloxacin in the two indications claimed is not over-impressive. In several cases, the lower 95% CI around the treatment differences in individual studies were borderline with instances of notable numerical inferiority for moxifloxacin versus comparators. There is no advantage to be expected from moxifloxacin over approved fluoroquinolones in the indications claimed except over ciprofloxacin in CAP (due to the inherently low activity of ciprofloxacin against *S. pneumoniae*). In particular there is no clinical evidence to support an assertion that moxifloxacin might remain clinically active against organisms that have acquired reduced susceptibility to other

fluoroquinolones. While the efficacy data are sufficient to support an indication for use in CAP they suggest that moxifloxacin may not be as good as some alternative regimens.

GROUNDS FOR POSITIVE OPINION AND AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

In conclusion, the CHMP considered that the use of IV moxifloxacin for treatment of community-acquired pneumonia (CAP) or complicated skin and soft tissue infections (cSSTI) should be qualified as follows:

> *[Moxifloxacin] 400 mg solution for infusion is indicated for the treatment of:*
> - *Community acquired pneumonia*
> - *Complicated skin and structure infections*
>
> *Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.*
>
> *Consideration should be given to official guidance on the appropriate use of antibacterial agents.*

It was considered that the efficacy of moxifloxacin in the two indications claimed is adequate.

The safety profile of oral moxifloxacin also applies to intravenous moxifloxacin and there are particular concerns regarding hepatotoxicity and adverse reactions resulting from the effects of moxifloxacin on cardiac conduction. The risks may be even greater with intravenous use due to the differences in pharmacokinetics and the likely higher predisposition of patients with more severe CAP and with cSSSI to develop certain adverse reactions.

Taking into account these considerations, the CHMP did not support the Applicant's assertion that the difference in benefit-risk relationship between oral and intravenous uses justifies an unqualified indication for the use of IV moxifloxacin to treat CAP.

Whereas

- the efficacy of IV (followed by PO) moxifloxacin in the treatment of CAP and cSSTI is established, however the safety profile of intravenous moxifloxacin when used to treat CAP or cSSTI raises some concerns, particularly with regard to hepatotoxicity and cardiac conduction effects,

- the benefit-risk relationship for use of moxifloxacin to treat these infections was considered to be favourable only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections,

the CHMP has recommended the amendment of the Summary of Product Characteristics and the granting of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Octegra and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note: This SPC, labelling and package leaflet is the version valid at the time of Commission Decision.

After the Commission Decision the Member State Competent Authorities, in liaison with the Reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Octegra and associated names (see Annex I) 400 mg/250 ml solution for infusion
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 bottle or 1 bag of 250 ml contains 400 mg moxifloxacin (as hydrochloride).
1 ml contains 1.6 mg moxifloxacin (as hydrochloride).

Excipient: 250 ml of solution for infusion contains 34 mmol sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion
Clear, yellow solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Octegra is indicated for the treatment of:
- Community acquired pneumonia (CAP)
- Complicated skin and skin structure infections (cSSSI)

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

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

4.2 Posology and method of administration

400 mg moxifloxacin, infused once daily.

Initial intravenous treatment may be followed by oral treatment with moxifloxacin 400 mg tablets, when clinically indicated.
In clinical studies most patients switched to oral therapy within 4 days (CAP) or 6 days (cSSSI). The recommended total duration of intravenous and oral treatment is 7 - 14 days for CAP and 7 - 21 days for cSSSI.

Renal/hepatic impairment
No adjustment of dosage is required in patients with mild to severely impaired renal function or in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis (see section 5.2 for more details).
There is insufficient data in patients with impaired liver function (see section 4.3).

Other special populations
No adjustment of dosage is required in the elderly and in patients with low bodyweight.

Children and adolescents

Moxifloxacin is contraindicated in children and growing adolescents. Efficacy and safety of moxifloxacin in children and adolescents have not been established (see section 4.3).

Method of administration
For intravenous use; **constant infusion over 60 minutes** (see also section 4.4).

If medically indicated the solution for infusion can be administered via a T-tube, together with compatible infusion solutions (see section 6.6).

4.3 Contraindications

- Hypersensitivity to moxifloxacin, other quinolones or to any of the excipients.
- Pregnancy and lactation (see section 4.6).
- Children and growing adolescents.
- Patients with a history of tendon disease/disorder related to quinolone treatment.

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to moxifloxacin, in the form of QT prolongation. For reasons of drug safety, moxifloxacin is therefore contraindicated in patients with:
- Congenital or documented acquired QT prolongation
- Electrolyte disturbances, particularly in uncorrected hypokalaemia
- Clinically relevant bradycardia
- Clinically relevant heart failure with reduced left-ventricular ejection fraction
- Previous history of symptomatic arrhythmias

Moxifloxacin should not be used concurrently with other drugs that prolong the QT interval (see also section 4.5).

Due to limited clinical data, moxifloxacin is also contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5fold ULN.

4.4 Special warnings and precautions for use

Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. The magnitude of QT prolongation may increase with increasing plasma concentrations due to rapid intravenous infusion. Therefore, the duration of infusion should not be less than the recommended 60 minutes and the intravenous dose of 400 mg once a day should not be exceeded. For more details see below and refer to sections 4.3 and 4.5.

- Treatment with moxifloxacin should be stopped if signs or symptoms that may be associated with cardiac arrhythmia occur during treatment, with or without ECG findings.
  Moxifloxacin should be used with caution in patients with any condition pre-disposing to cardiac arrhythmias (e.g. acute myocardial ischaemia) because they may have an increased risk of developing ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest. See also sections 4.3 and 4.5.
  Moxifloxacin should be used with caution in patients who are taking medication that can reduce potassium levels. See also section 4.3.
  Moxifloxacin should be used with caution in patients who are taking medications associated with clinically significant bradycardia. See also section 4.3.
  Female patients and elderly patients may be more sensitive to the effects of QTc-prolonging medications such as moxifloxacin and therefore special caution is required.
- Moxifloxacin solution for infusion is for intravenous administration only. Intra-arterial administration should be avoided since preclinical studies demonstrated peri-arterial tissue inflammation following infusion by this route.

- Hypersensitivity and allergic reactions have been reported for fluoroquinolones including moxifloxacin after first administration. Anaphylactic reactions can progress to a life-threatening shock, even after the first administration. In these cases moxifloxacin should be discontinued and suitable treatment (e.g. treatment for shock) initiated.
- Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of fulminant hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy.
  Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.
- Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.
- Quinolones are known to trigger seizures. Use should be with caution in patients with CNS disorders which may predispose to seizures or lower the seizure threshold.
- Antibiotic associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported in association with the use of broad spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhoea to fatal colitis. Therefore it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of moxifloxacin. If AAD or AAC is suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.
- Elderly patients with renal disorders should use moxifloxacin with caution if they are unable to maintain adequate fluid intake, because dehydration may increase the risk of renal failure.
- Moxifloxacin should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.
- Tendon inflammation and rupture may occur with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. At the first sign of pain or inflammation, patients should discontinue treatment with moxifloxacin and rest the affected limb(s).
- Patients with a family history of, or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with quinolones. Therefore, moxifloxacin should be used with caution in these patients.
- If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.
- Quinolones have been shown to cause photosensitivity reactions in patients. However, studies have shown that moxifloxacin has a lower risk to induce photosensitivity. Nevertheless patients should be advised to avoid exposure to either UV irradiation or extensive and/or strong sunlight during treatment with moxifloxacin.
- Clinical efficacy of moxifloxacin in the treatment of severe burn infections, fasciitis, major abscesses and diabetic foot infections with osteomyelitis has not been established.
- This medicinal product contains 787 mg (approximately 34 mmol) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.
- Moxifloxacin therapy may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth causing false negative results.
- Moxifloxacin is not recommended for the treatment of MRSA infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with medicinal products
An additive effect on QT interval between moxifloxacin and other medicinal products that may prolong the QTc interval cannot be excluded. This might lead to an increased risk of ventricular arrhythmias, including torsade de pointes. Therefore co-administration of moxifloxacin with any of the following medicinal products is contraindicated (see also section 4.3):

- antiarrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
- antiarrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- neuroleptics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride)
- tricyclic antidepressive agents
- certain antimicrobial agents (sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)
- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil).

Moxifloxacin should be used with caution in patients who are taking medication that can reduce potassium levels or medication that is associated with clinically significant bradycardia.

After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin approximately 30% without affecting AUC or trough levels. No precaution is required for use with digoxin.

In studies conducted in diabetic volunteers, concomitant administration of oral moxifloxacin with glibenclamide resulted in a decrease of approximately 21% in the peak plasma concentrations of glibenclamide. The combination of glibenclamide and moxifloxacin could theoretically result in a mild and transient hyperglycaemia. However, the observed pharmacokinetic changes for glibenclamide did not result in changes of the pharmacodynamic parameters (blood glucose, insulin). Therefore no clinically relevant interaction was observed between moxifloxacin and glibenclamide.

Changes in INR
A large number of cases showing an increase in oral anticoagulant activity have been reported in patients receiving antibacterial agents, especially fluoroquinolones, macrolides, tetracyclines, cotrimoxazole and some cephalosporins. The infectious and inflammatory conditions, age and general status of the patient appear to be risk factors. Under these circumstances, it is difficult to evaluate whether the infection or the treatment caused the INR (international normalised ratio) disorder. A precautionary measure would be to more frequently monitor the INR. If necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Clinical studies have shown no interactions following concomitant administration of moxifloxacin with: ranitidine, probenecid, oral contraceptives, calcium supplements, morphine administered parenterally, theophylline or itraconazole.

In vitro studies with human cytochrome P450 enzymes support these findings. Considering these results a metabolic interaction via cytochrome P450 enzymes is unlikely.

Interaction with food
Moxifloxacin has no clinically relevant interaction with food including dairy products.

4.6 Pregnancy and lactation

Pregnancy
The safety of moxifloxacin in human pregnancy has not been evaluated. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals and reversible joint

injuries described in children receiving some fluoroquinolones, moxifloxacin must not be used in pregnant women (see section 4.3).

Lactation
There is no data available in lactating or nursing women. Preclinical data indicate that small amounts of moxifloxacin are secreted in milk. In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals, breast-feeding is contraindicated during moxifloxacin therapy (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of moxifloxacin on the ability to drive and use machines have been performed. However, fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions (e.g. dizziness, see section 4.8) or acute and short lasting loss of consciousness (syncope, see section 4.8). Patients should be advised to see how they react to moxifloxacin before driving or operating machinery.

4.8 Undesirable effects

Adverse reactions observed in clinical trials with moxifloxacin 400 mg daily administered by the intravenous or oral route sorted by frequencies are listed below:

Apart from nausea and diarrhoea all adverse reactions were observed at frequencies below 3%.

System Organ Class	**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
Infections and infestations	Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis			
Blood and lymphatic system disorders		Anaemia Leucopenia(s) Neutropenia Thrombocytopenia Thrombocythemia Blood eosinophilia Prothrombin time prolonged / INR increased		Prothrombin level increased / INR decreased
Immune system disorders		Allergic reaction (see section 4.4)	Anaphylaxis incl. very rarely life-threatening shock (see section 4.4) Allergic oedema / angiooedema (incl. laryngeal oedema, potentially life-threatening, see section 4.4)	

System Organ Class	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
Metabolism and nutrition disorders		Hyperlipidemia	Hyperglycemia Hyperuricemia	
Psychiatric disorders		Anxiety reactions Psychomotor hyperactivity / agitation	Emotional lability Depression (in very rare cases potentially culminating in self-endangering behaviour) Hallucination	Depersonalization Psychotic reactions (potentially culminating in self-endangering behaviour)
Nervous system disorders	Headache Dizziness	Par- and Dysaesthesia Taste disorders (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorders (predominantly insomnia) Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo) Seizures incl. grand mal convulsions (see section 4.4) Disturbed attention Speech disorders Amnesia	Hyperaesthesia
Eye disorders		Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions, see section 4.4)		
Ear and labyrinth disorders			Tinnitus	
Cardiac and vascular disorders	QT prolongation in patients with hypokalaemia (see section 4.4)	QT prolongation (see section 4.4) Palpitations Tachycardia Atrial fibrillation Angina pectoris Vasodilatation	Ventricular tachyarrhythmias Syncope (i.e., acute and short lasting loss of consciousness) Hypertension Hypotension	Unspecified arrhythmias Torsade de Pointes (see section 4.4) Cardiac arrest (see section 4.4)
Respiratory, thoracic and mediastinal disorders		Dyspnea (including asthmatic conditions)		

System Organ Class	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
Gastrointestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Anorexia Constipation Dyspepsia Flatulence Gastritis Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (incl. pseudomembranous colitis, in very rare cases associated with life-threatening complications, see section 4.4)	
Hepatobiliary disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases, see section 4.4)
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria Dry skin		Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening, see section 4.4)
Musculoskeletal, connective tissue and bone disorders		Arthralgia Myalgia	Tendonitis (see section 4.4) Muscle cramp Muscle twitching	Tendon rupture (see section 4.4) Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis (see section 4.4)
Renal and urinary disorders		Dehydration	Renal impairment (incl. increase in BUN and creatinine) Renal failure (see section 4.4)	

System Organ Class	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
General disorders and administration site conditions	Injection and infusion site reactions	Feeling unwell (predominantly asthenia or fatigue) Painful conditions (incl. pain in back, chest, pelvic and extremities) Sweating Infusion site (thrombo-) phlebitis	Oedema	

The following undesirable effects have a higher frequency category in the subgroup of IV treated patients with or without subsequent oral therapy:

Common: Increased gamma-glutamyl-transferase

Uncommon: Ventricular tachyarrhythmias, hypotension, oedema, antibiotic associated colitis (incl. pseudomembranous colitis, in very rare cases associated with life-threatening complications, see section 4.4), seizures incl. grand mal convulsions (see section 4.4), hallucination, renal impairment (incl. increase in BUN and creatinine), renal failure (see section 4.4)

There have been very rare cases of the following side effects reported following treatment with other fluoroquinolones, which might possibly also occur during treatment with moxifloxacin: transient loss of vision, hypernatraemia, hypercalcaemia, haemolysis, rhabdomyolysis, photosensitivity reactions (see section 4.4).

4.9 Overdose

No specific countermeasures after accidental overdose are recommended. General symptomatic therapy should be initiated. Concomitant administration of charcoal with a dose of 400 mg oral or intravenous moxifloxacin will reduce systemic availability of the drug by more than 80% or 20% respectively. The use of charcoal early during absorption may be useful to prevent excessive increase in the systemic exposure to moxifloxacin in cases of oral overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones, ATC code: J01MA14

Mode of action

Moxifloxacin inhibits bacterial type II topoisomerases (DNA gyrase and topoisomerase IV) that are required for bacterial DNA replication, transcription and repair.

PK/PD

Fluoroquinolones exhibit a concentration dependent killing of bacteria. Pharmacodynamic studies of fluoroquinolones in animal infection models and in human trials indicate that the primary determinant of efficacy is the AUC_{24}/MIC ratio.

Mechanism of resistance

Resistance to fluoroquinolones can arise through mutations in DNA gyrase and topoisomerase IV. Other mechanisms may include over-expression of efflux pumps, impermeability, and protein-mediated protection of DNA gyrase. Cross resistance should be expected between moxifloxacin and other fluoroquinolones. The activity of moxifloxacin is not affected by mechanisms of resistance that are specific to antibacterial agents of other classes.

Breakpoints

EUCAST clinical MIC breakpoints for moxifloxacin (31.01.2006):

Organism	**Susceptible**	**Resistant**
Staphylococcus spp.	≤ 0.5 mg/l	> 1 mg/l
S. pneumoniae	≤ 0.5 mg/l	> 0.5 mg/l
Streptococcus Groups A, B, C, G	≤ 0.5 mg/l	> 1 mg/l
H. influenzae and *M. catarrhalis*	≤ 0.5 mg/l	> 0.5 mg/l
Enterobacteriaceae	≤ 0.5 mg/l	> 1 mg/l
Non-species related breakpoints*	≤ 0.5 mg/l	> 1 mg/l
* Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and are not for use with species where interpretative criteria remain to be determined (Gram-negative anaerobes).		

Microbiological Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information of resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought where the local prevalence of resistance is such that utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms *Staphylococcus aureus**[+] *Streptococcus agalactiae* (Group B) *Streptococcus milleri* group* (*S. anginosus, S. constellatus and S. intermedius*) *Streptococcus pneumoniae** *Streptococcus pyogenes** (Group A)
Aerobic Gram-negative micro-organisms *Haemophilus influenzae** *Klebsiella pneumoniae**[#] *Moraxella (Branhamella) catarrhalis*
Anaerobic micro-organisms *Prevotella* spp.
"Other" micro-organisms *Chlamydophila (Chlamydia) pneumoniae** *Coxiella burnetii* *Legionella pneumophila* *Mycoplasma pneumoniae**
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecalis**
Aerobic Gram-negative micro-organisms *Enterobacter cloacae** *Escherichia coli**[#] *Klebsiella oxytoca* *Proteus mirabilis**
Anaerobic micro-organisms *Bacteroides fragilis*
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Pseudomonas aeruginosa*
*Activity has been satisfactorily demonstrated in clinical studies. [+]Methicillin resistant *S. aureus* have a high probability of resistance to fluoroquinolones. Moxifloxacin resistance rate of > 50% have been reported for methicillin resistant *S. aureus*. [#]ESBL-producing strains are commonly also resistant to fluoroquinolones.

5.2 Pharmacokinetic properties

Absorption and Bioavailability

After a single 400 mg intravenous 1 hour infusion peak plasma concentrations of approximately 4.1 mg/l were observed at the end of the infusion corresponding to a mean increase of approximately 26% relative to those seen after oral administration (3.1 mg/l). The AUC value of approximately 39 mg·h/l after i.v. administration is only slightly higher than that observed after oral administration (35 mg·h/l) in accordance with the absolute bioavailability of approximately 91%.

In patients, there is no need for age or gender related dose adjustment on intravenous moxifloxacin.

Pharmacokinetics are linear in the range of 50 - 1200 mg single oral dose, up to 600 mg single intravenous dose and up to 600 mg once daily dosing over 10 days.

Distribution
Moxifloxacin is distributed to extravascular spaces rapidly. The steady-state volume of distribution (Vss) is approximately 2 l/kg. *In vitro* and *ex vivo* experiments showed a protein binding of approximately 40 - 42% independent of the concentration of the drug. Moxifloxacin is mainly bound to serum albumin.

Maximum concentrations of 5.4 mg/kg and 20.7 mg/l (geometric mean) were reached in bronchial mucosa and epithelial lining fluid, respectively, 2.2 h after an oral dose. The corresponding peak concentration in alveolar macrophages amounted to 56.7 mg/kg. In skin blister fluid concentrations of 1.75 mg/l were observed 10 h after intravenous administration. In the interstitial fluid unbound concentration time profiles similar to those in plasma were found with unbound peak concentrations of 1.0 mg/l (geometric mean) reached approximately 1.8 h after an intravenous dose.

Metabolism
Moxifloxacin undergoes Phase II biotransformation and is excreted via renal (approximately 40%) and biliary/faecal (approximately 60%) pathways as unchanged drug as well as in the form of a sulpho-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive.

In clinical Phase I and *in vitro* studies no metabolic pharmacokinetic interactions with other drugs undergoing Phase I biotransformation involving cytochrome P450 enzymes were observed. There is no indication of oxidative metabolism.

Elimination
Moxifloxacin is eliminated from plasma with a mean terminal half life of approximately 12 hours. The mean apparent total body clearance following a 400 mg dose ranges from 179 to 246 ml/min. Following a 400 mg intravenous infusion recovery of unchanged drug from urine was approximately 22% and from faeces approximately 26%. Recovery of the dose (unchanged drug and metabolites) totalled to approximately 98% after intravenous administration of the drug. Renal clearance amounted to about 24 - 53 ml/min suggesting partial tubular reabsorption of the drug from the kidneys. Concomitant administration of moxifloxacin with ranitidine or probenecid did not alter renal clearance of the parent drug.

The pharmacokinetic properties of moxifloxacin are not significantly different in patients with renal impairment (including creatinine clearance > 20 ml/min/1.73 m^2). As renal function decreases, concentrations of the M2 metabolite (glucuronide) increase by up to a factor of 2.5 (with a creatinine clearance of < 30 ml/min/1.73 m^2).

On the basis of the pharmacokinetic studies carried out so far in patients with liver failure (Child Pugh A, B), it is not possible to determine whether there are any differences compared with healthy volunteers. Impaired liver function was associated with higher exposure to M1 in plasma, whereas exposure to parent drug was comparable to exposure in healthy volunteers. There is insufficient experience in the clinical use of moxifloxacin in patients with impaired liver function.

5.3 Preclinical safety data

In conventional repeated dose studies moxifloxacin revealed haematological and hepatic toxicity in rodents and non-rodents. Toxic effects on the CNS were observed in monkeys. These effects occurred after the administration of high doses of moxifloxacin or after prolonged treatment.

In dogs, high oral doses (≥ 60 mg/kg) leading to plasma concentrations ≥ 20 mg/l caused changes in the electroretinogram and in isolated cases an atrophy of the retina.

After intravenous administration findings indicative of systemic toxicity were most pronounced when moxifloxacin was given by bolus injection (45 mg/kg) but they were not observed when moxifloxacin (40 mg/kg) was given as slow infusion over 50 minutes.

After intra-arterial injection inflammatory changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial administration of moxifloxacin should be avoided.

Moxifloxacinwas genotoxic in *in vitro* tests using bacteria or mammalian cells. In *in vivo* tests, no evidence of genotoxicity was found despite the fact that very high moxifloxacin doses were used. Moxifloxacin was non-carcinogenic in an initiation-promotion study in rats.

In vitro, moxifloxacin revealed cardiac electrophysiological properties that can cause prolongation of the QT interval, even though at high concentrations.

After intravenous administration of moxifloxacin to dogs (30 mg/kg infused over 15, 30 or 60 minutes) the degree of QT prolongation was clearly depending on the infusion rate, i.e. the shorter the infusion time the more pronounced the prolongation of the QT interval. No prolongation of the QT interval was seen when a dose of 30 mg/kg was infused over 60 minutes.

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (p.o. and i.v.) and monkeys (p.o.) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. A slightly increased incidence of vertebral and rib malformations was observed in foetuses of rabbits but only at a dose (20 mg/kg i.v.) which was associated with severe maternal toxicity. There was an increase in the incidence of abortions in monkeys and rabbits at human therapeutic plasma concentrations.

Quinolones, including moxifloxacin, are known to cause lesions in the cartilage of the major diarthrodial joints in immature animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)
Water for injections

6.2 Incompatibilities

The following solutions are incompatible with moxifloxacin solution for infusion:
Sodium chloride 10% and 20% solutions
Sodium bicarbonate 4.2% and 8.4% solutions
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Polyolefine bag: 3 years
Glass bottle: 5 years
Use immediately after first opening and/or dilution.

6.4 Special precautions for storage

Do not refrigerate or freeze.

6.5 Nature and contents of container

Polyolefine bags with polypropylene port sealed in aluminium foil overwrap. 250 ml pack available in cartons of 5 and 12 bags.
Colourless glass bottles (type 2) with a chlorobutyl rubber stopper as closure. The 250 ml bottle is available in packs of 1 and 5 bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This product is for single use only. Any unused solution should be discarded.
The following co-infusions were found to be compatible with moxifloxacin 400 mg solution for infusion: Water for injections, Sodium chloride 0.9%, Sodium chloride 1 molar, Glucose 5%/10%/40%, Xylitol 20%, Ringer's solution, Compound Sodium Lactate Solution (Hartmann's Solution, Ringer-Lactate Solution).
Moxifloxacin solution for infusion should not be co-infused with other drugs.
Do not use if there are any visible particulate matter or if the solution is cloudy.
At cool storage temperatures precipitation may occur, which will re-dissolve at room temperature. It is therefore recommended not to store the infusion solution in a refrigerator.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally.]

10. DATE OF REVISION OF THE TEXT

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON FOR UNIT PACK AND LABEL - GLASS BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Octegra and associated names (see Annex I) 400 mg/250 ml solution for infusion
[See Annex I - To be completed nationally]
Moxifloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 bottle of 250 ml contains 400 mg moxifloxacin (as hydrochloride).
1 ml contains 1.6 mg moxifloxacin as hydrochloride.

3. LIST OF EXCIPIENTS

Contains sodium chloride, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment) and water for injections.
Sodium content: 34 mmol/250 ml

4. PHARMACEUTICAL FORM AND CONTENTS

1 bottle with 250 ml solution for infusion
Component of a multipack

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Infused at a constant flow rate over 60 minutes.
Read the package leaflet before use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use immediately after first opening and/or dilution.

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKAGING FOR MULTIPACK - GLASS BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Octegra and associated names (see Annex I) 400 mg/250 ml solution for infusion
[See Annex I - To be completed nationally]
Moxifloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 bottle of 250 ml contains 400 mg moxifloxacin (as hydrochloride).
1 ml contains 1.6 mg moxifloxacin as hydrochloride.

3. LIST OF EXCIPIENTS

Contains sodium chloride, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment) and water for injections.
Sodium content: 34 mmol/250 ml

4. PHARMACEUTICAL FORM AND CONTENTS

5 bottles with 250 ml solution for infusion
Multipack

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Infused at a constant flow rate over 60 minutes.
Read the package leaflet before use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use immediately after first opening and/or dilution.

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OVERWRAP AND BAG

1. NAME OF THE MEDICINAL PRODUCT

Octegra and associated names (see Annex I) 400 mg/250 ml solution for infusion
[See Annex I - To be completed nationally]
Moxifloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 bag of 250 ml contains 400 mg moxifloxacin (as hydrochloride).
1 ml contains 1.6 mg moxifloxacin as hydrochloride.

3. LIST OF EXCIPIENTS

Contains sodium chloride, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment) and water for injections.
Sodium content: 34 mmol/250 ml

4. PHARMACEUTICAL FORM AND CONTENTS

1 bag with 250 ml solution for infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Infused at a constant flow rate over 60 minutes.
Read the package leaflet before use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use immediately after first opening and/or dilution.

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR OVERWRAP - BAG

1. NAME OF THE MEDICINAL PRODUCT

Octegra and associated names (see Annex I) 400 mg/250 ml solution for infusion
[See Annex I - To be completed nationally]
Moxifloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 bag of 250 ml contains 400 mg moxifloxacin (as hydrochloride).
1 ml contains 1.6 mg moxifloxacin as hydrochloride.

3. LIST OF EXCIPIENTS

Contains sodium chloride, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment) and water for injections.
Sodium content: 34 mmol/250 ml

4. PHARMACEUTICAL FORM AND CONTENTS

5 bags with 250 ml solution for infusion
12 bags with 250 ml solution for infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Infused at a constant flow rate over 60 minutes.
Read the package leaflet before use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use immediately after first opening and/or dilution.

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Octegra and associated names (see Annex I) 400mg/250ml solution for infusion

[See Annex I - To be completed nationally]

Active ingredient: Moxifloxacin

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

[To be completed nationally]

In this leaflet:

1. WHAT OCTEGRA IS AND WHAT IT IS USED FOR

Octegra contains moxifloxacin as the active ingredient which belongs to a group of antibiotics called fluoroquinolones. Octegra works by killing bacteria that cause infections if they are caused by bacteria that are susceptible to moxifloxacin.

Octegra is used in adults for treating the following bacterial infections:
- Infection of the lungs (pneumonia) acquired outside the hospital
- Infections of the skin and soft tissue

2. BEFORE YOU USE OCTEGRA

Contact your doctor if you are not sure if you belong to a patient group described below.

Do not use Octegra
- If you are allergic (hypersensitive) to the active ingredient moxifloxacin, any other quinolone antibiotics or any of the other ingredients (see section 6. *Further information*) of Octegra.
- If you are pregnant or breast-feeding.
- If you are a child or an adolescent still growing.
- If you have a history of tendon disease or disorder which was related to treatment with quinolone antibiotics (see sections *Take special care ...* and *4. Possible side effects*).
- If you were born with or have had any condition with certain abnormal electrocardiogram (ECG, electrical recording of the heart) changes.
- If you have salt imbalance in the blood, especially low concentrations of potassium in the blood (hypokalaemia) which are currently not corrected by treatment.
- If you have a very slow heart rate (bradycardia).

- If you have a weak heart (heart failure).
- If you have a history of abnormal heart rhythms (arrhythmias).
- If you are taking other medicines that result in certain abnormal ECG changes (see section *Taking other medicines*).
- If you have a severe liver disease or liver enzymes (transaminases) that are higher than 5 times the upper normal limit.

Take special care with Octegra

Before using Octegra for the first time
- Octegra can temporarily change your heart's ECG, which can very rarely lead to life-threatening disturbances of the heart rhythm. If you are female or elderly, you may be more sensitive to ECG changes. If the blood supply to your heart muscle is impaired, consult your doctor before you are given Octegra because this can increase the risk of heart rhythm disturbances.
- If you are currently taking any medicine that decreases your blood potassium levels, consult your doctor before taking Octegra because this can increase the risk of heart rhythm disturbances.
- If you experience palpitations or irregular heart beat during the period of treatment, you should stop taking Octegra and inform your doctor immediately.
- If you suffer from epilepsy or a condition which makes you likely to have convulsions, tell your doctor before taking Octegra.
- If you suffer from myasthenia gravis using Octegra may worsen the symptoms of your disease. If you think you are affected consult your doctor immediately.
- If you or any member of your family have glucose-6-phosphate dehydrogenase deficiency (a rare hereditary disease), inform your doctor, who will advise whether Octegra is suitable for you.

When using Octegra
- The risk of cardiac abnormalities may increase with the dose and the speed of the infusion into your vein.
- Octegra should be given intravenously (in the vein) only, and should not be administered into an artery.
- There is a rare chance that you may experience a severe, sudden allergic reaction (an anaphylactic reaction/shock) even with the first dose, with symptoms that may include tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing. If this happens treatment with Octegra solution for infusion has to be discontinued immediately.
- Octegra may cause a rapid and severe inflammation of the liver which could lead to life-threatening liver failure (including fatal cases, see section *4. Possible side effects*). Please contact your doctor before you continue the treatment if you suddenly start to feel unwell or notice yellowing of the whites of the eyes, dark urine, itching of the skin, a tendency to bleed or disturbances of thought or wakefulness.
- If you develop a skin reaction or blistering and/or peeling of the skin and/or mucosal reactions (see section *4. Possible side effects*) contact your doctor immediately before you continue the treatment.
- You may develop diarrhoea whilst taking, or after taking, antibiotics including Octegra. If this becomes severe or persistent or you notice that your stool contains blood or mucus you should stop taking Octegra immediately and consult your doctor. In this situation, you should not take medicines that stop or slow down bowel movement.
- If you are elderly with existing kidney problems take care that your fluid intake is sufficient because dehydration may increase the risk of kidney failure
- Octegra may occasionally cause pain and inflammation of your tendons, particularly if you are elderly or if you are currently being treated with corticosteroids. At the first sign of any pain or inflammation you should stop taking Octegra, rest the affected limb and consult your doctor immediately.
- If your eyesight becomes impaired or if you have any other eye disturbances whilst taking Octegra, consult an eye specialist immediately.

- Quinolone antibiotics may make your skin become more sensitive to sunlight or UV light. You should avoid prolonged exposure to sunlight or strong sunlight and should not use a sunbed or any other UV lamp while taking Octegra.
- There is limited experience on use of sequential intravenous/oral Octegra for the treatment of infection of the lungs (pneumonia) acquired outside the hospital.
- The efficacy of Octegra in the treatment of severe burns, infections of deep tissue, major purulent ulcers (abscesses) and diabetic foot infections with osteomyelitis (infections of the bone marrow) has not been established.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines besides Octegra, including medicines obtained without a prescription.
For Octegra be aware of the following:
- If you are taking other medicines that affect your heart during treatment with Octegra there is an increased risk for altering your heart rhythm. Therefore, do not take the following medicines during treatment with Octegra: Medicines that belong to the group of anti-arrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide), neuroleptics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride), tricyclic antidepressants, some antimicrobials (e.g. sparfloxacin, intravenous erythromycin, pentamidine, antimalarials particularly halofantrine), some antihistamines (e.g. terfenadine, astemizole, mizolastine), and other medicines (e.g. cisapride, intravenous vincamine, bepridil and diphemanil).
- Special care is need if you are taking other medicines that can lower your blood potassium levels or cause a slow heart rate because these can also increase the risk of serious heart rhythm disturbances while taking Octegra.
- If you are currently taking oral anti-coagulants (e.g. warfarin), it may be necessary for your doctor to monitor your blood clotting times.

Using Octegra with food and drink
The effect of Octegra is not influenced by food including dairy products.

Pregnancy and breast-feeding
Do not take Octegra if you are pregnant or breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Octegra may make you feel dizzy or light-headed or you might faint for a short period. If you are affected in this way do not drive or operate machinery.

Important information about some of the ingredients of Octegra
This medicinal product contains 787mg (approximately 34mmol) sodium per dose. If you are on a controlled-salt diet, please inform your doctor immediately.

3. HOW TO USE OCTEGRA

Octegra will always be given to you by a doctor or healthcare professional.

The usual dose for adults is one bottle bag once daily.

Octegra is for intravenous use. Your doctor should ensure that the infusion is given at a constant flow over 60 minutes.

No adjustment of the dose is required in elderly patients, patients with a low bodyweight or in patients with kidney problems.

Your doctor will decide on the duration of your treatment with Octegra. In some cases your doctor may start your treatment with Octegra solution for infusion and then continue your treatment with Octegra tablets. The duration of treatment depends upon the type of infection, and how well you respond to treatment but the recommended durations of use are:

- Infection of the lungs (pneumonia) acquired outside the hospital 7 - 14 days

Most patients with pneumonia were switched to oral treatment with Octegra tablets within 4 days.

- Infections of the skin and soft tissue 7 - 21 days

For patients with complicated skin and skin structure infections the mean duration of intravenous treatment was approximately 6 days and the average overall duration of treatment (infusion followed by tablets) was 13 days.

It is important that you complete the course of treatment, even if you begin to feel better after a few days. If you stop taking this medicine too soon your infection may not be completely cured, the infection may return or your condition may get worse, and you may also create a bacterial resistance to the antibiotic.

The recommended dose and duration of treatment should not be exceeded (see section *2. Before you use Octegra...*, *Take special care ...*).

If you receive more Octegra than you should
If you are concerned that you may have been received too much Octegra, contact your doctor immediately.

If you miss a dose of Octegra
If you are concerned that you may have missed a dose of Octegra, contact your doctor immediately.

If you stop using Octegra
If the treatment with this medicine is stopped too soon your infection may not be completely cured. Consult your doctor if you wish to stop the treatment with Octegra solution for infusion or Octegra tablets before the end of the course of treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Octegra can cause side effects, although not everybody gets them.

The following side effects have been observed during treatment with Octegra. The frequency of possible side effects listed below is defined using the following convention:

Very common: affects more than 1 user in 10
Common: affects 1 to 10 users in 100
Uncommon: affects 1 to 10 users in 1,000
Rare: affects 1 to 10 users in 10,000
Very rare: affects less than 1 user in 10,000
Not known: frequency cannot be estimated from the available data

Infections
Common: Infections caused by resistant bacteria or fungi e.g. oral and vaginal infections caused by Candida

Blood and Lymph System

Uncommon: Low red blood cell count, low white blood cells count, low numbers of special white blood cells (neutrophils), decrease or increase of special blood cells necessary for blood clotting, increased specialised white blood cells (eosinophils), decreased blood clotting
Very rare: Increased blood clotting

Allergic Reactions
Uncommon: Allergic reaction
Rare: Severe, sudden generalised allergic reaction incl. very rarely life-threatening shock (e.g. difficulty in breathing, drop of blood pressure, fast pulse), swelling (incl. potentially life-threatening swelling of the airway)

Changes in Laboratory Test Results
Uncommon: Increased blood lipids (fats)
Rare: Increased blood sugar, increased blood uric acid

Psychiatric Effects
Uncommon: Anxiety, restlessness/agitation
Rare: Emotional instability, depression (in very rare cases leading to self-harm), hallucination
Very rare: A feeling of self-detachment (not being yourself), insanity (potentially leading to self-harm)

Nervous System
Common: Headache, dizziness
Uncommon: Tingling sensation (pins and needles) and/or numbness, changes in taste (in very rare cases loss of taste), confusion and disorientation, sleep problems (predominately sleeplessness), shaking, sensation of dizziness (spinning or falling over), sleepiness
Rare: Impairment of skin sensation, changes in smell (incl. loss of smell), abnormal dreams, balance disorder and poor co-ordination (due to dizziness), convulsions, disturbed concentration, impaired speech, partial or total loss of memory
Very rare: Increase of skin sensitivity

Eye
Uncommon: Visual disturbances incl. double and blurred vision

Ear
Rare: Ringing/noise in the ears

Cardiovascular System
Common: Distinct alteration of the electrical activity of the heart (ECG) in patients with decreased blood potassium
Uncommon: Distinct alteration of the electrical activity of the heart (ECG), palpitations, irregular and fast heart beat, severe cardiac rhythm abnormalities, angina pectoris, flushing
Rare: Abnormal fast heart rate, fainting, high blood pressure, low blood pressure
Very rare: Unspecific abnormal heart rhythms, irregular heart beat (Torsade de Pointes), stopping of heart beat (see section *2. Before you use Octegra....*)

Respiratory System
Uncommon: Difficulty in breathing incl. asthmatic conditions

Gastrointestinal System
Common: Nausea, vomiting, stomach and abdominal ache, diarrhoea
Uncommon: Loss of appetite, wind and constipation, stomach upset (indigestion/heartburn), inflammation of the stomach, increase of a special digestive enzyme in the blood (amylase)

Rare:	Difficulty in swallowing, inflammation of the mouth, severe diarrhoea containing blood and/or mucus (antibiotic associated colitis incl. pseudomembranous colitis), which in very rare circumstances, may develop into complications that are life-threatening

Liver

Common:	Increase of a special liver enzyme in the blood (transaminases)
Uncommon:	Impaired liver function (incl. increase of a special liver enzyme in the blood (LDH)), increase of bilirubin in the blood, increase of a special liver enzyme in the blood (gamma-glutamyl-transferase and/or alkaline phosphatase)
Rare:	Jaundice (yellowing of the whites of the eyes or skin), inflammation of the liver
Very rare:	Fulminant inflammation of the liver potentially leading to life-threatening liver failure (incl. fatal cases)

Skin

Uncommon:	Itching, rash, skin hives, dry skin
Very rare:	Alterations of the skin and mucous membranes (painful blisters in the mouth/nose or at the penis/vagina), potentially life-threatening (Stevens-Johnson-Syndrome, toxic epidermal necrolysis)

Muscular and Joint System

Uncommon:	Joint pain, muscle pain
Rare:	Pain and swelling of the tendons (tendonitis), muscle cramp, muscle twitching
Very rare:	Rupture of tendon, inflammation of joints, muscle rigidity, worsening of the symptoms of myasthenia gravis

Kidney

Uncommon:	Dehydration
Rare:	Kidney impairment (incl. increase in special kidney laboratory test results like urea and creatinine), kidney failure

General Side Effects

Uncommon:	Feeling unwell (predominantly weakness or tiredness), aches and pains such as back, chest, pelvic and extremities pains, sweating
Rare:	Swelling (of the hands, feet, ankles, lips, mouth, throat)

Infusion site

Common:	Pain or inflammation at injection site
Uncommon:	Inflammation of a vein

The following symptoms have been observed more frequently in patients treated intravenously:

Common:	Increase of a special liver enzyme in the blood (gamma-glutamyl-transferase)
Uncommon:	Abnormal fast heart rate, low blood pressure, swelling (of the hands, feet, ankles, lips, mouth, throat), severe diarrhoea containing blood and/or mucus (antibiotic associated colitis) which in very rare circumstances, may develop into complications that are life-threatening, convulsions, hallucination, kidney impairment (incl. increase in special kidney laboratory test results like urea and creatinine), kidney failure

Furthermore, there have been very rare cases of the following side effects reported following treatment with other quinolone antibiotics, which might possibly also occur during treatment with Octegra: transient loss of vision, increased blood sodium levels, increased blood calcium levels, increased breakdown of red blood cells, muscle reactions with muscle cell damage, increased sensitivity of the skin to sunlight or UV light.

If you feel you are suffering from a side effect, especially if any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist immediately to get advice before taking the next dose.

5. HOW TO STORE OCTEGRA

Keep out of the reach and sight of children.

Do not use Octegra after the expiry date which is stated on the label on the bottle bag and carton.

Do not refrigerate or freeze.

Use immediately after first opening and/or dilution.

This product is for single use only. Any unused solution should be discarded.
At cool storage temperatures precipitation may occur, which will re-dissolve at room temperature.
Do not use if you notice any visible particulate matter or if the solution is cloudy.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Octegra contains

- The active substance is moxifloxacin. Each bottle bag contains 400mg moxifloxacin (as hydrochloride). 1 ml contains 1.6 mg moxifloxacin (as hydrochloride).
- The other ingredients are sodium chloride, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment) and water for injections

What Octegra looks like and contents of the pack

Octegra is a clear, yellow solution for infusion.

Octegra is packaged in cartons containing a 250ml glass bottle with a chlorobutyl rubber stopper. Packs of 1 and 5 bottles.

Octegra is packaged in cartons containing 250ml polyolefine bags with polypropylene port sealed in aluminium foil overwrap. Packs of 5 and 12 bags.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]
[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Octegra
Belgium:	Proflox

France:	Octegra
Germany:	Octegra
Greece:	Octegra
Luxembourg:	Proflox
The Netherlands:	Octegra
Portugal:	Proflox

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

The following information is intended for medical or healthcare professionals only:

Octegra can be administered via a T-tube together with the following solutions:
Water for injections, sodium chloride 0.9%, sodium chloride 1 molar, glucose 5%/10%/40%, Xylitol 20%, Ringer's solution, compound sodium lactate solution (Hartmann's solution, Ringer-lactate solution).
Octegra should not be co-infused with other drugs.

The following solutions were incompatible with Octegra:
Sodium chloride 10% and 20% solutions,
Sodium bicarbonate 4.2% and 8.4% solutions