### 1.3.1 Summary of Product Characteristics (SmPC)

#### 1.3.1.1 Name of the Medicinal Product

International Non– Proprietary Name (INN): Diclofenac injection

#### 1.3.1.2 ATC and Forensic Classification

ATC Classification: analgesic; anti-inflammatory.

#### 1.3.1.3. Qualitative and quantitative composition

Diclofenac injection

Each 3 ml Ampoule contains Diclofenac Sodium 75mg

#### 1.3.1.4. Pharmaceutical form

Liquid injection ;

3ml Ampoule containing a clear, colourless to yellowish solution

#### 1.3.1.5. Clinical particulars

1.3.1.5.1 Therapeutic indications

Treatment of:

• Exacerbations of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, osteoarthritis.
• Acute attacks of gout.
• Renal colic and biliary colic.
• Post-traumatic and post-operative pain, inflammation and swelling.
• Acute trauma and fractures

1.3.1.5.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

Adults:

Intramuscular injection: The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site.

One ampoule once (or in severe cases twice) daily intramuscularly by deep intragluteal injection into the upper outer quadrant. If two injections daily are required it is advised that the alternative buttock be used for the second injection. Alternatively, one ampoule of 75mg can be combined with other dosage forms of Diclofenac Injection (tablets or suppositories) up to the maximum daily dosage of 150mg.

Diclofenac Injection ampoules should not be given for more than 2 days; if necessary, treatment can be continued with tablets or suppositories.

Diclofenac Injection should not be administered by intravenous injection.

Renal colic: One 75mg ampoule intramuscularly. A further ampoule may be administered after 30 minutes if necessary.
The recommended maximum daily dosage of Diclofenac Injection is 150mg.
Older people (Patients aged 65 or above):
Although the pharmacokinetics of Diclofenac Injection are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight. Prolonged use of non-steroidal anti-inflammatory drugs in the elderly is not recommended.
Children and adolescents:
Diclofenac Injection ampoules are not suitable for children and adolescents. Diclofenac Injection ampoules are contraindicated in children up to 14 years.

1.3.1.5.3 Contraindications

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active or history of recurrent peptic ulcer/ haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
• Active gastric or intestinal ulcer, bleeding or perforation
• Last trimester of pregnancy (see Pregnancy and lactation).
• Hepatic failure
• Chronic Kidney Disease Grade 5 (GFR <15)
• Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
• Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac Injection is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs drugs with prostaglandin-synthetase inhibiting activity.
• Hypersensitivity to the active substance and to the excipients.
• Diclofenac Injection ampoules are contraindicated in children up to 14 years.

1.3.1.5.4 Special warnings and precautions for use

Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 1) are listed by MedRA system order class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent first. . Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on using the following convention (CIOMS III): very common (>1/10): common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000).

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea,

vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of coilitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.

The following table of undesirable effects include those reported with Diclofenac Injection solution for infusion and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

**Table 1**

| | |
|---|---|
| **Blood and lymphatic system disorders** | |
| Very rare: | Thrombocytopenia, leucopenia, anemia (including hemolytic anemia and aplastic anaemia), agranulocytosis. |
| **Immune system disorders** | |
| Rare: | Hypersensitivity reactions such as asthma, systemic anaphylactic and anaphylactoid reactions (including hypotension and shock). |
| Very rare: | Angioedema (including face edema). |
| **Psychiatric disorders** | |
| Very rare: | Disorientation, depression, insomnia, nightmares, irritability, psychotic disorder. |
| **Nervous system disorders** | |
| Common: | Headache, dizziness. |
| Rare: | Somnolence. |
| Very rare: | Paraesthesia, memory impairment, convulsions, anxiety, tremor, meningitis aseptic, dysgeusia, cerebrovascular accident. |
| **Eye disorders** | |
| Very rare: | Visual impairment(blurred vision, diplopia). |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo. |
| Very rare: | Tinnitus, hearing impaired. |
| **Cardiac disorders** | |
| Uncommon*: | Myocardial infarction, cardiac failure, palpitations, chest pain |
| **Vascular disorders** | |
| Very rare: | Hypertension, vasculitis. |
| Respiratory, thoracic and mediastinal disorders | |
| Rare: | Asthma/bronchospasm (including dyspnoea). |

| | |
|---|---|
| Very rare: | Pneumonitis. |
| **Gastrointestinal tract disorders** | |
| Common: | Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, decreased appetite. |
| Rare: | Gastritis, gastrointestinal hemorrhage, aematemesis, diarroea, hemorrhagic melena, gastric or intestinal ulcer (with or without bleeding or perforation) . |
| Very rare: | Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal lesions, diaphragm-like intestinal strictures, pancreatitis. |
| **Hepatobiliary disorders** | |
| Common: | Transaminases increased |
| Rare: | Hepatitis, with or without jaundice, liver disorder. |
| Very rare: | Hepatitis fulminant, hepatic necrosis, hepatic failure. |
| **Skin and subcutaneous tissue disorders** | |
| Common: | Rashes. |
| Rare: | Urticaria |
| Very rare: | Dermatitis bullous, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, alopecia, photosensitivity reaction, purpura, Henoch-Schonlein purpura, pruritus |
| **Infections and Infestations** | |
| Very rare: | Injection site abscess. |
| **Renal and urinary disorders** | |
| Very rare: | Renal failure acute, hematuria, proteinuria, nephritic syndrome, tubulointerstitial nephritis, renal papillary necrosis. |
| **General disorders and administration site conditions** | |
| Common: | Injection site reactions such as local pain and induration. |
| Rare: | Edema, injection site necrosis. |

*** The frequency reflects data from long-term treatment with a high dose (150 mg/day).**

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment.

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

1.3.1.5.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with Diclofenac Injection solution for injection and/or other pharmaceutical forms of diclofenac.
Observed interactions to be considered
Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.
Lithium: If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.
Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.
Diuretic and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

1.3.1.5.6 Pregnancy and lactation

Not applicable.

1.3.1.5.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Due to the occurrence of some adverse reactions (see section 4.8) the ability to drive and use machines may be impaired.

1.3.1.5.8 Undesirable effects
General :
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.
The concomitant use of diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.
Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body- weight.

Like other NSAIDs, Diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.
The sodium metabisulphite present in solution for injection can also lead to isolated severe hypersensitivity reactions and bronchospasm.
Diclofenac solution for injection must not be given to premature babies or neonates.
Benzylalcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years of age.
The use of diclofenac sodium may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac sodium should be considered.
Gastro-intestinal Effects:
Gastro-intestinal bleeding, ulceration or perforation, which can be fatal has been reported with all NSAIDs, including diclofenac and may occur at any time during treatment with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in the elderly. If gastro-intestinal bleeding or ulceration occurs in patients receiving Diclofenac Injection the drug should be withdrawn.
As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Diclofenac Injection in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, patients with ulcerative colitis or Crohn's disease and in patients suffering from impaired hepatic function, bleeding or perforation, (see Undesirable effects). The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see Contra-indications). The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.
To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.
Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin, or other medicinal products likely to increase gastrointestinal risk (see below and Interactions with other medicinal products and other forms of interaction).
Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, anti-platelet agents such as aspirin or selective serotonin-reuptake inhibitors (see drug Interactions).
Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn"s disease, as their condition may be exacerbated (see Adverse effects).
Hepatic effects
Close medical surveillance is required when prescribing Diclofenac Injection to patients with impaired hepatic function, as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Diclofenac Injection (e.g. in the form of tablets or suppositories) regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash, etc.), Diclofenac Injection should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.
Caution is called for when using Diclofenac Injection in patients with hepatic porphyria, since it may trigger an attack.
Renal effects
As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment being treated with diuretics or medicinal products that can significantly impact renal function (e.g. aminoglycosides), and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see Contraindications). Monitoring of renal function is recommended as a precautionary measure when using Diclofenac Injection in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.
Skin Effects
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including Diclofenac Injection (see Adverse effects). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Diclofenac Injection should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity. As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.
Cardiovascular and cerebrovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or congestive heart failure (NYHA-1) as fluid retention and oedema have been reported in association with NSAID therapy.
Clinical trial and epidemiological data suggest that the use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). .
Patients with congestive heart failure (NYHA-1) and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.
Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.
Haematological effects

During prolonged treatment with Diclofenac Injection, as with other NSAIDs, monitoring of the blood count is recommended.
Like other NSAIDs, Diclofenac Injection may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.
Pre-existing asthma
In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics/analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.
Special caution is recommended when Diclofenac Injection is used parenterally in patients with bronchial asthma because symptoms may be exacerbated.

1.3.1.5.9 Overdose

Symptoms
There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.
Therapeutic measures
Management of acute poisoning with NSAIDs, including diclofenac, consists essentially of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.
Special measures such as forced diuresis, dialysis, or haemoperfusion are probably unlikely to be helpful in accelerating the elimination of NSAIDs, including diclofenac, because of their high protein- binding rate and extensive metabolism.

### 1.3.1.6 Pharmacological properties

1.3.2.6.1 Pharmacodynamic properties

In rheumatic diseases, the anti-inflammatory and analgesic properties of Diclofenac Injection elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.
Diclofenac Injection has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin, an effect which sets in within 15 to 30 minutes.
Diclofenac Injection has also been shown to have a beneficial effect in migraine attacks.

In post-traumatic and post-operative inflammatory conditions, Diclofenac Injection rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.
When used concomitantly with opioids for the management of post-operative pain, Diclofenac Injection significantly reduces the need for opioids.
Diclofenac Injection ampoules are particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases and of painful conditions due to inflammation of non-rheumatic origin.
There is limited clinical trial experience of the use of diclofenac in Juvenile Rheumatoid Arthritis (JRA)/Juvenile Idiopathic Arthritis (JIA) paediatric patients. In a randomized, double-blind, 2-week, parallel group study in children aged 3-15 years with JRA/JIA, the efficacy and safety of daily 2-3 mg/kg BW diclofenac was compared with acetylsalicylic acid (ASS, 50-100 mg/kg BW/d) and placebo – 15 patients in each group. In the global evaluation, 11 of 15 diclofenac patients, 6 of 12 aspirin and 4 of 15 placebo patients showed improvement with the difference being statistically significant ($p < 0.05$). The number of tender joints decreased with diclofenac and ASS but increased with placebo. In a second randomized, double-blind, 6-week, parallel group study in children aged 4-15 years with JRA/JIA, the efficacy of diclofenac (daily dose 2-3 mg/kg BW, n=22) was comparable with that of indomethacin (daily dose 2-3mg/kg BW, n=23).

Diclofenac Injection contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic, and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain and fever.
Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

1.3.1.6.2 Pharmacokinetic properties

Absorption:
After administration of 75mg diclofenac by intramuscular injection, absorption sets in immediately and mean peak plasma concentrations of about 2.558 ± 0.968microgram/ml (2.5microgram/mL ≡ 8microμmol/L) are reached after about 20 minutes.
When 75mg diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.9 micrograms/mL (5.9 micromol/L). Shorter infusions result in higher peak plasma concentrations, while longer infusions give plateau concentrations proportional to the infusion rate after 3 to 4 hours. In contrast, plasma concentrations decline rapidly once peak levels have been reached following intramuscular injection or administration of gastro-resistant tablets or suppositories.
The area under the concentration curve (AUC) after intramuscular administration is about twice as large as it is following oral or rectal administration because about half the active substance is metabolized during its first passage through the liver ("first pass" effect) when administered via the oral or rectal routes. The amount absorbed is in linearly proportion to the size of the dose.
Pharmacokinetic behaviour does not change on repeated administration. Accumulation does not occur, provided the recommended dosage intervals are observed.
Distribution:

The active substance is 99.7% protein bound, mainly to albumin (99.4%).
Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma and remain higher for up to 12 hours.
Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.
Biotransformation/Metabolism:
Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.
Elimination:
Total systemic clearance of diclofenac in plasma is 263±56mL/min (mean value ±SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours.
About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.
Special Populations
Elderly: No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed, other than the finding that in five elderly patients, a 15 minute iv infusion resulted in 50% higher plasma concentrations than expected with young healthy subjects.
Patients with renal impairment: In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10mL/min, the calculated steady-state plasma levels of hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.
Patients with hepatic disease: In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.
1.3.1.6.3 Preclinical safety data

Acute Toxicity - Not determined for the product formulation. Information for ingredients is as follows:

| Ingredient(s) | Percent | Test Type | Route of Administration | Value | Units | Species |
|---|---|---|---|---|---|---|
| Diclofenac Sodium | 100 | LD50 | Oral | 53, 270<br>95<br>157<br>59 | mg/kg<br>mg/kg<br>mg/kg<br>mg/kg | Rat<br>Mouse<br>Rabbit<br>Dog |
| Diclofenac | 100 | LD50 | Intravenous | 117 | mg/kg | Rat |

| | | | | | | |
|---|---|---|---|---|---|---|
| Sodium | | | | 116<br><100<br>42 | mg/kg<br>mg/kg<br>mg/kg | Mouse<br>Rabbit<br>Dog |
| Hydroxypropyl betadex | 100 | LD | Intravenous | >5000 | mg/kg | Mouse |

LD 50: Dosage that produces 50% mortality

**1.3.1.7 Pharmaceutical Particulars**

1.3.1.7.1 Incompatibilities

None reported

1.3.1.7 2 Shelf life: 36 Months

1.3.1.7.3 Special precautions for storage :

Store below 30°C. Protect from light.

1.3.1.7.4 Nature and contents of container

75mg/3 ml – Amber Type II glass ampoule packs of 10 ampoules per box.

1.3.1.7.5 Special precautions for disposal

Single use only. Discard any unused contents.

The solution may darken from colourless to a pale yellow but this does not indicate a loss of potency.