Tacrolimus oral mouthwash

Note: See other stability summary for tacrolimus *oral suspension*.

Risk assessment of parent compound

A risk assessment survey completed by clinical pharmacists suggested that tacrolimus has a medium therapeutic index, with the potential to cause minor side-effects if inaccurate doses were to be administered (Lowey and Jackson, 2008). Current formulations used at NHS trusts for the mouthwash show a low technical risk, based on the number and complexity of manipulations and calculations. Tacrolimus mouthwash is therefore regarded as a low- to medium-risk extemporaneous product.

Note: This risk assessment applies to the mouthwash only. The use of tacrolimus as an oral suspension may be associated with a much higher risk (Box 14.46).

Summary

Tacrolimus mouthwash is used at a limited number of NHS centres in the UK. While there is reported to be some published and unpublished data to support its clinical use (e.g. Olivier *et al.*, 2002), there are no direct stability data available. Therefore, a cautious shelf-life of 7 days is recommended.

Future developments of the formulation may include investigation of the use of suspending agents rather than water, given the poor water solubility of the drug. Note that the handling of tacrolimus is associated with health and

Box 14.46 *Preferred formula – mouthwash*

Using a typical strength of 1 microgram/mL as an example:

- tacrolimus 1 mg capsule × 1
- sterile water to 1 litre.

Shelf-life

7 days at room temperature in amber glass. **Shake the bottle before use. Do not filter. Not to be swallowed.**

safety considerations, and should only be carried out in suitable facilities with appropriate protective equipment for the operator(s).

Clinical pharmaceutics

Points to consider

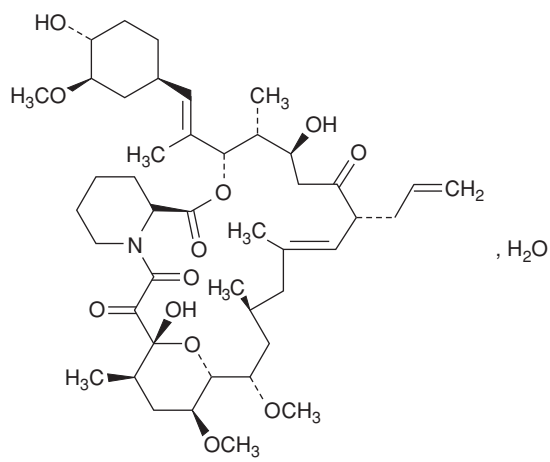
- The mouthwash should not be filtered, as this may remove some of the active drug.
- Although tacrolimus is very poorly soluble, the very low strength of this preparation should mean that most or all of the drug is in solution. However, some drug may be bound to insoluble excipients. As a precaution, the mouthwash should be shaken thoroughly before use. Future formulation developments may consider whether the use of a suspending agent is desirable.

Other notes

- Tacrolimus is not compatible with PVC plastics (Taormina *et al.* 1992; Summary of Product Characteristics, 2006).

Technical information

Structure



Empirical formula

$C_{44}H_{69}NO_{12},H_2O$ (Martindale, 2005).

Molecular weight

822 (Martindale, 2005).

Solubility

1–2 micrograms/mL in water (Yamashita *et al*., 2003; Han *et al*., 2006); 2–5 micrograms/mL in water (Namiki *et al*., 1995).

pK_a

Not known.

Optimum pH stability

2–6 (Namiki *et al*., 1995).

Stability profile

Physical and chemical stability

Tacrolimus is reported to be highly lipophilic and insoluble in water, but soluble in alcohol (Woods, 2001). It occurs as white crystals or crystalline powder (Trissel, 2000).

Tacrolimus exhibits maximum stability at pH 2–6; higher pH environments substantially increase degradation rates (Namiki *et al*., 1995).

Details of the degradation process for tacrolimus are not known to have been published. However, first principles would suggest that the primary route of degradation may be hydrolysis.

Tacrolimus is known to exhibit tautomerism. Further research is needed to establish the relevance of this phenomenon in oral liquid formulations.

Tacrolimus capsules require storage at controlled room temperature (<25°C). After opening of the blister packs, the capsules are reported to be stable for 12 months. Once the aluminium wrapper is opened, the capsules in the blister strips should be kept in a dry place (Summary of Product Characteristics, 2006).

Degradation products

No information.

Stability in practice

No data available.

Bioavailability data

No data are available when formulated as a mouthwash.

References

Han J, Beeton A, Long PF, Wong I, Tuleu C (2006). Physical and microbiological stability of an extemporaneous tacrolimus suspension for paediatric use. *J Clin Pharm Ther* 31: 167 172.

Lowey AR, Jackson MN (2008). A survey of extemporaneous dispensing activity in NHS trusts in Yorkshire, the North East and London. *Hosp Pharmacist* 15: 217 219.

Namiki Y, Fujiwara A, Kihara N, Oda S, Hane K, Yasuda T (1995). Factors affecting tautomeric phenomenon of a novel potent immunosuppressant (FK506) on the design for injectable formulation. *Drug Dev Ind Pharm* 21: 809 822.

Olivier V, Lacour J P, Mousnier A, Garraffo R, Monteil RA, Ortonne J P (2002). Treatment of chronic erosive oral lichen planus with low concentrations of topical tacrolimus. *Arch Dermatol* 138: 1335 1338.

Summary of Product Characteristics (2006). Prograf Capsules. www.medicines.org.uk (accessed 20 October 2006).

Sweetman SC (2009). *Martindale: The Complete Drug Reference*, 36th edn. London: Pharma ceutical Press.

Taormina D, Abdallah HY, Venkatamanan R, Logue L, Burckart GJ, Ptachcinski RJ *et al.* (1992). Stability and sorption of FK 506 in 5% dextrose injection and 0.9% sodium chloride injection in glass, polyvinyl chloride, and polyolefin containers. *Am J Hosp Pharm* 49: 119 123.

Trissel LA, ed. (2000). *Stability of Compounded Formulations*, 2nd edn. Washington DC: American Pharmaceutical Association.

Woods DJ (2001). *Formulation in Pharmacy Practice. eMixt, Pharminfotech*, 2nd edn. Dunedin, New Zealand. www.pharminfotech.co.nz/emixt (accessed 18 April 2006).

Yamashita K, Nakate T, Okimoto K, Ohike A, Tokunaga Y, Ibuki R *et al.* (2003). Establishment of new preparation method for solid dispersion formulation of tacrolimus. *Int J Pharm* 267: 79 91.

Tacrolimus oral suspension

Note: See other stability summary for tacrolimus *mouthwash*.

Risk assessment of parent compound

Tacrolimus has a narrow therapeutic index, with the potential to cause death if inaccurate doses are administered. Current formulations used at NHS trusts are generally of a moderate to high technical risk, based on the number and/or complexity of manipulations and calculations. Tacrolimus oral suspension is therefore regarded as a very high-risk extemporaneous preparation (Box 14.47).

Summary

There are several studies to support the stability of tacrolimus when formulated as an oral suspension. However, the bioavailability and efficacy of these suspensions are more controversial. It would appear a sensible step to convert the patient from oral suspension to capsules when practicable. Close monitoring of plasma drug levels should be considered, particularly given the high-risk nature of the patients treated with such preparations.

Purchase of the suspension from a 'Specials' manufacturer may be possible. Note that the method of manufacture may alter particle size and could lead to differences in bioavailability. The formulation should be reviewed by a suitably competent pharmacist before use.

Note that the handling of tacrolimus is associated with health and safety considerations, and should only be carried out in suitable facilities with appropriate protective equipment for the operator(s).

Clinical pharmaceutics

Points to consider

- Due to the very poor aqueous solubility of tacrolimus, the vast majority of drug is likely to be suspension rather than solution. **Shake the bottle before use to improve dosage uniformity.**
- Concerns have been raised with regard to poor bioavailability and erratic plasma concentrations for the oral suspension (Van Mourik *et al.*,

Box 14.47 *Preferred formula – oral suspension*

Note: 'Specials' are now available from reputable manufacturers. Extemporaneous preparation should only occur where there is a demonstrable clinical need.

Using a typical strength of **1 mg/mL** as an example:

- tacrolimus 5 mg capsules × 20
- Ora-Plus 50 mL
- Ora-Sweet to 100 mL.

Method guidance

The contents of the capsules can be ground to a fine, uniform powder in a pestle and mortar. A small amount of Ora-Plus may be added to form a paste, before adding further portions of Ora-Plus up to 50% of the final volume. Transfer to a measuring cylinder. The Ora-Sweet can be used to wash out the pestle and mortar of any remaining drug before making the suspension up to 100% volume. Transfer to an amber medicine bottle.

Shelf-life

28 days at room temperature in amber glass. **Shake the bottle before use.**

Alternative

Using a typical strength of **500 micrograms/mL:**

- tacrolimus 5 mg capsules × 10
- Ora-Plus 50 mL
- Syrup BP to 100 mL.

Shelf-life

28 days at room temperature in amber glass. **Shake the bottle before use.**

1999; Reding *et al.*, 2002; Han *et al.*, 2006). There are conflicting data with regard to the bioavailability of the suspension, with estimates ranging from around 50% to 100% of the bioavailability of the capsule (McGhee *et al.*, 1997; Reding *et al.*, 2002). Close monitoring of plasma levels is recommended.

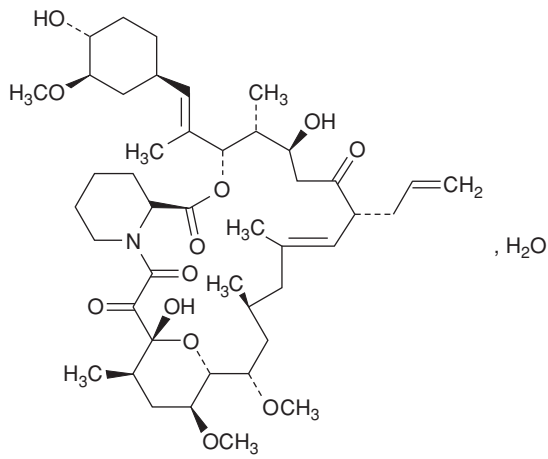
- Ora-Plus and Ora-Sweet are free from ethanol and chloroform. Ora-Plus is free from sucrose.
- The particle size of the suspension may vary according to the method of manufacture. Suspensions made with a pestle and mortar may differ in their bioavailability from those made with automated equipment.
- The combination of Ora-Plus and Ora-Sweet is preferred, as the combination of Ora-Plus and Syrup BP (or Simple Syrup NF as in the American literature) has not been widely validated as an effective suspending vehicle. Note that Syrup BP is sucrose 667 g with purified water sufficient to produce 1,000 mL. One or more suitable antimicrobial preservatives may be added. Syrup NF (simple syrup NF) is sucrose 850 g with purified water sufficient to produce 1,000 mL.

Other notes

- Tacrolimus is not compatible with PVC plastics (Summary of Product Characteristics, 2006).
- Preparation of tacrolimus powder papers is time-consuming and carries a high potential for error (Jacobson *et al.*, 1997).
- The intravenous formulation should be used with caution to compound an oral liquid due to the presence of dehydrated alcohol and hydrogenated castor oil as stabilizing agents (Elefante *et al.*, 2006).

Technical information

Structure



Empirical formula

$C_{44}H_{69}NO_{12},H_2O$ (Martindale, 2005).

Molecular weight

822 (Martindale, 2005).

Solubility

Reported separately as: 1–2 micrograms/mL in water (Yamashita *et al.*, 2003; Han *et al.*, 2006); 2–5 micrograms/mL in water (Namiki *et al.*, 1995).

pK_a

Not known.

Optimum pH stability

2–6 (Namiki *et al.*, 1995).

Stability profile

Physical and chemical stability

Tacrolimus is reported to be highly lipophilic and insoluble in water, but soluble in alcohol (Woods, 2001). It occurs as white crystals or crystalline powder (Trissel, 2000).

Tacrolimus exhibits maximum stability at pH 2–6; higher pH environments substantially increase degradation rates (Namiki *et al.*, 1995).

Details of the degradation process for tacrolimus are not known to have been published. However, first principles would suggest that the primary route of degradation may be hydrolysis.

Tacrolimus is known to exhibit tautomerism. Further research is needed to establish the relevance of this phenomenon in oral liquid formulations.

Tacrolimus capsules require storage at controlled room temperature (<25°C). After opening of the blister packs, the capsules are reported to be stable for 12 months. Once the aluminium wrapper is opened, the capsules in the blister strips should be kept in a dry place (Summary of Product Characteristics, 2006).

Degradation products

No information available.

Stability in practice

There are three main studies which describe the physical and chemical stability of tacrolimus in vehicles consisting of Ora-Plus and a syrup preparation, and Ora-Plus and Ora-Sweet.

Jacobson *et al.* (1997) have investigated the stability of tacrolimus 500 micrograms/mL in an extemporaneously compounded liquid. The contents of six 5 mg tacrolimus capsules were suspended in 60 mL of a 1:1 mixture of Ora-Plus and Simple Syrup NF (sucrose 850 g with purified water to 1,000 mL). Six identical suspensions were prepared and divided equally between storage in glass and plastic prescription bottles. All the samples were stored at room temperature, defined as 24–26°C.

A 1 mL sample was withdrawn from each bottle on days 0, 7, 15, 30, 45 and 56, and analysed using a stability-indicating assay. The lack of microbiological testing is justified by the authors due to the presence of effective preservatives in both Ora-Plus and Simple Syrup NF. Ora-Plus contains a hydroxybenzoate preservative system. The preservative in the Simple Syrup NF preparation used by Jacobson *et al.* (1997) is not known.

At least 98% of the initial tacrolimus concentration remained in all the suspensions throughout the 56 days. No significant changes were detected in colour, odour or pH (starting mean pH 4.6). The authors describe a sweet flavour with a slightly bitter aftertaste. The plastic in the bottles was polypropylene resin, not PVC.

Following concerns regarding physical stability and particle size (see below), Han *et al.* (2006) studied the physical and microbiological stability of a formulation very similar to that described by Jacobson *et al.* (1997), although they used a BP grade syrup preparation in place of Simple Syrup NF. Note that Syrup BP contains 667 g sucrose, purified water to 1,000 mL, and that one or more suitable antimicrobial preservatives may be added. The authors refer to the syrup preparation as 'simple syrup of BP grade'. The lead author has confirmed that the formulation used Syrup BP with preservatives (J. Han, personal communication, 2007).

Although the preparation process was essentially the same as that described by Jacobson *et al.* (1997), one extra homogenisation step was added. The contents of the tacrolimus capsules were mixed into Ora-Plus using a pestle and mortar, followed by stepwise addition of the syrup. After thorough mixing, the suspensions were further homogenised using a high shear mixer (Model L4RT; Silverson Machine Ltd) at a speed of 7,500 rpm for 2 minutes. The suspensions were made on behalf of the authors by a UK Specials manufacturer (Specials Laboratories Ltd, Low Prudhoe, UK) under good manufacturing practice (GMP) conditions. Three batches of the suspension were packed into 50 mL amber glass bottles with screw-cap seals and supplied for testing. Analysis began less than 24 hours after production.

Allowing for normal experimental error and drift, no significant changes were detected in particle size, using laser diffraction and microscopical examination. The particle size measured was the mean particle size, including drug and excipient components. None of the samples showed any microbiological contamination.

Ora-Plus contains a blend of suspending agents, which may have helped to form a structured gel-like matrix of high viscosity reducing the coalescence and sedimentation of the particles (Ofner *et al.*, 1996). Han *et al.* (2006) suggest that cellulosic derivatives in the Ora-Plus and the high viscosity of the media may have suppressed crystal growth. The low pH of the formulation and the antimicrobial nature of tacrolimus may have contributed to the lack of microbial growth.

In conclusion, the reported low bioavailability and erratic plasma concentration could not be correlated to physical or microbiological instability. The authors suggest that poor dosing (e.g. impractically small volumes) or poor shaking may warrant further investigation as potential causes of erratic plasma concentrations.

The method of manufacture of the suspension may also be a factor, as suspensions made with automated equipment may display different physical characteristics to those suspensions made by hand using only the traditional pestle and mortar approach.

Elefante *et al.* (2006) studied the long-term stability of a 1 mg/mL tacrolimus suspension, after the 500 micrograms/mL suspension described above led to administration errors and the confusion of milligrams with millilitres. The contents of six 5 mg capsules were placed in an amber plastic bottle and 5 mL of water was added. The bottle was agitated until the powder dispersed to form a slurry. Equal volumes of Ora-Plus and Ora-Sweet were added to a final volume of 30 mL. Study samples of 3 mL were prepared in triplicate and stored at room temperature (23–26°C) in capped plastic bottles.

The samples were analysed by a stability-indicating HPLC assay on days 0, 78 and 132. Although statistical analysis found no difference between the results on these three days, the range of values at day 132 extended down to 91.3% of the original concentration. If more data points had been available, the statistical package used may have detected a trend. The study is limited by the number of data points, and by the use of 3 mL samples volumes, which would not mimic the practical usage of the suspension.

The authors note the difficulty associated with degrading the tacrolimus during assay validation, in addition to the long-term stability of the suspension over four months at room temperature.

Bioavailability data

Oral absorption of tacrolimus, including licensed preparations, is reported to be erratic. Oral bioavailability varies widely, with typical mean oral bioavailability from the capsules quoted at 20–25% (Summary of Product Characteristics, 2006). The variation in bioavailability may not be highly important for the mouthwash preparation, but may become crucial if an oral suspension is formulated. Given the known variation in bioavailability from

the capsules, it follows that oral suspensions derived from the capsules will also display a marked variation in plasma levels.

Although Jacobson *et al.* (1997) acknowledge that the bioavailability of the Ora-Plus/Simple Syrup NF formulation was not assessed formally, the authors suggest that its bioavailability should not differ significantly from that of the capsule. The authors also state that adults and children have shown satisfactory plasma levels using this formulation. The exact procedure for making the suspension is presented, using a pestle and mortar.

McGhee *et al.* (1997) have subsequently reported the successful use of the formulation described by Jacobson *et al.* (1997) in 20 paediatric patients. Nineteen of the patients were solid organ recipients (heart, $n = 5$; heart–lung, $n = 4$; lung, $n = 4$; liver–intestine, $n = 4$; liver, $n = 3$; intestine, $n = 2$; multivisceral, $n = 1$) and one patient had dermatomyositis. The suspension was administered orally or via an enteral tube (nasogastric, nasojejunal, gastrostomy, gastrojejunal or jejunostomy tube). McGhee *et al.* (1997) suggest that all patients were able to maintain therapeutic drug levels (normal range quoted as 5–20 ng/mL) at standard doses comparable to those used with capsules.

Nine patients continued the suspension as outpatients, with no loss of efficacy. The authors conclude that the suspension is an effective method of delivering tacrolimus to infants and children who cannot swallow, as well as patients who require administration via an enteral tube.

Reding *et al.* (2002) found the bioavailability of the suspension to be approximately 50% lower than that of the capsule, when used in paediatric liver transplant recipients. The oral suspension was administered to 15 paediatric liver transplant recipients (mean age 1.4 years), and the data compared to corresponding data with tacrolimus capsules. Graft and survival rates were 100%, with acute rejection and steroid-resistant rejection encountered in 9/15 and 3/15 patients, respectively.

The authors suggest that the oral absorption of tacrolimus was lower for the oral suspension than for the capsules. However, the comparator data for patients taking capsules is derived from a separate study based on a different cohort of patients (Wallemacq and Reding, 1993). This difference may make some of the comparisons inaccurate. Moreover, no direct correlation could be shown between pharmacokinetic parameters and rejection, and a similar rejection incidence was found with both formulations (60% versus 55% for the suspension and capsules, respectively). The authors conclude by stating that the oral suspension may be useful for dose titration in low body weight recipients in the early post-transplant phase. However, prompt conversion to capsules is recommended. Overall bioavailability for the oral suspension is estimated at 12.9%, compared with a figure of 25% described in the separate cohort of patients taking capsules rather than suspension (Reding *et al.*, 2002).

Van Mourik *et al.* (1999) have reported erratic trough levels in the first few days of administration in a group of 20 children. The authors suggest that this finding may be linked to an increased risk of acute graft rejection, which was approximately double that of a control group treated with granules or capsules. It is unclear whether this difference is due to hepatic metabolism or intestinal absorptive barriers of the children, or due to formulation factors including poor physical stability (particle size changes, especially crystal growth during storage) or poor dosing (Han *et al.*, 2006).

The work carried out by Han *et al.* (2006) did not find any significant change in particle size over eight weeks for the 500 micrograms/mL tacrolimus suspension in a 1:1 mixture of Ora-Plus and Syrup BP. The authors suggest that dosing techniques and poor shaking may warrant further investigation (Han *et al.*, 2006).

References

Elefante A, Nuindi J, West K, Dunford L, Abel S, Paplham P *et al.* (2006). Long term stability of a patient convenient 1 mg/ml suspension of tacrolimus for accurate maintenance of stable therapeutic levels. *Bone Marrow Transplant* 37: 781 784.

Han J, Beeton A, Long PF, Wong I, Tuleu C (2006). Physical and microbiological stability of an extemporaneous tacrolimus suspension for paediatric use. *J Clin Pharm Ther* 31: 167 172.

Jacobson PA, Johnson CE, West NJ, Foster JA (1997). Stability of tacrolimus in an extempora neously compounded oral liquid. *Am J Health Syst Pharm* 54: 178 180.

McGhee B, McCombs JR, Boyle G, Webber S, Reyes JR (1997). Therapeutic use of an extempo raneously prepared oral suspension of tacrolimus in paediatric patients. *Transplantation* 64: 941.

Namiki Y, Fujiwara A, Kihara N, Koda S, Hane K, Yasuda T (1995). Factors affecting tautomeric phenomenon of a novel potent immunosuppressant (FK506) on the design for injectable formulation. *Drug Dev Ind Pharm* 21: 809 822.

Ofner CM, Schnaare RL, Schwartz JB (1996). Oral aqueous suspensions. In: Lierberman HA, Rieger MM, Banker GS, eds. *Pharmaceutical Dosage Forms Disperse Systems*, Vol. 2. New York: Marcel Dekker, pp. 149 181.

Olivier V, Lacour J P, Mousnier A, Garraffo R, Monteil RA, Ortonne J P (2002). Treatment of chronic erosive oral lichen planus with low concentrations of topical tacrolimus. *Arch Dermatol* 138: 1335 1338.

Reding R, Sokal E, Paul K, Janssen M, Evrard V, Wilmotte L *et al.* (2002). Efficacy and phar macokinetics of tacrolimus oral suspension in pediatric liver transplant recipients. *Pediatr Transplant* 6: 124 126.

Summary of Product Characteristics (2006). Prograf Capsules. www.medicines.org.uk (accessed 20 October 2006).

Sweetman SC (2009). *Martindale: The Complete Drug Reference*, 36th edn. London: Pharma ceutical Press.

Taormina D, Abdallah HY, Venkatamanan R, Logue L, Burckart GJ, Ptachcinski RJ *et al.* (1992). Stability and sorption of FK 506 in 5% dextrose injection and 0.9% sodium chloride injection in glass, polyvinyl chloride, and polyolefin containers. *Am J Hosp Pharm* 49: 119 123.

Trissel LA, ed. (2000). *Stability of Compounded Formulations*, 2nd edn. Washington DC: American Pharmaceutical Association.

Van Mourik IDM, Holder G, Beath S, McKiernan PUB, Kelly D (1999). Increased risk of acute graft rejection in paediatric liver transplant recipients on tacrolimus suspension. Paper pre sented at the 3rd International Congress on Immunosuppression, San Diego, USA.

Wallemacq P, Reding R (1993). FK 506 (Tacrolimus), a novel immunosuppressant in organ transplantation: clinical, biomedical and analytical aspects. *Clin Chem* 39: 2219 2228.
Woods DJ (2001). *Formulation in Pharmacy Practice. eMixt, Pharminfotech*, 2nd edn. Dunedin, New Zealand. www.pharminfotech.co.nz/emixt (accessed 18 April 2006).
Yamashita K, Nakate T, Okimoto K, Ohike A, Tokunaga Y, Ibuki R *et al.* (2003). Establishment of new preparation method for solid dispersion formulation of tacrolimus. *Int J Pharm* 267: 79 91.