Antibiotic consumption in pigs can be optimized by developing treatment guidelines, which encourage veterinarians to use effective drugs with low probability of developing resistance of importance for human health. In Denmark, treatment guidelines for use in swine production are currently under review at the Danish Veterinary and Food Administration. Use of pleuromutilins in swine has previously been associated with a very low risk for human health. However, recent international data and sporadic findings of novel resistance genes suggest a change of risk. Consequently, a reassessment was undertaken inspired by a risk assessment framework developed by the European Medicines Agency. Livestock-associated methicillin-resistant Staphylococcus aureus of clonal complex 398 (MRSA CC398) and enterococci were identified as relevant hazards. The release assessment showed that the probability of development of pleuromutilin resistance was high in MRSA CC398 (medium uncertainty) and low in enterococci (high uncertainty). A relatively small proportion of Danes has an occupational exposure to pigs, and foodborne transmission was only considered of relevance for enterococci, resulting in an altogether low exposure risk. The human consequences of infection with pleuromutilin-resistant MRSA CC398 or enterococci were assessed as low for the public in general but high for vulnerable groups such as hospitalized and immunocompromised persons. For MRSA CC398, the total risk was estimated as low (low uncertainty), among other due to the current guidelines on prevention of MRSA in place at Danish hospitals, which include screening of patients with daily contact to pigs on admittance. Moreover, MRSA CC398 has a medium human–human transmission potential. For enterococci, the total risk was estimated as low due to low prevalence of resistance, low probability of spread to humans, low virulence, but no screening of hospitalized patients, high ability of acquiring resistance genes, and a limited number of alternative antimicrobials (high uncertainty). This assessment reflects the current situation and should be repeated if pleuromutilin consumption increases substantially, resulting in increased prevalence of mobile, easily transmissible resistance mechanisms. Continuous monitoring of pleuromutilin resistance in selected human pathogens should therefore be considered. This also includes monitoring of linezolid resistance, since resistance mechanisms for pleuromutilins and oxazolidones are often coupled.